

CROFTON AND DOUGLAS'S  
RESPIRATORY DISEASES

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# CROFTON AND DOUGLAS'S RESPIRATORY DISEASES

EDITED BY

**ANTHONY SEATON** CBE, BA, MD, FRCP, FRCPE, FFOM, FMedSci

*Professor of Environmental & Occupational Medicine, University of Aberdeen, Scotland*

*Honorary Consultant Physician, Aberdeen Royal Hospital NHS Trust*

**DOUGLAS SEATON** MD, FRCP

*Consultant Physician, Department of Respiratory Medicine, The Ipswich Hospital NHS Trust, Suffolk, England*

**The late A. GORDON LEITCH** BSc, MB, PhD, FRCPE, FCCP

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# CONTENTS

Contributors, vii

Preface, ix

Acknowledgements, x

## Volume 1

- 1 Development and Structure, 1  
*Anthony Seaton*
- 2 Functions of the Lung, 26  
*A. Gordon Leitch*
- 3 Epidemiology, 63  
*Anthony Seaton*
- 4 Lung Defences and Immunology, 83  
*Christopher Haslett*
- 5 Genetics of Lung Disease, 91  
*Julian M. Hopkin*
- 6 Clinical Aspects, 102  
*Anthony Seaton*
- 7 Diagnostic Imaging, 119  
*Arthur J.A. Wightman*
- 8 Minimally Invasive Diagnostic Procedures, 148  
*Douglas Seaton*
- 9 Drugs in Lung Disease, 193  
*Douglas Seaton*
- 10 Smoking, 311  
*Ian A. Campbell*
- 11 Air Pollution, 324  
*Anthony Seaton*
- 12 Acute Upper Respiratory Tract Infection, 335  
*Douglas Seaton*
- 13 Pneumonia, 356  
*Douglas Seaton*
- 14 Empyema, 445  
*Douglas Seaton*
- 15 Lung Abscess, 460  
*Douglas Seaton*
- 16 Tuberculosis: Pathogenesis, Epidemiology and Prevention, 476  
*A. Gordon Leitch*
- 17 Pulmonary Tuberculosis: Clinical Features, 507  
*A. Gordon Leitch*
- 18 Extra-Pulmonary Tuberculosis, 528  
*R. Andrew Seaton*
- 19 Management of Tuberculosis, 544  
*A. Gordon Leitch*
- 20 Opportunistic Mycobacterial Disease, 565  
*A. Gordon Leitch*
- 21 Actinomycotic and Fungal Diseases, 573  
*Anthony Seaton*
- 22 Parasitic Diseases, 604  
*Anthony Seaton*
- 23 Chronic Bronchitis and Emphysema, 616  
*William MacNee*
- 24 Respiratory Failure, 696  
*William MacNee*
- 25 Pulmonary Embolism, 718  
*Douglas Seaton and Anthony Seaton*
- 26 Pulmonary Hypertension, 748  
*Anthony Seaton*



27 Pulmonary Oedema and Adult Respiratory Distress Syndrome, 766  
*Christopher Haslett*

28 Bronchiectasis, 794  
*Douglas Seaton*

Index

## Volume 2

29 Bronchiolar Disease, 829  
*Anthony Seaton*

30 Cystic Fibrosis, 839  
*Andrew P. Greening*

31 Pulmonary Fibrosis, 877  
*Anthony Seaton*

32 Asthma: Epidemiology, 894  
*Peter G.J. Burney*

33 Asthma: Cellular and Humoral Mechanisms, 907  
*Christopher Haslett*

34 Asthma: Clinical Features, 922  
*Anthony Seaton and Graham Crompton*

35 Asthma: Management, 973  
*Graham Crompton*

36 Reactive Airways Dysfunction Syndrome, 998  
*Anthony Seaton*

37 Hypersensitivity Lung Diseases, 1002  
*Anthony Seaton*

38 Pulmonary Eosinophilias, 1020  
*A. Gordon Leitch*

39 Sarcoidosis, 1035  
*A. Gordon Leitch*

40 Pulmonary Lymphocytic Angiitis and Granulomatosis, 1063  
*Anthony Seaton*

41 Lung Cancer, 1077  
*Ronald J. Fergusson*

42 Other Pulmonary Neoplasms and Related Conditions, 1124  
*Anthony Seaton*

43 Diseases of the Pleura, 1152  
*Anthony Seaton*

44 Pneumothorax, 1182  
*Douglas Seaton*

45 Chest Wall and Neuromuscular Disorders, 1212  
*Anthony Seaton*

46 Abnormalities and Diseases of the Diaphragm, 1234  
*Anthony Seaton*

47 Sleep Apnoea/Hypopnoea Syndrome, 1250  
*Neil J. Douglas*

48 Hyperventilation Syndromes, 1264  
*Anthony Seaton*

49 Diseases of the Mediastinum, 1269  
*Douglas Seaton*

50 Developmental Disorders of the Lungs, 1309  
*Douglas Seaton and Anthony Seaton*

51 Some Less Common Pulmonary Diseases, 1330  
*Anthony Seaton*

52 Respiratory Infection in the Immunosuppressed, 1346  
*R. Andrew Seaton, Julian M. Hopkin and Douglas Seaton*

53 Pulmonary Manifestations of Systemic Disease, 1380  
*Anthony Seaton*

54 Occupational Lung Diseases, 1404  
*Anthony Seaton*

55 Drug-induced Lung Disease, Oxygen Toxicity and Related Syndromes, 1458  
*Anthony Seaton*

56 Some Paediatric Influences on Adult Lung Disease, 1476  
*George Russell*

57 Diving and the Lung, 1481  
*Stephen J. Watt*

58 Assisted Ventilation, 1495  
*John M. Shneerson*

59 Lung Transplantation, 1516  
*Timothy W. Higgenbottam*

60 Terminal Care in Respiratory Disease, 1524  
*Douglas Seaton*

61 Medicolegal Aspects of Lung Disease, 1536  
*Anthony Seaton*

Index

*Colour plate section falls between pages 630 and 631, Vol. 1.*

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# CONTRIBUTORS

PETER G.J. BURNEY MA, MD, FRCP, FFFPHM,  
*Department of Public Health Sciences, King's College London,  
Capital House, 42 Weston Street, London SE1 3QD*

IAN A. CAMPBELL BSc, MD (Lond.), FRCP,  
*Consultant Chest Physician, Llandough Hospital, Cardiff  
CF64 2XX*

GRAHAM CROMPTON MBCHB, FRCPE,  
*Consultant Physician, Department of Respiratory Medicine,  
Western General Hospital, Crewe Road, Edinburgh EH4 2XU*

NEIL J. DOUGLAS MD, FRCPE, *Department of Respi-  
ratory Medicine, Royal Infirmary of Edinburgh, Lauriston Place,  
Edinburgh EH3 9YW*

RONALD J. FERGUSON MD, FRCPE, *Consultant  
Physician, Respiratory Medicine Unit, Western General  
Hospital, Edinburgh EH4 2XU*

ANDREW P. GREENING FRCPE, *Consultant  
Physician and Senior Lecturer Department of Respiratory  
Medicine, Western General Hospital, Crewe Road, Edinburgh  
EH4 2XU*

CHRISTOPHER HASLETT BSc (Hons), MbchB  
(Hons) FRCP, FRCPE, FMedSci, *Head of Department of Respi-  
ratory Medicine Unit, University of Edinburgh, Royal Infirmary  
Edinburgh, Lauriston Place, Edinburgh EH3 9YW*

TIMOTHY W. HIGGENBOTTAM BSc, MA, MD,  
FRCP, *Consultant Physician, Section of Respiratory and  
Molecular Medicine, Department of Medicine and Pharmacol-  
ogy, University of Sheffield, Royal Hallamshire Hospital,  
Sheffield S10 2JF*

JULIAN M. HOPKIN MD, MSc, MA, FRCP, FRCPE,  
*Professor of Experimental Medicine, Experimental Medicine  
Unit, University of Wales, Swansea SA2 8PP*

A. GORDON LEITCH [Deceased] RVCC, *Chalmers  
Hospital, Lauriston Place, Edinburgh EH3 9HA*

WILLIAM MACNEE MD, FRCPE, *Department of  
Respiratory Medicine, Royal Infirmary of Edinburgh, Lauriston  
Place, Edinburgh EH3 9YW*

GEORGE RUSSELL MB, FRCP, FRCPE, FRCPCH,  
*Department of Child Health, Royal Aberdeen Children's  
Hospital, University of Aberdeen, Cornhill Road, Aberdeen  
AB25 2ZD*

R. ANDREW SEATON MD, MRCP, DTM & H,  
*Directorate of Medicine, Tayside University Hospitals NHS  
Trust, Ninewells Hospital, Dundee DD1 9SY*

ANTHONY SEATON CBE, BA, MD, FRCP, FRCPE,  
FFOM, FMedSci, *Professor of Environmental and Occupa-  
tional Medicine, Aberdeen Royal Infirmary, Foresterhill,  
Aberdeen AB25 2ZD*

DOUGLAS SEATON MD, FRCP, *Consultant Physician,  
Department of Respiratory Medicine, The Ipswich Hospital  
NHS Trust, Heath Road, Ipswich IP4 5PD*

JOHN M. SHNEERSON MA, DM, FRCP, *Director,  
Respiratory Support and Sleep Centre, Papworth Hospital,  
Papworth Everard, Cambridge CB3 8RE*

STEPHEN J. WATT BSc, FRCPEd, AFOM, *Department  
of Environmental & Occupational Health, University of  
Aberdeen, Foresterhill, Aberdeen AB25 2ZD*

ARTHUR J.A. WIGHTMAN MBBS, DMRD, FRCR,  
*Consultant Radiologist, Royal Infirmary Edinburgh, Lauriston  
Place, Edinburgh EH3 9YW*



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# PREFACE

A decade has passed since we wrote the previous edition of Crofton and Douglas, in conjunction with our late colleague Gordon Leitch. Gordon's untimely death, giving his life while saving those of others, was a very sad blow not only to his family but also to his many friends and colleagues in Scotland and over the world. His work in the control and management of tuberculosis continued in the footsteps of Sir Robert Philip and Sir John Crofton, and he would undoubtedly have made a most important contribution to the international battle against the disease had he survived. He was also a splendid all-round physician; something of the flavour of this comes across in the chapters he contributed to this book and which he delivered to us just the day before he left on his tragic holiday.

The first edition of this book was published in 1969, at the end of an era in which medical research had made the most notable contributions to the direct care of patients and to the prevention of disease, marked by the discovery of antibiotics and antituberculous chemotherapy, the demonstration of the harmful effects of smoking, and the elucidation of the structure of DNA. The original volume was a relatively slim one, written by our distinguished predecessors, John Crofton and Andrew Douglas, who had themselves played a major role in the battle against tuberculosis. At that time, respiratory medicine was looking towards an uncertain future, as tuberculosis declined and other respiratory diseases remained firmly in the realm of the generalist. *Crofton and Douglas's Respiratory Diseases* was perhaps the major factor in helping chest physicians of that era find their new role, allowing us to assert the importance of respiratory disease as a cause of morbidity and mortality in both the developed and poor worlds.

The intervening three decades have seen great changes in the practice and basic science of respiratory medicine, which is now recognized as a main-line acute specialty responsible for the care of a high proportion of the sick in all countries. That our patients are often from the least privileged sections of society has meant that funds for research and clinical care have not always been so easy to obtain as in more glamorous disciplines, but we can look back with some satisfaction to the control of tuberculosis

in Britain and the improved outlook for young victims of cystic fibrosis. We have, however, made little impact on the prognosis of lung cancer, have not had as much success as we would have liked in the battle against the amoral tobacco industry, and have watched in dismay as poor medical practice in other countries has encouraged the development of multi-drug resistant tuberculosis. And, in spite of all the research in the subject, we have seen asthma become progressively more prevalent in children. In our day-to-day care of sick patients, we must not take our eyes off the public health aspects of our specialty.

The previous edition of this book was well-received, and its translation into Greek and Italian, together with its production in a low-cost Asian edition, served as a reminder to us of the need to write for a world-wide readership. In this edition, we have reflected the increase in understanding of disease processes that has accrued from basic research, but we have also endeavoured to maintain the tradition of writing for the practising physician, who sees a multitude of patients with diseases common and rare, and who needs guidance on diagnosis and management. We are grateful to a number of friends and colleagues for agreeing to contribute to this edition and believe that their chapters, emphasizing the common and important, will contribute greatly to the value of the book.

One of the benefits of writing a book such as this is the amount one learns or re-learns by reading the references necessary to check up on one's statements. We have maintained a substantial bibliography, and this includes a number of older references that give graphic original accounts of diseases. It is not uncommon for old lessons to be forgotten and omitted from modern databases; while no textbook can hope to be as up-to-date as these databases, we hope we will help readers to avoid missing important earlier work while still keeping abreast of recent advances. We see this as a book to be used on the ward and in the office, where clinical problems arise and questions are asked and need clear answers.

Anthony Seaton  
Douglas Seaton

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# ACKNOWLEDGEMENTS

The observant reader will have noticed the similar names of the two editors. We should like to acknowledge certain aspects of our genetic and environmental heritage. Our late father, Dr Ronald Seaton FRCP, was a pioneer in anti-malarial chemotherapy. He inspired us to become doctors and passed on to us a broad, lively and sometimes slightly cynical interest in medicine. From our mother, Julia, a nurse who worked with Lord Moynihan in Leeds and is still busy looking after others as she approaches her tenth decade, we have inherited an aversion to a moment's idleness. We have been fortunate in our teachers, notably the late Harold Edwards who introduced us to biology and evolutionary theory at school, Dr Colin Ogilvie of Liverpool who first interested us in respiratory medicine, and Professor Keith Morgan who introduced us to the scientific basis of clinical and preventive medicine in the wilds of West Virginia, USA. Many other teachers and colleagues have of course influenced us and continue to do

so, not least our juniors who impose a constant challenge to keep up-to-date.

With respect to the production of this book, we acknowledge with gratitude the tolerance of Blackwell's over our problems with deadlines and, especially, the courtesy and efficiency of Anna Woodford and the production staff. Our thanks also to the copy editor Jo Phillips for his attention to detail and his patience. We should also like to acknowledge the help of Dr Keith Kerr in providing pathological photomicrographs, Dr Lesley Gomersall for help in providing radiographs, and the Medical Illustration Department of Aberdeen University Medical School.

Most importantly, we record our gratitude to our wives, Jill and Anja, for putting up with our prolonged absence at our computers and for nevertheless helping and supporting us throughout this protracted endeavour. We promise to spend more time with them in future.

# DEVELOPMENT AND STRUCTURE

ANTHONY SEATON

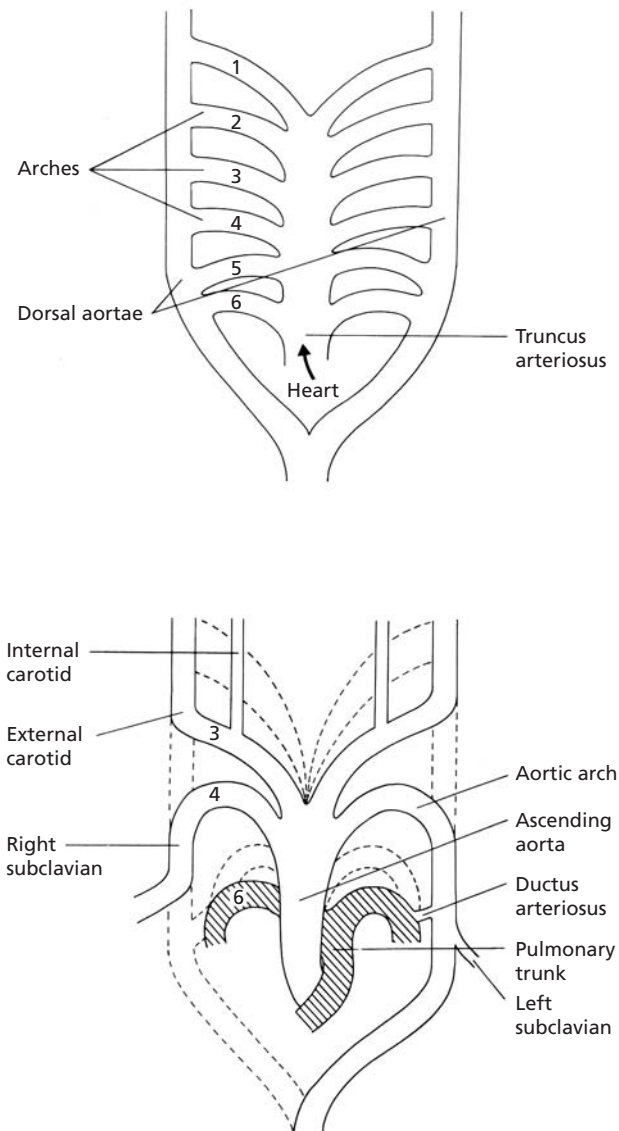
The respiratory system brings air into close relationship with the mixed venous blood, allowing tissue respiration by uptake of oxygen into the circulation and elimination of carbon dioxide. In addition to this primary function, the lungs have other functions, for example water balance, the maintenance of pH, elimination of inhaled particles and organisms, filtration of particulate matter from the circulation, and metabolism of certain drugs and enzymes. They also serve as a vehicle for the administration of anaesthetic and other drugs. The intimate contact between inspired air (with the multiplicity of organisms, particles and gases that it contains) and the internal epithelium of the lungs (with a surface area some three times that of the body) leads not only to efficient gas exchange but also to repeated opportunities for damage to the lungs and absorption of harmful substances into the body. In order to understand both the normal function of the lungs and the pathology of the diseases with which this book is mainly concerned, it is useful to know something of the development and structure of the organ. In particular, it is now becoming clear that subtle influences on the development of the lung *in utero* and in the early months of extrauterine life may have important effects on lung health in later life, and that the seeds of later chronic airflow obstruction may be sown during the period of intrauterine lung development.

## Development of the lungs

### Development of the airways and vessels

The lung appears first as an epithelial bud at the caudal end of the laryngotracheal groove on the 26th day after ovulation [1,2]. It thus shares its origin with the foregut, reflecting the evolution in our invertebrate ancestors of a respiratory apparatus from the food-sieving mechanism. This bud, derived from endoderm, will form the epithelium of the airways and of the acini. As it elongates, it becomes invested in mesenchyme derived from mesoderm, and this mesenchymal layer exerts control over its

pattern of branching [3]. The mesenchyme itself develops into the connective tissue, cartilage, smooth muscle and vessels of the lung. In the first few weeks of development, nerve fibres arising from the ectoderm migrate into the mesenchyme to give the lung its motor and sensory connections [4]. The developing lung bud divides into two halves and elongates, growing caudally on either side of the oesophagus. By about 33 days the trachea has become separated from the foregut, and pouches representing the five lobes are clearly apparent. Subsequent dichotomous division leads to the development of the full adult complement of segments by 41 days and to completion of the bronchial tree as far as the terminal bronchioles by 16 weeks [5]. While the embryonic lung is developing, changes are also occurring in the circulatory system [6]. The primitive branchial arches come and go, leaving the third to form the carotids, the fourth the aorta and the sixth the pulmonary trunk (Fig. 1.1). This appears at about 32 days, becoming separated from the primitive truncus arteriosus by the development of a spiral septum, and joins the vascular plexus that has already formed in the lung bud. By 37 days, the single ventricle of the heart has divided into two chambers, the blood supply to the lungs coming from the right side. At this stage the right sixth arch artery has disappeared and the lung's main blood supply, the pulmonary artery, comes solely from the left arch. Its branches divide approximately in correspondence with those of the bronchial tree, but so-called supernumerary arteries occur with increasing frequency towards the periphery and supply structures adjacent to the main bronchi. Ultimately they will supply alveoli of neighbouring acini when these have developed. Before the formation of this pulmonary arterial supply, the lung receives its blood from pairs of segmental arteries arising from the aorta above the coeliac axis in the region of the fetal neck. These arteries migrate caudally and eventually disappear, being replaced by new bronchial arteries that arise from the aorta between about 9 and 12 weeks. The persistence of the original primitive bronchial arteries is the explanation for the occasional supply of sequestered



**Fig. 1.1** Development of the pulmonary arteries and aortic arch from the branchial arches.

lung segments by a transdiaphragmatic artery from the aorta above the coeliac axis, a potential hazard well known to thoracic surgeons [7] (Fig. 1.2).

The venous drainage of the developing lungs is initially into the systemic cardinal and postcardinal veins and the visceral veins of the abdomen. These develop into the two venae cavae, the innominate vein and their tributaries. By about 10 weeks a diverticulum arises from the left atrium that connects with those veins draining the lungs, so that the four pulmonary veins finally enter the left atrium. Abnormalities in this development result in anomalous pulmonary veins leading into the vena cava or right atrium or a separate chamber connected to the left atrium, *cor triatriatum* [8]. Drainage of the right lung by an anomalous vein into the inferior vena cava gives rise to the

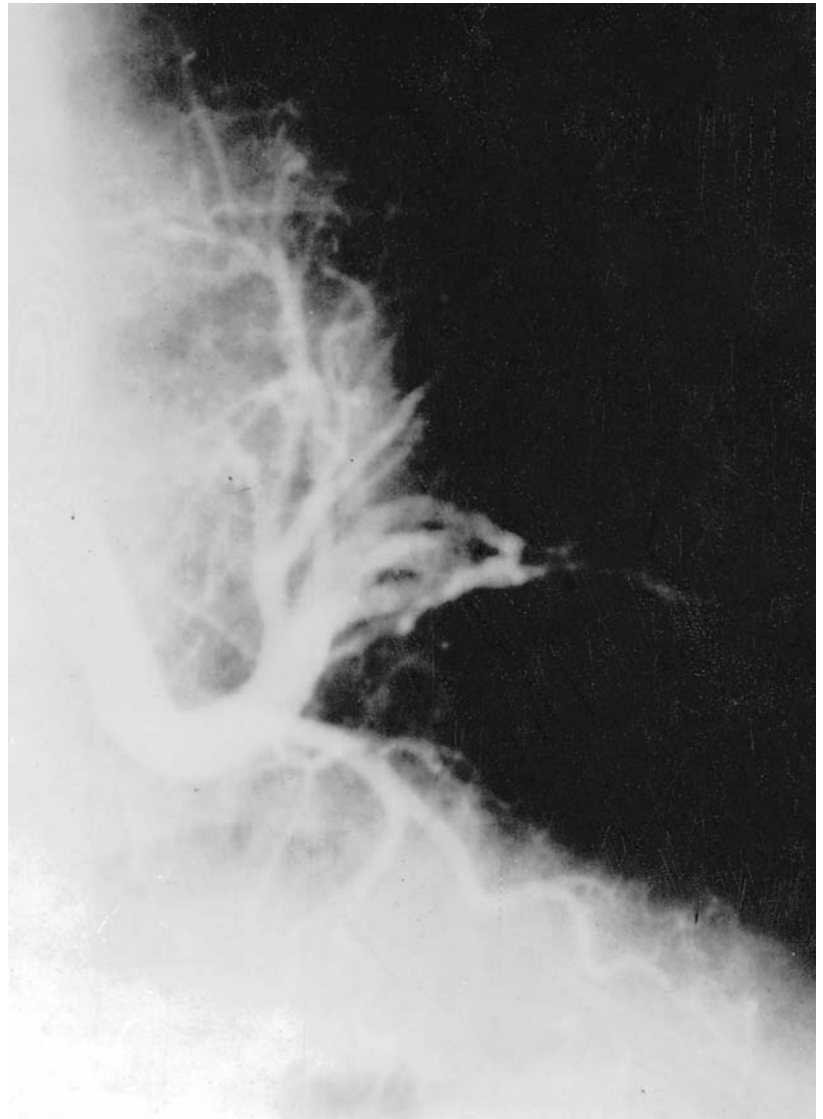
scimitar sign on the chest radiograph (Fig. 1.3). Thus, by about 16 weeks of intrauterine life, the preacinar structures of bronchi, pulmonary arteries and veins, and bronchial arteries are all present in the numbers and anatomical distribution that they will maintain throughout life. However, important changes are still to occur in these structures at the microscopic level, while they have of course to grow and the acinar structures to develop.

### Cellular development of the lung

Until about 16 weeks, the developing lung has a pseudoglandular appearance, i.e. narrow tubes surrounded by a cuboidal or columnar epithelium on a basal lamina and in a mesenchymal stroma [1,9,10]. By 16 weeks, both goblet cells and mucous glands have developed and ciliated cells are present throughout the bronchial epithelium. From 16 until about 26 weeks the lung's appearance is described as canalicular. The epithelium thins out, the cells becoming flatter and the future air spaces larger. The mesenchyme becomes very vascular, and as the more peripheral airways develop their epithelium becomes very thin, allowing close approximation of blood to the air space. This is a period of rapid growth, during which the lung's DNA doubles [11].

These terminal saccules become well defined towards 26 weeks, when the appearance of the lung is described as saccular. By this time type I and type II pneumocytes can be identified in the saccular epithelium and osmiophilic bodies appear in the type II cells, indicating that the lung has developed the ability to secrete surfactant. This production of surfactant may be promoted by the administration of glucocorticosteroids to the mother in some species [12], a fact that is relevant in improving the survival chances of premature infants. Meanwhile, cartilage, which appears in the trachea at 4 weeks and gradually spreads down the airways to reach segmental bronchi at 12 weeks, has by 26 weeks developed far down the bronchial tree, though further extension occurs until the early weeks of postnatal life. Similarly, smooth muscle, which first appears in the lobar bronchi and above at about 6 weeks, has also spread down to the terminal bronchioles. In the pulmonary arteries smooth muscle appears at about 12 weeks and has reached vessels at the level of the terminal bronchiole by 26 weeks; this vascular smooth muscle will grow further down the arterial tree after birth, reaching alveolar walls in adult life. Thus the lung at about 26 weeks has reached a stage of maturity at which it is capable of supporting life.

The rest of the time spent *in utero*, from 26 weeks to term, is occupied by the development and subdivision of the respiratory bronchioles and their saccules, with a variable amount of alveolar development, and by the growth of the airways. At one time it was thought that there were very few alveoli present at birth, but more recent studies have



**Fig. 1.2** Aortogram showing aberrant arterial supply of sequestered lung segment from aorta.

shown that some alveoli may be present as early as 30 weeks and that as much as 50% of the final adult number may be evident at the time of birth, though this proportion is very variable [13,14].

### **Postnatal development**

At the time of birth there is an adult complement of about 24 million terminal bronchioles [15–17]. From the time of birth there is an initial rapid increase in the numbers and then in size and complexity of alveoli, which start appearing *in utero*, first on the peripheral saccules and then up towards the proximal respiratory bronchioles. Some may even develop on the terminal bronchiole. Some 127 million alveoli are present at about 1 year and most by the age of 2; the final adult complement of about 280 million may have developed by the age of 8, although some authorities suggest that alveolar multiplication continues

at a slower rate until somatic growth ceases, the numbers in adults being estimated to vary between 200 and 600 million. Growth of the airways and modelling of the lung to match the shape of the thorax and its contents continues until the body stops growing. Any abnormality of shape of the thoracic cavity will affect this; for example, a congenital diaphragmatic hernia, when the normal separation of thoracic and abdominal cavities does not occur at 7 weeks, causes a small lung in which the numbers of both airways and alveoli are reduced [18], while kyphoscoliosis developing in early childhood causes a small lung with reduced alveolar numbers [19]. Other important influences on airway or alveolar development are fetal nutrition, which if impaired in mid-gestation may result in smaller or even fewer airways, and oligohydramnios, which may constrict lung growth and lead to smaller airways [20,21]. These influences are currently a matter of considerable research interest to those who wish to understand why one person





**Fig. 1.3** Anomalous vein draining from lower lobe into the inferior vena cava: the 'scimitar' sign.

develops lung disease and another does not when subjected to the same environmental influences in later life. It is clear that some environmental factors, such as poor diet and cigarette smoke, can have an effect at a very early stage in lung development as well as the potential to damage the developed lung.

The most dramatic change in the lung occurs at the time of birth. Fetal breathing movements occur *in utero* and are known to be essential to normal lung development [22], but with the first postnatal breaths the lung inflates and resistance to flow in the pulmonary arteries falls; within a few days the pulmonary pressure has fallen to half systemic pressure. Over the first few weeks the ductus arteriosus and foramen ovale have closed, the small muscular pulmonary arteries have dilated and their muscle coat thinned to adult dimensions, and the pulmonary arterial pressure has fallen almost to its adult level, which it eventually achieves at about 6 months.

## Structure of the respiratory tract

### Upper respiratory tract

The upper respiratory tract is arbitrarily regarded as that part above the cricoid cartilage. It has several important

functions besides air conduction, including swallowing, air conditioning, smell and speech.

### Nose

The nose plays a part in air conduction and conditioning, and clearance of particles and microorganisms [23]. The resistance to airflow in the nose is normally 50% of the total airways resistance and becomes important during exercise (hence the change to mouth breathing in this circumstance) and with nasal obstruction by polyps and rhinitis. The mucous membrane of the nose is lined with ciliated epithelium, which functions in an identical manner to the epithelium of the rest of the respiratory tract in terms of antimicrobial defences. The cilia of the anterior part of the nares, before the turbinates, beat anteriorly and propel mucus and entrapped particles towards the nostrils. From the turbinates backwards, the cilia beat so as to propel particles towards the pharynx. This is made use of in a simple screening test of ciliary function: a small particle of saccharin is placed on the mucous membrane of the inferior turbinate and the subject asked to indicate when the taste is perceived; with normal ciliary function, and in the absence of other nasal or sinus disease, the taste should be noticed within 60 min [24].

The structure of the nose is adapted to its important function of warming and humidification of inspired air [25]. The vascular mucosa and the large surface area presented by the turbinates are important in this respect. Air is heated to approximately body temperature on passage through the nose while its relative humidity is raised to 95%. The lower airways, though able to adapt to the absence of these mechanisms, as in patients with laryngectomies [26], will dry out and become more liable to infection if nose breathing is impossible. This becomes clinically important in patients with tracheostomies or long-term endotracheal intubation, when humidification of inspired air is necessary. During exercise, particularly in cold or dry air, there may be considerable loss of water from the airway vasculature, together with cooling of the bronchial walls. In people with asthma, this may increase the osmolality of the surface lining fluid sufficiently to cause mast cell degranulation and consequent bronchoconstriction [27–29].

Humidification of inspired air is achieved by transudation through the epithelium and, to a lesser extent, by secretion of mucus. Approximately 0.75L of fluid are required for the 10000L of air inspired every 24h. Nervous control of the vascular and glandular mechanisms involved is by the autonomic system.

### Pharynx

The pharynx lies behind the nasal cavities, the mouth and the larynx, ending at the level of the sixth thoracic vertebra where it is continuous with the oesophagus. It is lined in its upper part by ciliated columnar epithelium, which changes through transitional to stratified squamous epithelium over the lower part. The wall is richly endowed with lymphatic tissue, aggregations forming the posterior nasal adenoids and the lingual, eustachian and palatine tonsils. Three circumferential muscles, the superior, middle and inferior constrictors, and two longitudinal muscles, the stylopharyngeus and salpingopharyngeus, complete its wall. Their coordinated action is responsible for swallowing, including prevention of aspiration of food into the trachea. Failure of these mechanisms in patients with bulbar and pseudobulbar palsy and other conditions affecting the vagus and glossopharyngeal nerves is a cause of recurrent pneumonias. The need for the air and food passages to cross over in humans and other mammals is an unfortunate consequence of our evolution from air-breathing aquatic animals.

The inferior pharyngeal constrictor consists of upper oblique fibres and lower circumferential fibres. Between the two is a zone, known as Killian's dehiscence, through which the mucosa may herniate as a pharyngeal pouch. This usually occurs posteriorly, the pouch enlarging downwards and to the left. It causes dysphagia and regurgitation of undigested food and presents a considerable

hazard of perforation to the unwary oesophagoscopist (Fig. 1.4).

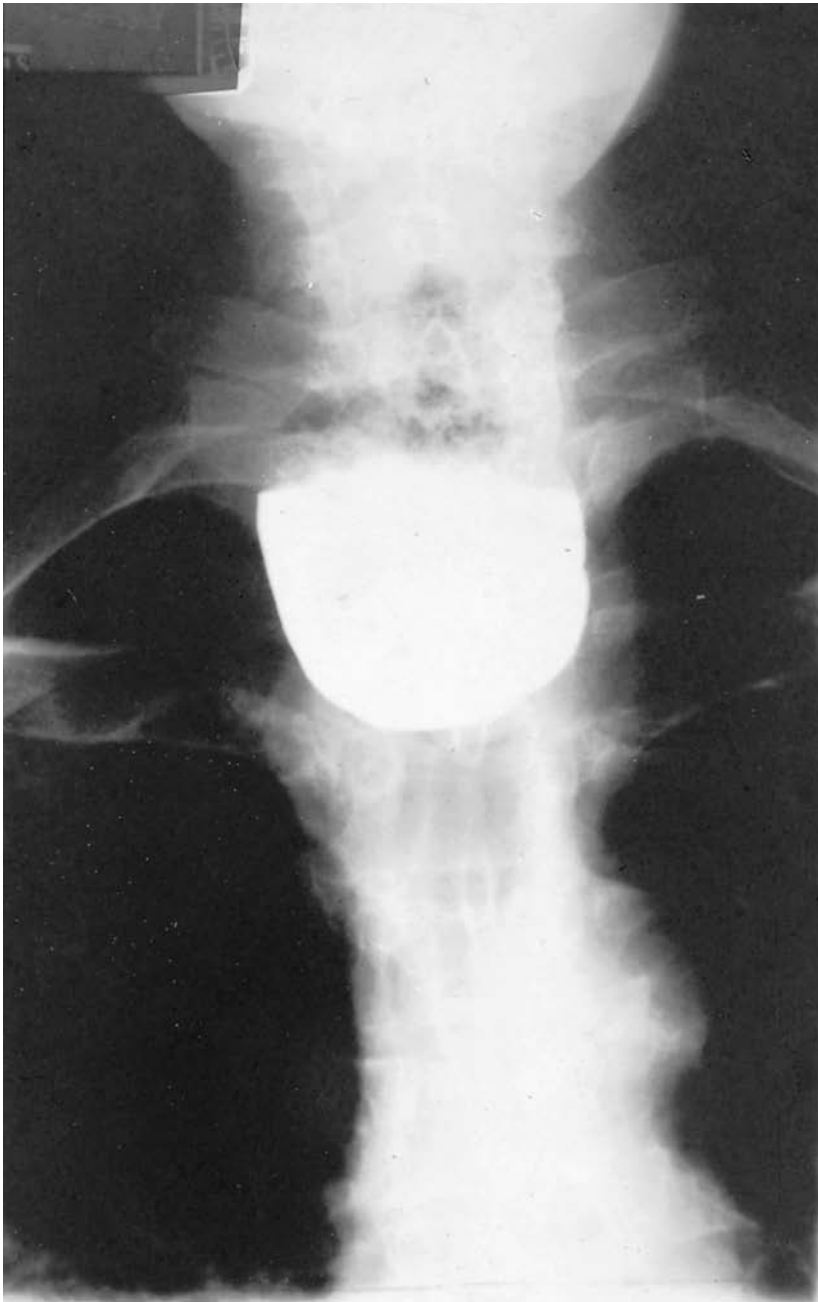
Certain patients may have their sleep punctuated by recurrent episodes of apnoea (see Chapter 47). In some of these, the apnoea is due to an obstructive mechanism in the pharynx, whereby the posterolateral walls are invaginated into the lumen during attempted inspiration, possibly due to lack of tonic contraction of the pharyngeal muscles. The pharynx may also be obstructed by the tongue falling backwards in unconscious patients lying supine; nursing such patients on their sides prevents both this and aspiration of regurgitated stomach contents. Finally, posterior pharyngeal carcinomas may present with dyspnoea, due to upper airways obstruction. The respiratory physician should be alert to this as a cause of dyspnoea of relatively recent onset, often associated with stridor.

### Paranasal sinuses and eustachian tube

These structures fall within the realm of the otorhinolaryngologist and are only dealt with briefly here. They are of interest to the respiratory physician in that, sharing a common mucous membrane with the bronchi, they often become inflamed at the same time, for example in allergic conditions. They may also be the source of bleeding that can be mistaken for haemoptysis. The nose is of course the preferred portal of entry for fiberoptic bronchoscopes and prolonged endotracheal intubation.

The paranasal sinuses may play a role in temperature insulation and voice resonance, although their functions are not clear and individuals born with atrophic sinuses seem to come to no harm. The paired maxillary sinuses, between the orbit and the molars, are the largest, with a capacity of about 15mL each. Each has one ostium that opens into the middle meatus between the superior and inferior turbinates. This high position of the ostium makes it liable to accumulate fluid and infections are common, especially in childhood. The ciliated columnar epithelium contains many mucous glands, the cilia sweeping the mucus towards and through the ostium. The maxillary sinus is vulnerable to infection as a result of facial injuries, dental sepsis and barotrauma. The frontal sinuses, above the orbits, drain inferiorly into the middle meatus, while the ethmoid and sphenoidal sinuses drain into the superior and middle meatuses. These structures are all liable to be affected by respiratory tract infections and allergy. In addition, the rare adenocarcinoma of the nasal sinuses may be a consequence of exposure to inhaled carcinogens in the workplace [30,31]. Wegener's granuloma is another nasal condition that may occur in association with lung disease (see Chapter 40).

The eustachian tube connects the middle ear to the pharynx. It is about 4cm in length and is normally collapsed, opening during yawning and swallowing as a



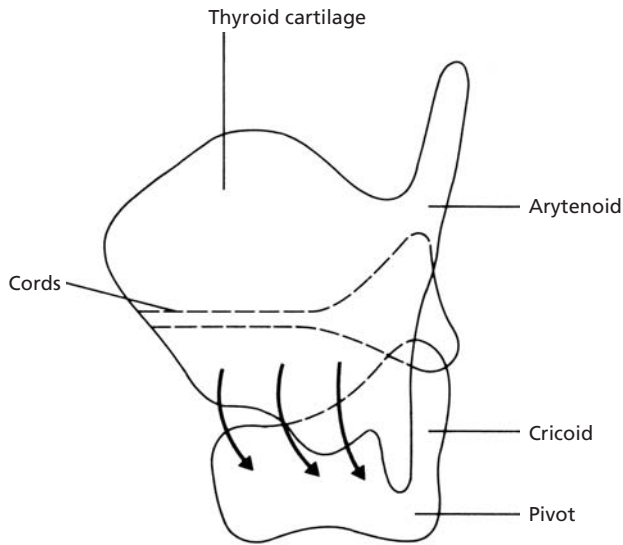
**Fig. 1.4** Barium swallow showing large pharyngeal pouch that caused dysphagia and aspiration pneumonia.

result of the action of the tensor veli palatini muscle [32]. It assumes importance during diving and aviation, when active expiration against a closed nose is necessary to equalize pressures between throat and ear (see Chapter 57). Inability to do this, due to infection or mucosal oedema, may result in trauma to the ear-drum. A pressure of about 4.0 kPa (30 mmHg) is required to open the tube [33].

### Larynx

The respiratory physician must have some knowledge of the larynx because intrinsic laryngeal disease sometimes

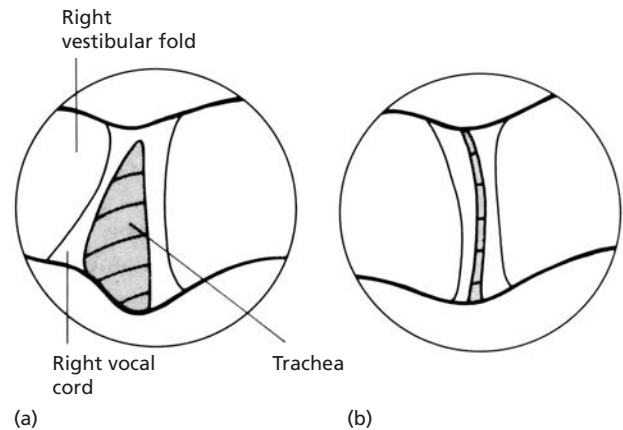
presents as airways obstruction with wheeze and dyspnoea and also because involvement of the recurrent laryngeal nerve may make voice changes the first sign of serious intrathoracic disease. The larynx consists of three articulating cartilages, the thyroid, cricoid and arytenoid [34]. The vocal cords pass from the arytenoids posteriorly to the thyroid anteriorly. They are tensed by the action of the cricothyroid muscles, which pull the thyroid cartilage anteriorly and downwards (Fig. 1.5), while they are abducted by rotation of the arytenoids by the posterior cricoarytenoid muscles. The transverse arytenoids and lateral cricoarytenoids are responsible for adduction of the cords. When examining the larynx, abduction can be seen



**Fig. 1.5** The cricothyroid muscles pull the thyroid cartilage anteriorly and downwards, thus tensing the cords.

to occur on inspiration. Adduction occurs on phonation, the usual practice being to ask the patient to say 'eeeeee'. All the intrinsic muscles of the larynx except the cricothyroids are supplied by the recurrent laryngeal nerves. Injury to these nerves therefore prevents abduction or adduction, the cords lying in a neutral position. Bilateral paralysis, which may occur as a result of thyroid carcinoma or following thyroidectomy, causes fixation of both cords and therefore a seriously compromised airway. If the damage to the nerves is incomplete the result can be life-threatening, as the abductors tend to be paralysed before the adductors. More usually, unilateral paralysis occurs as a result of tumour, or occasionally fibrosis or surgery, and one cord is then fixed (Fig. 1.6). The cricothyroid muscles are supplied by the superior laryngeal nerves. If they are paralysed, as may occur following thyroidectomy, the cords are unable to be tensed.

All the laryngeal nerves derive from the vagus, which therefore also carries sensory messages from the laryngeal mucosa. Combined paralysis of superior and recurrent nerves may occur as a result of lesions of the medulla oblongata, such as poliomyelitis and syringobulbia, tumours involving the vagus at the brainstem and lesions of the thyroid gland. The most common paralytic lesion seen is that due to damage to the left recurrent laryngeal nerve, which leaves the vagus at the level of the aortic arch, hooks round the aorta and ligamentum arteriosum and runs up the mediastinum between trachea and oesophagus, deep to the thyroid, to reach the larynx beneath the lower edge of the inferior pharyngeal constrictor muscle. This long intrathoracic course makes the nerve vulnerable to involvement by pulmonary and other neoplasms around the aortic arch, as well as by the much rarer aortic aneurysm. Involvement of the nerve



**Fig. 1.6** Left recurrent laryngeal nerve palsy with immobile left cord: (a) on inspiration, right cord abducts; (b) on phonation, right cord crosses the midline.

in fibrosis, either idiopathic or following drugs (such as practolol), tuberculosis or radiotherapy may occasionally cause paralysis. The right recurrent nerve has a much shorter course, arising in the neck at the level of the subclavian artery which it hooks round before passing up deep to the thyroid. Either nerve may be affected by tumour in the cervical lymph nodes or at the thoracic inlet, by thyroid carcinoma, aneurysm or surgery on the thyroid gland. Anaesthesia of the larynx, as during fiberoptic bronchoscopy, may paralyse the superior laryngeal nerves, causing lax cords.

Apart from neurological dysfunction, the larynx may be affected by other conditions that cause symptoms resulting in referral to chest physicians. Carcinoma of the larynx may present with breathlessness and hoarseness, as may rheumatoid disease of the cricoarytenoid joints. Laryngeal tuberculosis and syphilis are now rarities, but damage to the cords by prolonged or inexperienced intubation may occur.

The usual symptom of left recurrent nerve paralysis is hoarseness and loss of voice power. Since adduction of the cords is required for the explosive component of cough, this is lost and the cough is described as bovine. As time passes, the contralateral cord may be able to compensate for unilateral paralysis and the voice and cough may recover. If this does not occur, injection of Teflon into the paralysed cord can bring it closer to the midline and allow closure to be more complete. Bilateral cord paralysis usually causes inspiratory stridor and breathlessness. Characteristic impairment of peak expiratory and inspiratory flow rates occurs, causing a rounded flow-volume curve (see Chapter 2). Hysterical aphonia may sometimes be seen and in such cases the cords appear unable to adduct; however, pure adductor paralysis does not occur as a neurological lesion and if the patient can be persuaded to cough the cords can be seen to approximate to each other.

Benign tumours of the larynx may be found incidentally at bronchoscopy and may sometimes be the only explanation for haemoptysis; these include fibro-angiomatous polyp and laryngeal granuloma. The latter is usually due to previous intubation. Singer's nodules on the cord are organized haematomas that are presumably due to vocal trauma. Sarcoidosis, Wegener's granuloma and relapsing polychondritis, as well as rheumatoid disease, may also affect the larynx. For a detailed account of the structure, function and pathology of the larynx, the reader is referred to the review by Proctor [34].

## Lower respiratory tract

### Trachea

The trachea extends from the larynx, which fixes it through the hyoid bone to the skull, down to its bifurcation in the mediastinum at the level of the fifth thoracic vertebra [34]. At its lower end it is anchored to the mediastinum by the two main bronchi and by oblique connective tissue fibres running to the dorsal surface of the pericardium. The bifurcation is displaced slightly to the right of the midline, and the trachea runs postero-inferiorly from its origin, only usually being superficial over its first few centimetres. Its length varies with movements of the head and respiration but averages about 10–12 cm in the adult. Its extrathoracic portion extends down to the sixth cartilage and is closely related to the thyroid gland laterally and its isthmus anteriorly. The recurrent laryngeal nerves also run laterally, beneath the thyroid, while the oesophagus is directly behind, separating it from the vertebrae. The lower half of the trachea is intrathoracic, and thus lesions causing its narrowing may have different physiological effects depending on their site. In general, extrathoracic narrowing causes predominant inspiratory obstruction and reduction of peak expiratory flow rate, whereas intrathoracic obstruction causes mainly expiratory obstruction (see Chapter 2). As it enters the chest, the trachea is related anteriorly to the remains of the thymus, the left innominate vein, the right innominate artery and the left common carotid artery. A retrosternal extension of the thyroid may occasionally compress it at this point (Fig. 1.7). To its right are the innominate vein, superior vena cava and azygos vein, while on its left lies the aortic arch. The left recurrent laryngeal nerve runs up between the aortic arch and trachea and then in the ridge between the trachea and oesophagus, where it may be involved by neoplastic nodes from bronchial or oesophageal tumours. At its lower end the trachea divides into the right and left main bronchi. The ridge between the bronchi seen through the bronchoscope is the carina. It normally narrows on inspiration but may be widened by enlarged mediastinal nodes or by a dilated left atrium. The former may be subjected to transtracheal needle biopsy at this point.



**Fig. 1.7** Chest radiograph showing severe compression of the trachea by the retrosternal thyroid. The patient presented with stridor.

The trachea is oval in cross-section, being slightly longer in transverse than in sagittal diameter. It is lined with a mucous membrane of pseudostratified, ciliated, columnar epithelium containing goblet cells. There is a submucosa containing elastic fibres arranged in longitudinal bands and also connected to circular fibres in the fibrocartilaginous layers. A capillary plexus and mucous glands are also found in the submucosa. The tracheal cartilages are semicircular, the gap being in the posterior part where the circle is completed by a 'membranous' portion. Smooth muscle connects the posterior tips of the cartilage, its contraction resulting in narrowing of the trachea and stabilization of its otherwise easily invaginated posterior wall. The cartilages are connected to each other by fibrous tissue extending from their perichondrium.

The trachea is mobile, being pulled as much as 3 cm at the top and 1 cm at the bifurcation on swallowing. Inspiration causes caudal stretching of the trachea as well as movement anteriorly from the vertebral column. This limited mobility may be enhanced by the thoracic surgeon during tracheal reconstruction, e.g. after resection of strictures or tumours, by division of its inferior connections with the pericardium and mediastinum.

## Bronchi and their divisions

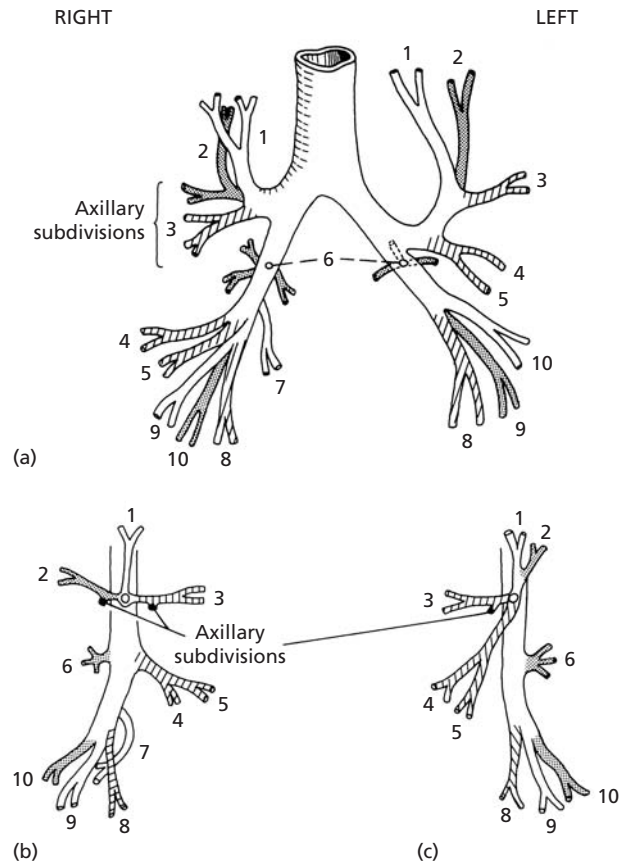
### Gross anatomy

The trachea divides into right and left main bronchi [35]. The left runs more horizontally than the right, above the left atrium. It is about 5 cm long and is related to the aortic arch above, the descending aorta and thoracic duct posteriorly, and the left pulmonary artery anteriorly then superiorly. The right main bronchus, being a more direct continuation of the trachea, is the more usual path for inhaled foreign bodies. It is only about 1–2.5 cm long; the right pulmonary artery runs below then anterior to it, while the azygos vein arches over it superiorly. The right main bronchus divides into the right upper lobe bronchus, which in turn divides into anterior, apical and posterior segmental bronchi, and the bronchus intermedius. This latter gives off middle lobe and apical lower lobe bronchi, then divides into the four basal segmental bronchi: anterior, medial (cardiac), posterior and lateral. The middle lobe bronchus divides into medial and lateral segmental bronchi. The left main bronchus gives off upper and lower lobe bronchi; the upper lobe bronchus divides into apico-posterior and anterior segmental bronchi and a lingular bronchus that in turn divides into superior and inferior bronchi. The left lower lobe bronchus gives off an apical bronchus and then divides into anterior, lateral and posterior segmental bronchi. There is no left medial basal segmental bronchus.

The usual pattern of bronchial branching is shown in Fig. 1.8. However, anomalous bronchi are relatively frequent [36,37]; subapical bronchi in the lower lobes and a bronchus arising from the trachea to supply the apical segment of the right upper lobe are not infrequent examples. Details of variations in segmental anatomy have been given by Boyden [36] and bronchoscopic illustrations by Stradling [38].

The trachea, main bronchi and lower lobe bronchi are outside the lung substance. All other bronchi are situated within the lung, and as they enter it they take with them an invagination of the visceral pleura, forming a peribronchial sheath separated from the bronchi by a potential space.

The lower airways are known as bronchi down to the smallest divisions containing cartilage, however sparse. Thereafter they become bronchioles, the final branch of this type being the terminal bronchiole. Subsequent divisions contain increasing numbers of alveoli in their walls and are called respiratory bronchioles; these give off the alveolar ducts and the air sacs and alveoli. The ultimate lung unit from each terminal bronchiole is called the acinus. From the tracheal bifurcation the smallest bronchi are reached after some 8–13 divisions, depending on the area of lung supplied. There is variation depending on the size and shape of the segments; for example, in the apical



**Fig. 1.8** Segmental bronchi: (a) anterior, (b) right lateral and (c) left lateral. Upper lobes: 1, apical; 2, posterior; 3, anterior; 4 and 5, superior and inferior lingular branches (left only). Middle lobe: 4, lateral; 5, medial branches. Lower lobes: 6, apical lower; 7, medial (right only); 8, anterior; 9, lateral; 10, posterior branches. (After Brock [37].)

lower segment, where the bronchi run a relatively short course, the terminal bronchioles may be reached after 15 generations from the origin of the segmental bronchus, whereas in the lingula it may be 25. There tend to be fewer generations in lateral than in axial branches [39]. From the smallest bronchi, which are about 1 mm in diameter, there are about three to four further subdivisions of bronchioles before the terminal one is reached. There are about 25000 terminal bronchi, each of which divides dichotomously into respiratory bronchioles [35]. There are usually two subsequent divisions of respiratory bronchioles, the more peripheral branches bearing more alveoli, and a final division into alveolar ducts, which are completely surrounded by alveoli. Up to nine generations of alveolar ducts occur before the alveolar sacs arise as the terminal unit of the airways. There are thus about 28 orders of division of the tracheobronchial tree. The total number of alveoli has been estimated to be between 200 and 600 million [40,41].

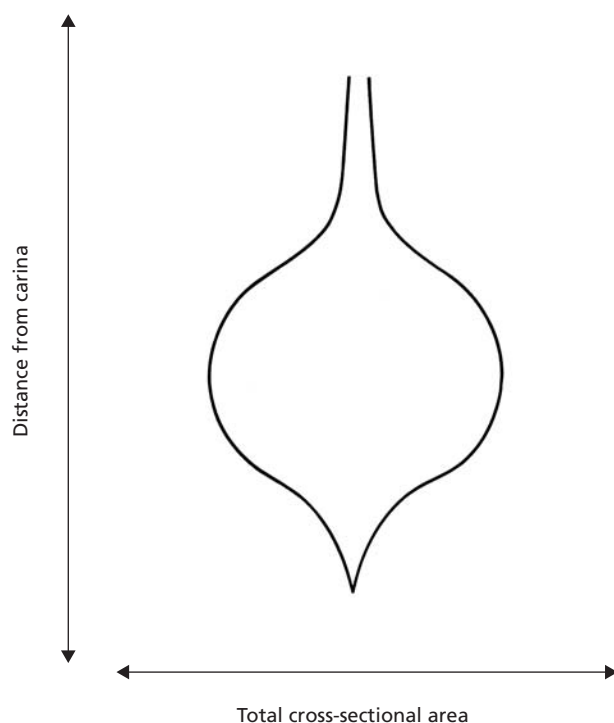


### Total cross-sectional area of the airways

The total cross-sectional area of the airway in the trachea is about  $2\text{ cm}^2$ , and this does not increase in the first one or two divisions. Thereafter, increasing division produces a greater area, estimated to be about  $14\text{ cm}^2$  after 14 orders,  $80\text{ cm}^2$  at the level of the terminal bronchiole and  $700\,000\text{ cm}^2$  at the level of the alveolar ducts [42]. Thus maximum resistance to airflow occurs in the large airways. This fact, coupled with the observation that much of the damage associated with cigarette smoking can be found in small airways (often arbitrarily defined as those  $2\text{ mm}$  in diameter or less), has led to a search for tests of small airways obstruction that will allow early detection of smoking-associated airways disease (see Chapter 2). However, these estimates do not take account of the asymmetry of bronchial branching, longer parts of the bronchial tree having more divisions than shorter ones. Thus a more accurate model of total cross-sectional area against distance from the trachea would imply a diminution in total area beyond the maximal point [35,43] because of the progressively smaller numbers of bronchioles in the more distal parts of the lung (Fig. 1.9).

### Segmental anatomy

The lobes of the lung are divided into segments corresponding to the segmental bronchi. These segments repre-

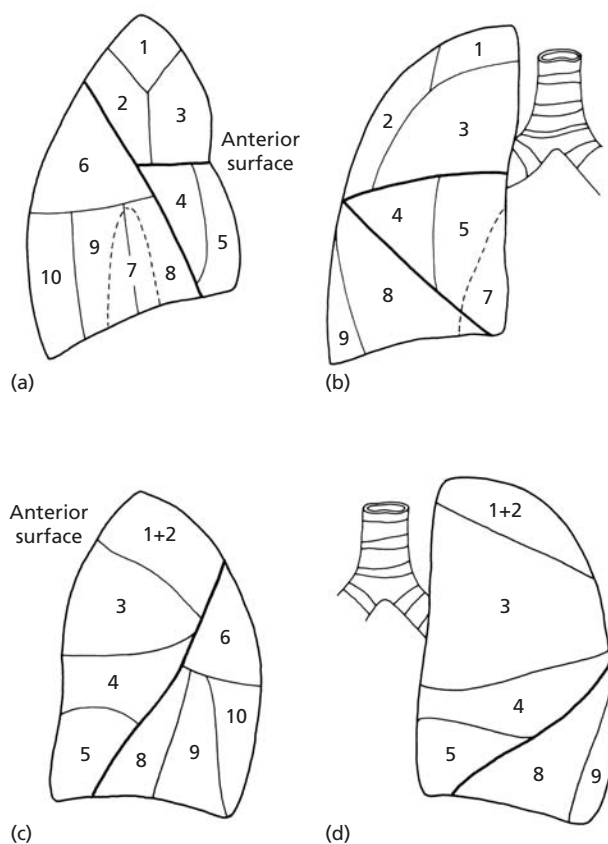


**Fig. 1.9** Model of total cross-sectional area of airways from carina to periphery, taking account of different lengths of bronchi. (From Horsfield [35].)

sent units that can usually be distinguished by the surgeon and removed without dividing other major vessels or bronchi. However, they are not completely separated from each other, being divided partially by fibrous septa peripherally. Occasionally, infoldings of pleura into partial fissures between segments may be seen radiologically. The segments may further be distinguished by branches of the pulmonary veins, which run between them. Segmental division of the lungs is variable, and the most frequent arrangements are shown in Fig. 1.10.

In about 0.25% of right lungs, the so-called azygos lobe may be seen radiologically. This is a developmental anomaly caused by the azygos vein looping over a portion of the apical segment of the upper lobe rather than directly over the right main bronchus. This causes an infolding of the pleural layers, which shows as a thin outwardly convex line ending in an oval shadow below, the latter representing the azygos vein. There is no associated abnormality of bronchial anatomy.

A sequestered segment is a part of the lung that has become isolated during development [44,45]. Its bronchi, which are usually cystic and dilated, do not connect with the bronchial tree, while its blood supply is derived from



**Fig. 1.10** Segmental anatomy of the lung: (a) right lateral, (b) right anterior, (c) left lateral and (d) left anterior. For explanation of numbers see Fig. 1.8.

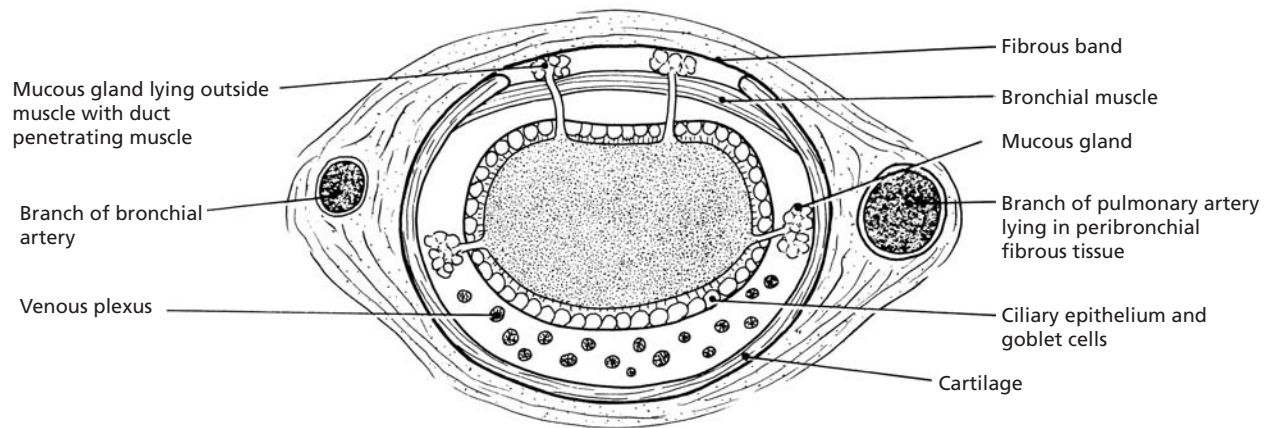


Fig. 1.11 Cross-section of a large bronchus.

the aorta, occasionally through the diaphragm. It is most common in the lower lobe, especially on the left. It may cause problems by becoming infected (see Chapter 50).

#### *Microscopic anatomy of the airways*

The bronchial walls contain three layers, the mucosa, sub-mucosa and fibrocartilaginous layer, the latter including the smooth muscle [46] (Fig. 1.11).

#### *Mucosa*

The mucosa has now been shown to be a true stratified, rather than pseudostratified, squamous epithelium set on an elastic lamina. Basal cells are attached to the lamina by integrin molecules, and these contribute to the desmosomes that are responsible for adhesion of columnar cells to the basal cells [47]. In the inflammation characteristic of asthma, the mucosa splits off between basal and columnar cell layers [48]. The mucosa thins progressively as it becomes more peripheral, finally merging with the flat epithelium of the alveoli. Flat areas of unciliated squamous epithelium occur over the proximal carinae, but most of the mucosa is covered by groups of ciliated cells interspersed with polygonal non-ciliated Clara cells, joined at the epithelial surface by tight junctions. Eight different cell types have been described in the human bronchial epithelium.

The *ciliated cell* has approximately 200 cilia, each between 5 and 10  $\mu\text{m}$  in length [49]. Microvilli occur between the cilia. The epithelium contains some 1500–2000 cilia/ $\text{cm}^2$ , although the cells become more sparse in peripheral airways. The cilia beat about 1000 times per minute, always with an active stroke in the direction of the oropharynx, followed by an inactive recovery stroke (Fig. 1.12). The net effect is to convey bronchial secretions towards the pharynx whence they

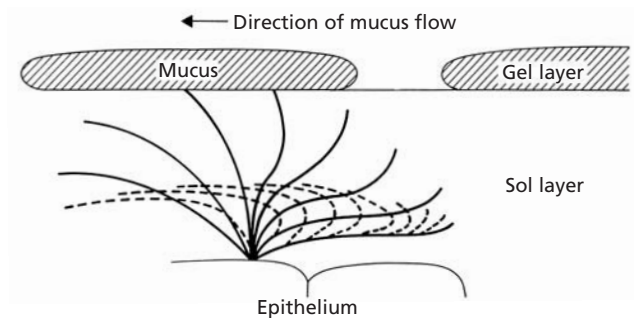
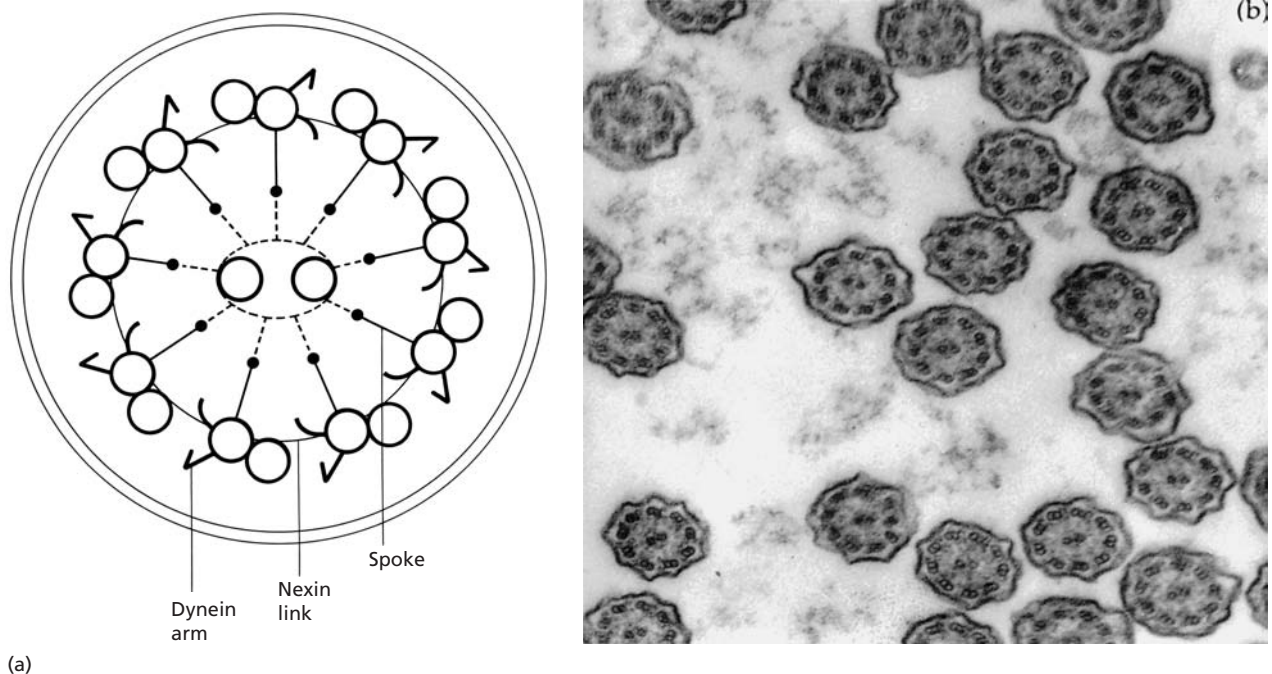


Fig. 1.12 Mechanism of ciliary beat: effector stroke (solid line) moves raft of mucus towards pharynx; recovery stroke (broken line) reduces risk of reverse movement.

can be swallowed or coughed up [50]. Under the electron microscope, the tip of the cilium has been observed to have small claws that protrude into the mucus on the active stroke, helping to propel it [46]. In cross-section the cilium shows an almost identical ultrastructure regardless of whether it is on a bronchial epithelial cell, a flagellate protozoon, a fish gill or a spermatozoal tail [51] (Fig. 1.13).

The shaft consists of longitudinal fibrils in a cytoplasmic matrix. There are nine paired outer fibrils and two inner ones. These fibrils are specialized protein microtubules. The peripheral nine pairs each consist of one complete and one partial microtubule. Adjacent pairs are connected by so-called nexin links, while the outer fibrils are connected to the central pair by radial spokes. These linking structures are proteins, like the microtubules themselves. From each of the complete outer microtubules two arms extend towards the adjacent pair. These are known as dynein arms and consist of an ATPase protein. From the base of each cilium, the peripheral tubules extend some short distance within the cell, where they connect the cross-striated root fibres that anchor the cilium more deeply into the cell. A laterally projecting foot also connects with the base of the tubules, extending in the direction of the active stroke.





**Fig. 1.13** (a) Cross-section of a cilium: the nine outer microtubule doublets and two central single microtubules are linked by dynein arms, nexin links and spokes. (After Afzelius & Mossberg [52].) (b) Electron micrograph of cross-section of normal cilia ( $\times 44\,000$ ).

Bending of the cilium appears to result from an active sliding movement between adjacent pairs of tubules, powered by an ATP-dependent shearing force developed by the dynein arms linking them. The short, rapidly beating cilia of bronchial epithelium are well adapted to the transport of mucus floating on a layer of watery fluid. The cilia of an individual cell beat synchronously, while there is a degree of coordination between adjacent cells in that those at right angles to the effective stroke beat synchronously and those parallel to it beat in sequence. This results in the propagation of a wave over the ciliary surface (metachronism). Many of the studies of cilia have been carried out on cells from other species and it seems likely that metachronism is somewhat less well developed in mucus-carrying systems than in those systems responsible for propulsion of the organism.

Recent evidence suggests that ciliated epithelial cells may have a secretory function in the airway inflammation characteristic of asthma [53]. Expression of interleukin (IL)-1, IL-6 and IL-8 may play a part in attraction and proliferation of T lymphocytes, while granulocyte-macrophage colony-stimulating factor may be produced and activate eosinophils. Transforming growth factor  $\beta$ , a cytokine with immunomodulatory and tissue homeostatic roles, has been demonstrated in these cells [54], as has another cytokine, endothelin, which may be produced by

asthmatic epithelium [55] and which is able to stimulate mucus production and to cause proliferation of smooth muscle. Epithelial cells have also been shown to produce an as yet uncharacterized factor, which relaxes smooth muscle, and nitric oxide (NO), which has similar effects [56].

Although nerves have been observed in relation to ciliated cells, it is thought that the cilia of the respiratory tract are not under nervous control; their frequency of beating seems to be affected by cellular metabolism, and probably by mechanical stimulation and by drugs that influence metabolism.

The *goblet cell* is responsible for the secretion of mucin. It is present in large numbers in the proximal airways and becomes more sparse in the peripheral bronchi and bronchioles. It contains large, electron-lucent secretory granules and an irregular basal nucleus [49].

The *Clara cell* is most profuse in the bronchioles and distal bronchi. It bulges above the ciliated cells into the airway lumen and has a secretory function [57,58]. It has an irregular nucleus, an abundant smooth endoplasmic reticulum and mottled secretory granules at the luminal end. These cells, like type II alveolar cells, produce surfactant-associated glycoprotein [59]. It has been suggested that this cell may be a progenitor of atypical alveolar epithelial hyperplasia and adenocarcinoma [60].

The *serous cell* is another secretory cell, also with an irregular nucleus, but with small, very electron-dense granules and a rough endoplasmic reticulum. Microvilli are present on the surface. It is more frequently observed in fetal airways and it is possible that it can transform into the goblet cell as a result of irritation [46].

*Basal cells* are small conical cells on the basement membrane that are overlapped by the ciliated and secretory cells. They are undifferentiated cells with the potential to develop into the more specialized epithelial cells [46] and, as mentioned above, express adhesion molecules [47]. Basal cells are found mainly in bronchi and infrequently in bronchioles.

*Intermediate cells* are more elongated than basal cells and may reach the airway lumen [49]. They have microvilli on their surface but have not yet acquired cilia or secretory granules. They are found equally in central and peripheral airways and represent another undifferentiated precursor cell.

*Brush cells* occur throughout the airways [61]. They have a well-marked surface covering of microvilli up to 2 µm in length. It is thought, by analogy with intestinal cells, that they have a fluid absorptive function.

The *endocrine cell* (also called Kulchitsky, Feyrter or APUD cell) is basally situated in main to subsegmental bronchi [62], and is the cell from which both carcinoid and oat cell tumours may arise [63]. These cells contain many small electron-dense granules, which have been shown to contain 5-hydroxytryptamine (5-HT) and a range of other bronchoconstrictor and vasoactive substances [64]. Increased numbers and degranulation are found in association with hypoxic conditions, suggesting that they have a role as chemoreceptors [65]. This is supported by the finding that groups of these cells may be supplied by nerves, when they have been called neuroepithelial bodies [66]. They may also play a part in the airway response to inhaled allergen by release of their mediators [67].

### *Submucosa*

The submucosa is a thicker layer external to the basement membrane and contains elastic fibres, mainly in longitudinal bundles but also connected with the mucous membrane and with the circular fibres of the fibrocartilaginous layer. In addition the submucosa contains mucous glands, smooth muscle, nerves and lymphatics. Mucous glands are most numerous in medium-sized bronchi. In the large bronchi they are situated between mucosa and cartilage, but often extend out between the cartilage. They may lie external to the muscle with their ducts passing through it. Mucous glands are the main source of bronchial secretion and contain both mucous and serous cells. The glands consist of a ciliated duct, which communicates with the airway lumen, a wider collecting duct and mucous and serous secretory tubules. In general the serous tubules are more distal, forming buds off the mucous tubules [68], and are lined by serous cells containing small electron-dense granules [69], which secrete neutral glycoprotein, lysozyme and lactoferrin. The serous cells are joined by tight junctions, although intercellular canaliculi occur. The mucous cells contain larger, electron-lucent granules that

aggregate together [69]; they secrete acid glycoprotein. The collecting duct is lined by columnar cells with densely packed mitochondria, thought by some to have a role in fluid regulation, while the ciliated duct has an epithelium similar to that of the airway. In addition to these cells, lymphocytes and plasma cells, which are probably responsible for the production of IgA [70], and myoepithelial cells, which are thought to be contractile and to aid transport of secretions out of the gland, are found in the bronchial mucous gland. Unmyelinated nerves supply all parts of the gland and the myoepithelial cells. Capillaries are found especially around the collecting duct.

The mucous glands may be up to 1 mm in length. Chronic airway irritation by cigarette smoke or dust results in increased numbers of glands and also increase in their size [71]. This enlargement appears to be due to hyperplasia (increased numbers of cells) rather than cellular hypertrophy [72]. Enlargement of the lumina of acini is probably related to increased amounts of secretion.

### *Fibrocartilaginous layer*

The airway smooth muscle in the trachea and main bronchi is arranged mainly in transverse bundles connecting the posterior ends of the cartilages. Contraction here brings the tips of the cartilage plates together, causing the mucous membrane posteriorly to bulge into the airway lumen. Fine longitudinal bundles of smooth muscle also occur outside the transverse band. Passing further down the airways, the transverse muscle is inserted further anteriorly on the cartilages and eventually becomes a complete ring. The fibres also pass more obliquely, forming spirals to both left and right that branch and interconnect resulting in a geodesic network. Contraction of muscle within the intrapulmonary airways down to the respiratory bronchioles therefore results in narrowing and shortening of the airways. In pathological states, such as asthma or anaphylaxis, the narrowing can completely occlude the airway. The thickness of muscle relative to the airway wall is greatest in terminal bronchioles and reduces more peripherally, although muscle bundles can still be seen in the walls of alveolar ducts.

The bronchial muscle has resting tone, which may be demonstrated by a reduction in airway resistance and increase in anatomical dead space after inhalation of sympathomimetic agents or parasympathetic antagonist drugs. In addition, airways narrow and shorten on expiration. This muscular tone may be increased by inhalation of irritants, histamine and 5-HT, parasympathetic agents and prostaglandin  $F_{2\alpha}$ . Hypoxia, hypocapnia and possibly hypercapnia also cause muscular contraction. Relaxation of tone occurs with lung inflation and sympathetic and vagolytic drugs. The larger the airways, the greater the anatomical dead space (i.e. the volume of air in the respiratory tract not in contact with alveoli) and therefore the

greater the respiratory work necessary to maintain a given alveolar ventilation rate. On the other hand, constriction of the airways increases their resistance to airflow, the resistance increasing inversely in proportion to the fourth power of the radius. Thus there must be an optimum anatomical dead space for a given alveolar ventilation rate; for quiet breathing this has been calculated to be about 125 mL.

The fibrocartilaginous layer continues from the trachea, with its horseshoe-shaped cartilages, down to the smallest bronchus. Bronchioles, by definition, contain no cartilage. In the intrapulmonary airways the cartilage becomes arranged in plates, connected to each other by a fibrous layer consisting of longitudinal bundles of collagen and elastin. The plates of cartilage become smaller and sparser further down the airways and the fibrous layer becomes thinner, eventually merging with the connective tissue of the lung and the fibrous framework around the alveolar ducts. Nerves, blood vessels and mucous glands pierce the fibrous layer on their way to and from the submucosa and mucosa.

#### *Mast cells*

Mast cells may be found occasionally in the bronchial submucosa and mucosa. They assume importance in asthma, where they are a major source of mediators of bronchial inflammation and smooth muscle contraction [73]. They are morphologically similar to the circulating basophil, containing an inconspicuous nucleus and dense basophilic granules. The latter are about  $0.5\mu\text{m}$  in diameter and surrounded by a membrane. In asthmatic airways the granules may disappear, indicating release of mediators. They may also be relevant to bronchiolo-alveolar inflammation in syndromes of pulmonary fibrosis, where they have been found in excess numbers in lavage fluid [74].

#### *Secretions of the airways*

The secretions of the airways [75,76] are familiar to the clinician as sputum. However, this substance is the product of an abnormal bronchial tree and may differ both qualitatively and quantitatively from the normal bronchial secretions. Sputum is a mixture of bronchial secretions, cells and cellular debris, cleared organisms and saliva. The bronchial secretions themselves, even in normal airways, are contaminated by surfactant from alveoli and by fluid transudate. The bulk is secreted by the serous and mucous cells of the bronchial glands, with important contributions from the goblet cells of the bronchial epithelium as well as from the serous and Clara cells.

Mucus is present over the bronchial epithelium as a continuous sol layer, in which the cilia beat, and a gel layer,

which at bronchiolar level appears as distinct rafts floating on the sol layer; these gradually merge together to provide an almost complete covering of the epithelium in the larger airways. The depth of the sol layer is probably about  $5\mu\text{m}$ , just sufficient to cover the cilia during their effective stroke so that the gel layer is propelled over the surface. While the gel layer is clearly secreted by the mucous glands and goblet cells, the sol layer is probably derived largely from the Clara cells with some contribution from transudated fluid.

The watery sol layer has been shown to contain albumin, lysozyme, immunoglobulins,  $\alpha_1$ -antitrypsin,  $\alpha_1$ -antichymotrypsin and glycoprotein, with very little lipid. The gel layer, which forms the bulk of mucoid sputum produced by the bronchitic patient, contains 95% water, protein, carbohydrate and lipid (about 1% each) and DNA and electrolytes. The proteins are mainly complex polydispersed glycoproteins called mucins, which give mucus its characteristic physical properties, and immunoglobulins, especially IgA. The glycoproteins of mucus have a high molecular mass ( $1.5\text{--}2\times 10^6$  kDa), with a long protein core and carbohydrate side-chains, of which the main ones are galactose, *N*-acetylglucosamine and *N*-acetylgalactosamine. The glycoproteins may be neutral or contain sialic acid or sulphate. These long molecules are organized into fibrous strands connected by cross-bonds of hydrogen and disulphide, the whole structure being responsible for the viscoelastic properties of mucus.

The functions of bronchial mucus include waterproofing, thus diminishing water loss from the respiratory tract; protection of the epithelium, by forming a barrier between it and particles in the inhaled air; and defence, by removal of inhaled particles as a result of ciliary activity, and by acting as a vehicle for immunoglobulins.

The two most characteristic physical properties of bronchial mucus are its viscosity and elasticity [77]. Viscosity is a measure of a fluid's resistance to flow, whereas elasticity is a measure of a solid's ability to store applied energy in order to return to its original shape after a deforming force has been removed. In terms of bronchial clearance, the viscosity of mucus allows the cilia to engage it during their effector stroke (which proceeds relatively unimpeded through the non-viscous sol layer) and to stretch it, because of its elasticity, in an upwards direction. The elastic properties of mucus also allow it to transfer the energy imparted by the cilia to the transport of particles caught upon its surface. Experiments using *in vitro* mucociliary systems have shown that both viscous and elastic properties are important in mucus transport and that there is an optimal value for each beyond which transport is less effective.

IgA is an important component of bronchial mucus. It is secreted originally by lymphocytes and plasma cells in the

bronchial glands [70], probably as the monomer that is also found in serum. In the course of passage through the gland, two IgA molecules are linked by a peptide known as secretory piece to form the dimer, secretory IgA [78,79]. It is not known whether this conjugation occurs within cells or in the gland lumen. It then becomes incorporated into the glycoprotein structure of the bronchial mucus, probably by hydrogen or disulphide bonding. It is able to protect the mucous membrane by forming complexes with proteins, such as those of bacteria, and also plays a role in increasing the strength and stability of the mucus itself.

Many other proteins are found in bronchial secretions. It is likely that their presence depends on passive diffusion from the blood, as in general the ratios of their concentration in sputum to that in serum are in inverse proportion to their molecular weights. However, qualitative studies of the constituents of bronchial secretions are complicated by considerable technical problems [80,81]. Water is, of course, the major component of bronchial secretions. Since the sol layer provides a continuous covering for the distal airways, with their considerable total surface area, one of the functions of the airway epithelium must be to reabsorb much of this fluid as it passes upwards. The brush cells may serve this function.

## Acinus

### General structure

The acinus is that part of the lung distal to the terminal, non-alveolated bronchiole [42]. It thus consists of up to three orders of respiratory bronchioles, each with alveoli arising from its walls, usually three but up to nine generations of alveolar ducts, terminal alveolar sacs and alveoli. The terminal bronchiole and the respiratory bronchioles usually divide dichotomously, but three or more divisions may occur in alveolar ducts. Alveoli arise relatively infrequently from the first respiratory bronchiole and more profusely subsequently, so that alveolar ducts are in fact very short tubes surrounded almost entirely by the orifices of alveoli, while alveolar sacs are even shorter, hemispherical structures, the walls of which are composed of alveoli. There are approximately 25 000 acini in the human lung, giving rise to some 300 million alveoli. The total surface area of the alveoli has been estimated to be between 40 and 80 m<sup>2</sup>.

The walls of the respiratory bronchioles contain some muscle bundles, diminishing in amount peripherally, and muscle fibres may also be present between the orifices of alveoli that branch off the alveolar ducts. Muscle and collagen fibres, reticulin and elastin form the supporting structure of the alveolar ducts. The epithelium of the respiratory bronchioles away from the alveolated portions is cuboidal and contains the same cells as the more proximal

airways, with ciliated and Clara cells prominent. The alveolar epithelium is flattened and composed largely of the very thin type I pneumocyte and the more cuboidal type II pneumocyte (see below). Each respiratory bronchiole is accompanied on one side by a muscular pulmonary artery, and this side is devoid of alveoli. The vessel gives off arteriolar branches that in turn supply the capillaries to alveoli. Each alveolus is surrounded by a network of capillaries with very thin walls composed of endothelial cells. The alveolar wall thus consists of a layer of alveolar epithelial cells, their basement membrane, a thin interstitial space that may contain small amounts of collagen and elastin, unmyelinated nerves and occasional macrophages, the capillary basement membrane and capillary endothelial cells [82]. In many places the basement membranes fuse, thus eliminating the interstitial space and minimizing the distance for gas diffusion from alveolar space to red blood cell to about 0.2 µm at its narrowest.

The alveolar capillaries join together to form venules, alongside the respiratory bronchioles, that in turn merge into pulmonary veins. These vessels, in contrast to the pulmonary arteries, do not run alongside bronchi but in the interlobular septa. These septa are connective tissue divisions between what are known as *secondary lung lobules*. They separate groups of between three and five terminal bronchioles and their acini from each other and are easily visible as the smallest segment of lung bounded by connective tissue when a slice of lung is examined with the naked eye. Lobules also represent that part of the lung where airway branching changes abruptly from a frequency of one every 0.5 cm to one every 2–3 mm. Care should be exercised with this terminology, since a *primary lobule* is defined as an alveolar duct and its distal connections.

Ventilation of alveoli may occur via collateral pathways as well as directly down the bronchiolar tree [83]. Small (10–15 µm) openings in alveolar walls, known as pores of Kohn [84], allow gas to pass between adjacent alveoli, even from adjoining segments. These pores have not been observed in the prenatal lung and appear to become both more profuse and larger throughout life [85]. In addition to these pores, short bronchiole–alveolar communications lined with epithelium [86] allow gas to pass from one bronchiole to alveoli of a neighbouring acinus. They are about 30 µm in diameter and many remain open regardless of the degree of bronchiolar smooth muscle constriction elsewhere. There is also evidence that larger diameter interbronchiolar communications may occur between adjacent respiratory bronchioles [87]. It is likely that collateral ventilation also occurs at the level of alveolar ducts [88].

### Alveolar wall

The alveolar wall consists of types I and II pneumocytes,

basement membranes, interstitial tissue and capillary endothelial cells [82]. The interstitial tissue contains some bundles of elastin and collagen, nerve fibres and nerve endings. It is normally only 5–10 µm in diameter. Macrophages may be found in the interstitial space as well as in the alveolar or airway lumens.

#### *Type I pneumocytes*

Type I pneumocytes are the pavement epithelium of alveoli, specialized for the diffusion of gas from alveolus to capillary. Although fewer in number than type II cells, their surface area is much greater as they are extremely flattened; they thus cover most of the alveolar surface (Fig. 1.14). Under the electron microscope they can be seen to contain pinocytic vesicles. Type I cells are connected to each other by tight junctions, which prevent leakage of fluid into the alveolar lumen. They are derived from type II cells and do not themselves undergo mitosis [89]. There is evidence that they are able to transport fluid, small molecules and dust particles from the alveolar lumen by pinocytosis [90].

#### *Type II pneumocytes*

Type II pneumocytes are more numerous than type I cells. They are cuboidal in shape and have microvilli on their alveolar surface. They tend to be grouped in the corners of the alveoli. The cytoplasm is rich in mitochondria and endoplasmic reticulum and also contains characteristic vacuoles containing osmophilic lamellar bodies (Fig. 1.15). These are secreted into the alveolar lumen as surfactant [91]. The type II cell is also the precursor of type I cells, a role that can sometimes be observed in acute alveolar injury, when type II proliferation takes place and intermediate cells may be seen [89]. With chronic injury, the alveoli may become lined exclusively with proliferating type II cells. It is also likely that these cells have a role in secreting components of the basement membrane [92].

#### *Endothelial cells*

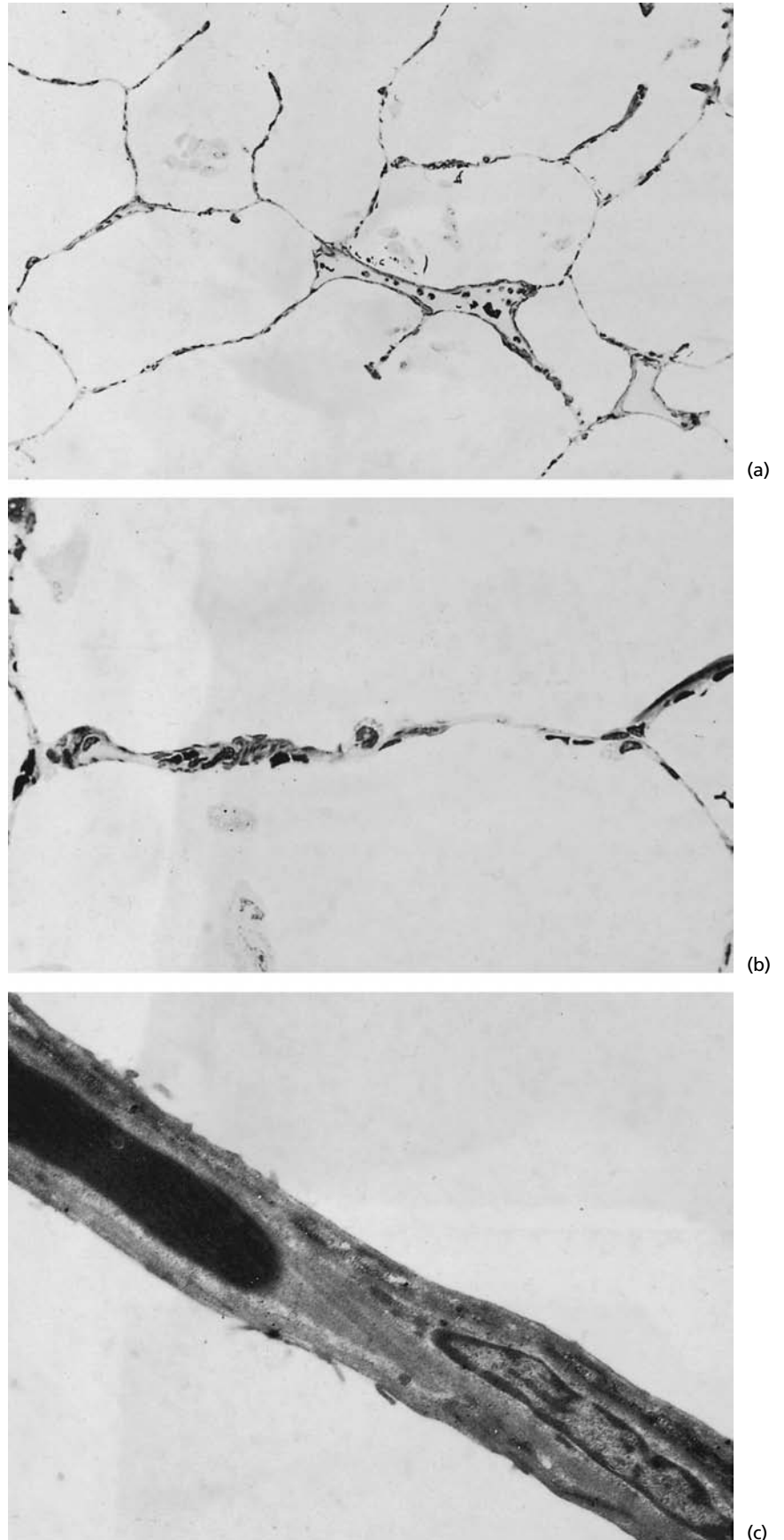
Endothelial cells line the alveolar capillaries and are the most numerous of the alveolar cells. Unlike the epithelial cells, they are not connected by tight junctions and thus allow small molecules and fluid to escape. The most notable ultrastructural feature of endothelial cells is the presence of pinocytic vesicles. Where these meet the luminal surface they form caveolae, which appear to be separated from the lumen by a fine membrane. The walls of the caveolae are sites of intense enzymatic activity; 5-HT and prostaglandins are degraded here and angiotensin-converting enzyme is present also. The luminal surface of the capillary endothelial cell is relatively smooth, while that of more proximal vessels tends

to have protrusions, especially at the margins of the cells [93]. Endothelial cells are the primary lung source of the smooth muscle relaxing factor, NO [94]. This radical, produced by the action of nitric oxide synthetase on L-arginine, acts on smooth muscle by increasing the levels of cyclic GMP. It is an important natural pulmonary vasodilator.

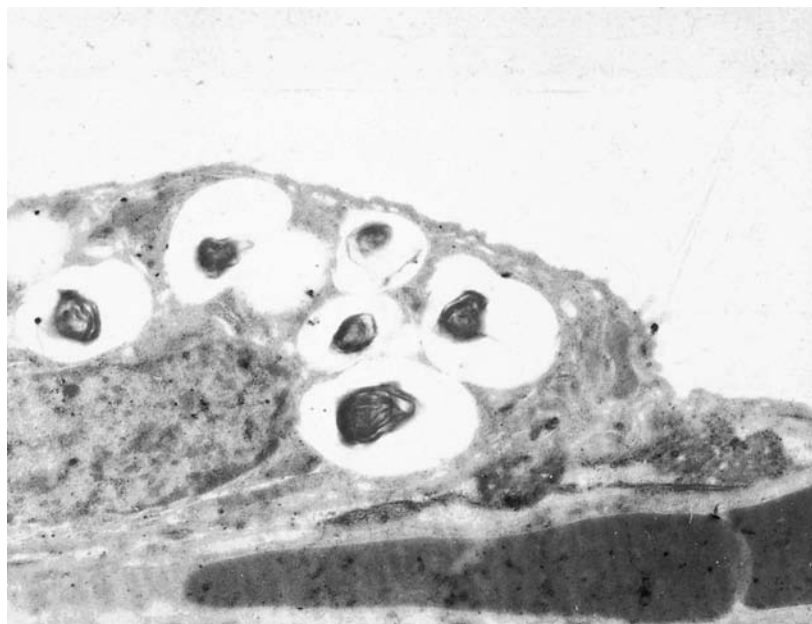
#### *Alveolar macrophages*

Alveolar macrophages are the main phagocytic cell, and hence the primary defence mechanism, of the acinus, although both type II and type I cells have some phagocytic activity. In common with other tissue macrophages, they are derived from bone marrow pro-monocyte stem cells, which enter the circulation as monocytes and reach the lung by diapedesis through the capillary endothelium [95]. Their numbers increase with age in non-smokers [96], and large increases are seen as a consequence of smoking and inhalation of toxic or irritant substances. Their production by bone marrow is regulated by a cytokine, macrophage colony-stimulating factor, which in turn is produced by a wide range of cells. They are capable of penetrating the alveolar epithelium, probably between type I and type II cells mainly, and come to lie in the surfactant layer. They are amoeboid cells and their cytoplasm is rich in electron-dense lysosomal bodies (Fig. 1.16). Frequent phagosomes, containing particulate matter and whorled structures probably representing ingested surfactant, are seen. Alveolar macrophages, being accessible to bronchoalveolar lavage, have been much studied of late. As befits a defence cell analogous in evolutionary terms to soil protozoa, apart from its phagocytic function the alveolar macrophage synthesizes and, when activated, secretes a large number of active products, including lysozyme, proteases, complement components, plasminogen activator, thromboplastin,  $\alpha_2$ -macroglobulin and numerous cytokines, most notably interferon  $\alpha$ , tumour necrosis factor  $\alpha$  and IL-1 and IL-8 [97,98]; it can also release superoxide radical and NO as part of its antibacterial role. Alveolar macrophages play the central role not only in defence of the lung against inhaled organisms and organic and inorganic substances, but also in the inflammatory and immunological reactions that may lead to lung damage by both fibrosis and emphysema [99,100].

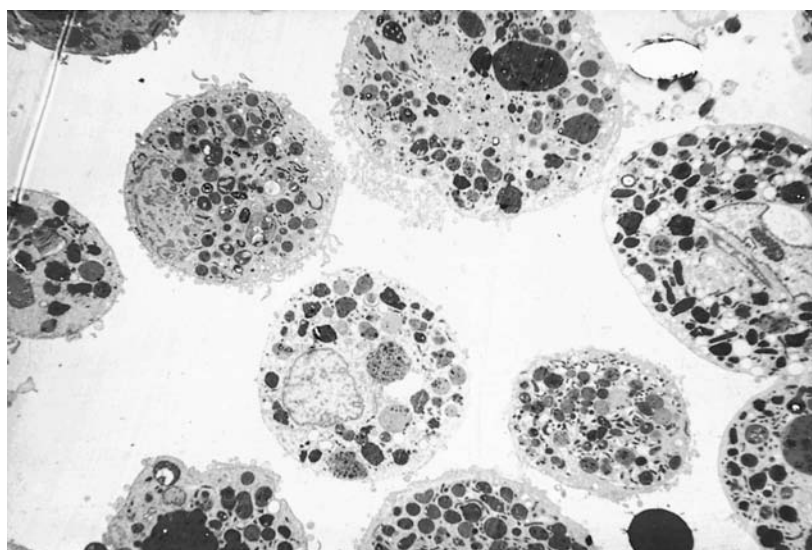
Most macrophages, having reached the alveolar surface, either migrate up into the airways, where they are carried to the pharynx in the mucociliary escalator, or die *in situ* and are in turn scavenged by younger phagocytes. There is dispute as to whether macrophages, having engulfed foreign particles, can repenetrate alveolar epithelium and transport the particles into the lymphatics. It is equally likely that the particles themselves penetrate the epithelium by pinocytosis and are phagocytosed by



**Fig. 1.14** (a) Low-power section of alveoli showing normal thin alveolar walls with small interstitial blood vessels and some intra-alveolar macrophages (toluidine blue  $\times 80$ ). (b) Higher-power view showing central and junctional type II cells, very thin type I cells and intracapillary erythrocytes (toluidine blue  $\times 250$ ). (c) Electron micrograph of part of alveolar wall showing section through darkly stained red blood cell to left and nucleus and cytoplasm of type I cell to right and surrounding the capillary (uranyl acetate and lead citrate  $\times 4500$ ).



**Fig. 1.15** Electron micrograph of type II alveolar cell containing lamellar bodies; two erythrocytes lie in a capillary below the cell (uranyl acetate and lead citrate  $\times 7200$ ).



**Fig. 1.16** Electron micrograph of human alveolar macrophages obtained at bronchoalveolar lavage showing phagolysosomes containing inclusions derived from cigarette smoke and occasional lamellar bodies ( $\times 2025$ ). The relatively smooth membranes are associated with cigarette smoke exposure. (Courtesy of Dr R. Agius.)

macrophages resident in the interstitial tissues and thence carried by these cells to lymphatics.

### Surfactant

The inner surface of the alveolar epithelium is separated from the alveolar gas by a thin layer of surface-active material, consisting mainly of dipalmitoyl lecithin and dipalmitoyl phosphatidylethanolamine, combined with apoproteins that are the most hydrophobic proteins known [101,102]. These cationic substances, by means of a positively charged quaternary ammonium ion that separates their two palmitic acid chains, attach themselves to the negatively charged epithelial surface. It was believed

that a liquid layer is present between this surfactant and the epithelial cells and that this is responsible for the inherent instability of alveoli. However, evidence for this liquid layer is scanty while a teleological reason for it is hard to perceive, as it would only increase the instability of alveoli and the force required to keep them inflated. The presence of surfactant reduces the surface tension of the alveolar lining layer to almost zero. This major function of surfactant, decreasing the surface tension of the alveolar wall during expiration and therefore reducing the work of lung inflation, is probably only part of its role; it is likely also that it has an important function as a waterproofing material [103,104]. It has been shown that the presence of surfactant increases considerably the pressure required for

fluid to leak from the alveolar interstitium into alveolar spaces. Moreover, once fluid does escape into alveoli, the hydrophobic surface would tend to break it up into droplets which on the irregular alveolar surface would accumulate in angles and corners. Here the pressure generated by the surface tension of small drops could be sufficient to force fluids back into the interstitium, even against an osmotic gradient [104].

Surfactant is manufactured by the type II alveolar cells, each of which is capable of secreting almost its own weight of the material each day. It is synthesized in the smooth endoplasmic reticulum and appears first as a multivesicular body, which converts into the lamellar body. This changes form to a tubular myelin, a monolayer and a micellar form, and much is then taken back into type II cells for reprocessing [105,106].

As mentioned previously, surfactant synthesis starts after about 26 weeks of fetal life. Thus premature infants run the risk of surfactant deficiency, causing the condition known as respiratory distress syndrome or hyaline membrane disease. At this stage alveoli have not developed and surfactant is necessary to facilitate lung inflation and reduce the work of respiration for the critical first few hours of extrauterine life. Babies with this disease show tachypnoea, chest retraction, expiratory grunting and cyanosis. The chest radiograph may show fine mottling and the lungs feel stiff on ventilation. When death occurs, the lungs show peribronchiolar fibrosis and prominent hyaline membranes in the immature air spaces. Surviving babies may be left with pulmonary fibrosis, a condition known as bronchopulmonary dysplasia, possibly related to the need for treatment with high concentrations of oxygen and assisted ventilation [107]. Mortality from this condition has been reduced dramatically by the use of surfactant replacement therapy using either natural pig or cow surfactant or synthetic phospholipid mixtures [108].

## Blood vessels of the lung

### Bronchial circulation

The bronchial arteries usually arise, either as a pair or as a common trunk, from the descending aorta below the origin of the left subclavian artery [109,110]. There is considerable anatomical variation, the vessels occasionally being branches of the internal mammary artery or intercostal arteries, while small supplementary arteries may arise separately from further down the aorta. Sometimes part of the blood supply of the anterior spinal artery may come from bronchial vessels, an anomaly to beware if bronchial artery embolization for haemoptysis is to be contemplated. The bronchial arteries leave the aorta at an upwards angle, against the direction of blood flow, send branches to oesophagus, mediastinum, lymph nodes and nerves, and on reaching the main bronchi divide into vis-

ceral pleural branches to the mediastinal pleura and true bronchial arteries to the bronchial tree. These latter vessels run a spiral course around the bronchi, one on either side of each bronchus but anastomosing frequently with each other. The vessels form an arterial plexus in the adventitia from which branches pierce the muscle layer to enter the submucosa, where they break up into a capillary plexus. Apart from supplying bronchi, the bronchial arteries also supply nerves, the walls of the pulmonary vessels and intrapulmonary lymph nodes. Arteriolar branches of the visceral pleural vessels pass along interlobular septa, reaching the interstitial tissue of the lung acinus. The true bronchial arteries reach as far down the airways as the terminal bronchiole.

Much of the bronchial arterial blood, having gone through submucosal capillaries, passes into a venous plexus in the adventitia. This low-pressure system can be obstructed by bronchial muscle contraction, probably explaining in part the oedematous mucosa seen in asthma. Veins from this plexus then join the pulmonary venous system. However, bronchial veins have been described from terminal bronchioles to the hilum, also communicating with pulmonary veins or draining directly into the left atrium. The pleurohilar veins, in contrast, drain into the azygos and hemiazygos systems and thus into the right side of the heart. However, there is free communication between pulmonary, bronchial and pleurohilar venous systems within the lung.

### Pulmonary circulation

The pulmonary artery arises from the infundibulum of the right ventricle at the pulmonary valve and runs posteriorly slightly upwards and to the right to divide below the aortic arch into right and left branches (Fig. 1.17). The right runs laterally under the arch and posterior to the ascending aorta and superior vena cava before dividing at the hilum into upper and lower branches, which supply upper lobe and middle and lower lobes respectively. Thereafter branching is very variable, although in general the pattern approximates to that of the bronchial tree. The left main pulmonary artery runs laterally and slightly upwards and posteriorly, anterior to the descending aorta to which it is connected by the ligamentum arteriosum (the remnant of the ductus arteriosus). The left recurrent laryngeal nerve winds round the ligamentum arteriosum, explaining why left hilar disease may cause vocal cord paralysis. The left pulmonary artery divides usually into upper and lower branches, which subdivide in a variable pattern as on the right side. Counting from peripheral small arteries to the main pulmonary trunk, there are 17 orders of branching on both sides [111]. Beyond the first-order vessels lie pulmonary arterioles supplying the acini. These are true end arteries, breaking up into the pulmonary capillaries that form networks around the alveoli.





Fig. 1.17 Normal pulmonary arteriogram.

The pulmonary trunk and large pulmonary arteries exceeding 1 mm in diameter are classified as elastic arteries [112]. The media of these vessels consists predominantly of elastic fibrils (five or more layers) with some smooth muscle fibres, collagen and a mucopolysaccharide ground substance. The elastic tissue pattern in the pulmonary trunk varies with the different phases of development from fetal to adult life, the adult pattern becoming established by the end of the second year. By this time the media is only half to three-quarters as thick as that of the aorta and the elastic tissue is irregular and more sparse, contrasting with the long, parallel, uniform fibrils of the aortic media. Central to a thick internal elastic lamina is a fibrous intima and the vascular endothelium.

The elastic arteries give rise to muscular arteries with a diameter less than 1 mm. These vessels have a thin media of circular smooth muscle between internal and external elastic laminae, the latter having first appeared in the smaller elastic arteries. The thin fibrous intima gradually disappears, leaving the internal elastic lamina bounded by endothelial cells. The muscular arteries are closely associated with bronchioles, branching with them. They in turn give rise to pulmonary arterioles, defined as vessels below 0.1 mm in diameter. These essentially consist of an endothelial lining, a single elastic lamina and very thin or absent adventitia. They are indistinguishable from pul-

monary venules except when they can be traced to their origin from a muscular artery.

Pulmonary capillaries consist of endothelial cells stretched over basement membrane. These capillaries spread as a network around the alveoli and collect together to form venules that start near bronchioles but then run into the connective tissue septa between secondary veins which run in the interlobular septa. Pulmonary veins have a thick fibrous adventitia, a media of irregularly disposed collagen and muscle fibres, an internal elastic lamina and endothelium. Usually the veins join into four main vessels, two from each lung, before entering the left atrium.

The pulmonary endothelial cell appears almost featureless on light microscopy, with a flattened cytoplasm and bulging nucleus. Silver stains demonstrate a pavement pattern that differs in shape in different vessels, while electron microscopy of rat pulmonary endothelium has shown the cytoplasm to have both projections into the lumen and vesicular structures called *caveolae intracellulares* [93]; these may communicate with the vessel lumen through small openings. Endothelial cells are the site of enzymes concerned with the conversion of angiotensin I into angiotensin II, and are the main cells concerned with the synthesis of NO, a smooth muscle relaxing factor [94,113]. The pulmonary circulation is known to be

responsible for degradation of a number of circulating hormones and drugs and it is likely that many of these functions are also subserved by the endothelial cell, either on its surface or by pinocytosis.

Endothelial cells account for almost 40% of the cell population of the lung and have a rapid rate of turnover. In the larger vessels they are connected by tight junctions [93], while in capillaries small gaps between cells may occur that allow passage of fluid into the interstitial space. Such fluid is normally unable to pass into alveoli because of the tight junctions between epithelial cells and therefore drains to the lymphatics around the pulmonary venules in the interlobular septa. The endothelial cell is vulnerable to injury caused by, for example, radiation, drugs such as bleomycin, or high concentrations of oxygen. The damage, probably mediated by free oxygen radicals, results in vacuolation, swelling and rupture of endothelial cells, platelet deposition on basement membrane, interstitial oedema and ultimately alveolar epithelial damage and alveolar oedema [89]. Thrombotic occlusion of the capillary may occur. At an early stage these changes are reversible, the endothelial cell having a remarkable regenerative capacity.

## Lymphatics of the lung

Two lymphatic networks drain the lung. The superficial system arises in the pleura, forming an arrangement of irregular polyhedra marking the edges of the secondary lung lobules [109]. The deep system arises in connective tissue between the acini and around bronchi and vessels [114]. The two networks communicate in the pleura and at the hila. The vessels themselves are thin-walled, being lined with endothelium and consisting of collagen, elastic fibres and some longitudinal muscle bundles [109]. Their wall varies in thickness and often consists almost entirely of the endothelium. They contain numerous valves, which have a conical structure, approximately 1–2mm apart. These valves are placed so as to direct flow for variable distances along the pleura, but ultimately most pleural vessels enter the parenchyma and pass towards the hila through interlobular and peribronchovascular channels. Lymph drains finally into the systemic venous system at the junctions of the subclavian and internal jugular veins via the thoracic duct on the left and the right lymphatic duct on the right.

Aggregations of lymphoid tissue are found in the angles of bronchial branches from the periphery inwards. The most distal of these aggregations surround the division of the last respiratory bronchiole into alveolar ducts. True lymph nodes (the bronchopulmonary nodes) are not found until the first division of the lobar bronchi [115]. The hilar nodes, around the main lobar bronchi, form part of a large group clustered about the lung root. The nodes lying lateral and inferior to the tracheal bifurcation are the

upper and lower tracheobronchial groups. The lower group lies in the carina and unites the tracheobronchial groups of the two sides. The upper tracheobronchial group is usually larger on the right. On the left side, one or more para-aortic nodes are separated from the upper tracheobronchial group by the aorta and pulmonary artery. These are closely associated with the ligamentum arteriosum, recurrent laryngeal nerve and vagal fibres to the pulmonary plexus. On either side of the trachea, paratracheal nodes are also close to the recurrent laryngeal nerve and involvement of these nodes by bronchial carcinoma commonly results in vocal cord paresis. Efferent vessels from the paratracheal nodes pass to the lower deep cervical nodes. Other intrathoracic groups are the sternal nodes, on the inner surface of the anterior chest wall along the distribution of the internal mammary arteries, the internal intercostal nodes near the heads of the ribs, and the anterior and posterior mediastinal nodes.

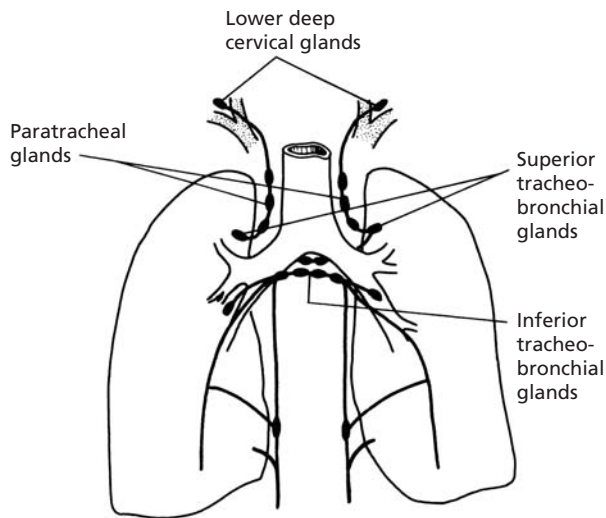
The pattern of pulmonary lymph drainage is complex and variable. Extrapulmonary drainage may occur through interconnecting mediastinal, paratracheal and subdiaphragmatic channels. The classical pathways have been described as follows [115].

- 1 Upper two-thirds right upper lobe: right tracheobronchial nodes.
- 2 Lower third right upper lobe: dorsolateral hilar nodes.
- 3 Right middle lobe: hilar nodes around middle lobe bronchus.
- 4 Dorsolateral parts of right lower lobe: dorsolateral hilar nodes.
- 5 Ventromedial parts of right lower lobe: ventromedial hilar and carinal nodes.
- 6 Apex left upper lobe: para-aortic nodes.
- 7 Rest of left upper lobe: anterior and posterior hilar and carinal nodes.
- 8 Left lower lobe: similar to right lower lobe.

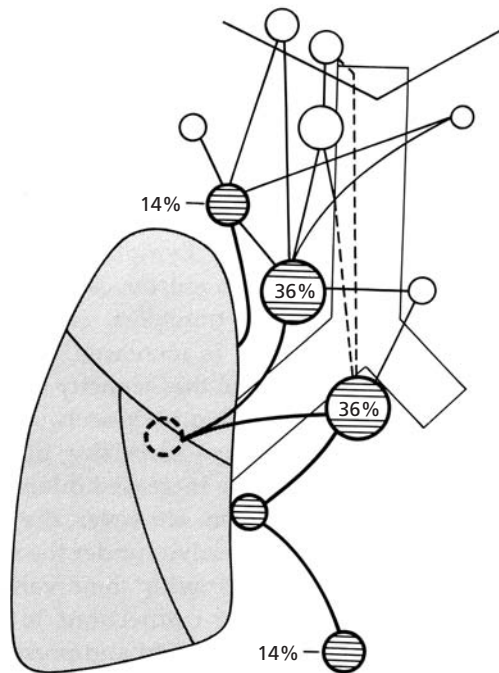
The lower lobes also drain to nodes in the posterior mediastinum and, through the diaphragm, to retroperitoneal nodes (Fig. 1.18). The main primary and secondary drainage pathways of the lungs are shown in Figs 1.19 and 1.20 [116].

In normal lung, the lymphatics are barely visible microscopically. However, they become very distended and easily visible in pulmonary oedema and their presence may become apparent on chest radiographs. Distended anastomotic channels between perivenous- and peribroncho-arterial vessels are seen as Kerley A lines, while thickening of the interlobular septa around dilated subpleural interlobular lymphatics is seen as Kerley B lines. Such appearances occur typically in pulmonary oedema, lymphatic spread of carcinoma and some pneumoconioses [117].

Homeostasis in relation to the volume of pulmonary interstitial fluid depends on lymphatic drainage, as implied above. Lymphatic vessels, containing valves and

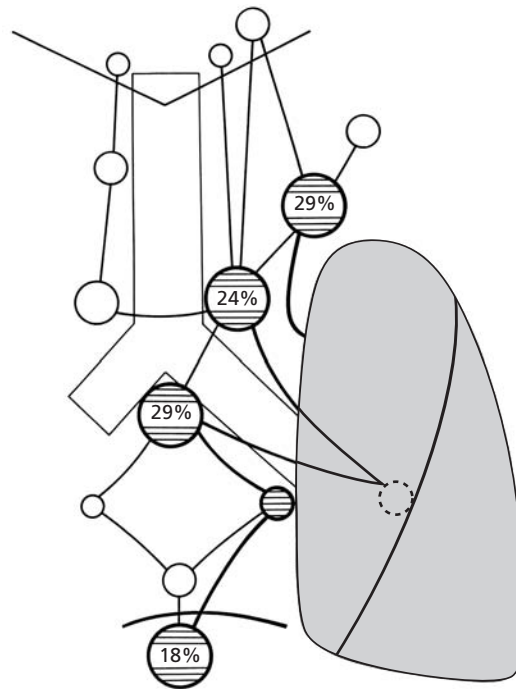


**Fig. 1.18** Pulmonary lymph glands: note connections with neck and abdominal glands (From von Hayek [115].)



**Fig. 1.19** Schematic representation of the primary (heavy line and shaded circles) and secondary (thin lines and open circles) lymphatic drainage pathways of the right lung following injection of the lobar lymph node complex shown. (From Dyon [116].)

smooth muscle, can probably actively increase lymph transport when the amount of interstitial fluid is increased [118,119]. Pulmonary oedema occurs when this capacity is overwhelmed. The dilatation of lymph vessels seen in pulmonary oedema is perhaps surprising in view of their delicate walls and the increased interstitial pressure that



**Fig. 1.20** Schematic representation of the primary (heavy line and shaded circles) and secondary (thin lines and open circles) lymphatic drainage pathways of the left lung following injection of the lobar lymph node complex shown. (From Dyon [116].)

surrounds them. However, they contain fluid themselves under the same pressure, and this, together with their valvular mechanism and fine fibrillar connections to surrounding tissue, keeps them patent and preserves their ability to drain fluid [120,121].

## Innervation of the lung

Autonomic nerves from the vagi and second to fourth thoracic sympathetic ganglia form the pulmonary plexus from which arise branches to supply the bronchi and vessels of the lung [122–125]. The trachea receives branches directly from the right vagus and recurrent laryngeal nerve. In cartilage-containing airways, a plexus is present both outside and within the plates. Non-myelinated fibres innervate the smooth muscle of the bronchi and bronchioles and the bronchial glands. Similar fibres pass along the pulmonary and bronchial arteries, while the pulmonary veins receive their nerves from those supplying the left atrium [109].

Parasympathetic nerves from the vagus carry afferent messages from stretch receptors within the lung, from juxtacapillary J receptors and from bronchial irritant receptors [125]. Efferent parasympathetic fibres mediate bronchoconstriction [126], bronchial gland secretion and probably pulmonary vasodilatation. Sympathetic innervation of vascular smooth muscle has been demonstrated

in most animals studied, although its role in pulmonary vasoconstriction in humans is unknown. Sympathetic innervation of bronchial smooth muscle is probably absent or of no functional significance [122].

There is evidence of a third component of the autonomic nervous system in the lung, as in other tissues such as the gut and the cardiovascular system [122,127]; this is called the peptidergic or non-adrenergic non-cholinergic system. These nerves travel with other autonomic nerves but are distinguishable histochemically and in experiments on isolated smooth muscle. The mediators are peptides, of which four seem particularly important. Vasoactive intestinal peptide is a 28-amino-acid peptide that relaxes bronchial and vascular smooth muscle and has an anti-inflammatory effect [122,128]. It has been found in human bronchial muscle, mucous glands, pulmonary and bronchial vessels, and in neutrophils, eosinophils and monocytes. It probably acts within the cell by activation of adenylate cyclase, like sympathetic stimulation, increasing levels of cyclic AMP [129]. The opposite effect, resulting in smooth muscle constriction, vasodilatation, increased vascular permeability and fluid transudation, and increased mucus secretion, is mediated via sensory nerves that respond to irritant stimuli by release of substance P, neurokinin A and calcitonin gene-related peptide [130–132].

Understanding of the interrelationships of the three components of the autonomic control of airways and lung vasculature is far from complete. It seems likely that neural control is largely exerted by parasympathetic and peptidergic systems, while humoral control is mediated via the adrenal medulla. New research in this area should have important practical applications in the understanding of asthma and pulmonary hypertension, and has major implications for new methods of therapy.

## Pleura

The pleura is a serous layer of mesodermal origin. It consists of a single layer of mesothelial cells, without a basement membrane. A layer of compressed connective tissue, which may be up to 100  $\mu\text{m}$  thick, separates it from the adipose tissue of the chest wall and from alveoli [133]. The visceral pleura, which covers the lung and is indented into the fissures, is continuous at the hilum with the parietal pleura that lines the hemithorax. A thin double fold of pleura below the hilum and extending almost to the diaphragm is called the pulmonary ligament.

The parietal and visceral layers have traditionally been thought to be separated normally by a small quantity of

lubricating fluid. This fluid is probably derived largely from parietal pleural capillaries and reabsorbed by lymphatics, predominantly in costal and mediastinal parietal pleura [134]. This drainage pathway may be blocked when tumour cells are introduced and deposits form in the draining lymph nodes, leading to pleural effusion. The pleural space only becomes apparent when such transudation or exudation of fluid between the two layers exceeds the drainage capacity of pleural lymphatics (see Chapter 43). However, a convincing case has been made for surfactant rather than fluid as the principal lubricating system of the pleural surfaces [135]. The cells of the pleural membrane have ovoid nuclei and thin cytoplasm. The subjacent connective tissue varies in different parts of the pleura, being predominantly collagenous over the pericardium and elastic over the diaphragm and ribs. Beneath the visceral pleura there is a thin layer of elastic and collagen fibres, a strong fibrous layer and a vascular connective tissue layer contiguous with the interlobular septa. Outside the parietal pleura is a band of compressed connective tissue, a fatty layer and another band of predominantly elastic tissue that separates it from rib perichondrium, intercostal muscle and diaphragm.

The visceral pleura is supplied mainly by branches of the bronchial artery that divide into a network of very dilated capillaries [109,115]. The costal parts of the parietal pleura are supplied by intercostal arteries, while the diaphragmatic and mediastinal parts are supplied by the pericardiophrenic branch of the internal mammary artery. The lymphatics of the visceral pleura drain subpleurally into interlobular vessels and thence to hilar nodes as described above. The lymphatics from the costal parietal pleura drain into internal mammary and intercostal nodes, providing a useful site for biopsy in the diagnosis of pleural disease [136]. Vessels over the diaphragmatic visceral pleura drain to internal mammary and anterior and posterior mediastinal nodes, while those from mediastinal pleura accompany the pericardiophrenic artery draining into the posterior mediastinal nodes.

The visceral pleura is supplied by autonomic nerves only. However, sensory nerves are present in the parietal pleura, from spinal nerves over the ribs and from the phrenic nerve over the central part of the diaphragm. The peripheral diaphragmatic pleura receives sensory fibres from intercostal nerves. Pleural pain therefore represents stimulation of the parietal receptors, and the presence of a phrenic supply to the central diaphragmatic pleura explains the referral of pain from diaphragmatic pleurisy to the shoulder tip. Other pleural pain is referred to the chest wall.

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# FUNCTIONS OF THE LUNG

A. GORDON LEITCH

The principal functions of the lungs are to add oxygen ( $O_2$ ) to, and remove carbon dioxide ( $CO_2$ ) from, pulmonary arterial blood. Achievement of these functions is reflected by the maintenance of the partial pressures of these gases in systemic arterial blood within the normal ranges, i.e.  $P_{aO_2}$  10.5–13.5 kPa (80–100 mmHg) and  $P_{aCO_2}$  4.8–6.0 kPa (36–45 mmHg). Normality of arterial blood gas tensions is maintained by the efficient transfer of gas from the alveoli through the alveolar membrane to the mixed venous blood that passes through the pulmonary capillaries. There are thus three components contributing to the process of gas exchange.

1 *Ventilation*: movement of gas in and out of the lungs is provided by their bellows' action and must be adequate in volume and appropriate in distribution to perfused alveoli.

2 *Perfusion*: the output of mixed venous blood from the right ventricle must also be adequate in volume and appropriate in distribution to capillaries perfusing ventilated alveoli.

3 *Diffusion*: where gas and blood are brought into contact across the alveolar–capillary membrane, there should be no significant impediment to the diffusion of gases between them.

Ventilation and perfusion are remarkably integrated in health by a series of complex mechanisms, and the whole process of pulmonary gas exchange is achieved with the minimum expenditure of energy by the respiratory and cardiovascular systems.

## Ventilation

Pulmonary ventilation, or the mass movement of gas up and down the bronchial tree, depends on the rhythmic inflation and deflation of the lungs. Contraction of the intercostal muscles and of the diaphragm causes an upward and outward movement of the ribs and flattening of the diaphragm during quiet inspiration. During vigorous breathing the accessory muscles of respiration (the sternomastoids, the scaleni, the pectorals and the latis-

simus dorsi) also come into play. Expiration is essentially passive but may be assisted during vigorous breathing by contraction of the abdominal muscles. Contraction of the inspiratory muscles lowers the intrathoracic and alveolar pressures so that air flows from atmospheric pressure at the mouth or nose to the subatmospheric pressures prevailing in the alveoli. During expiration the elastic recoil of the chest wall and lungs raises intrathoracic and alveolar pressures so that gas flow is reversed. The rhythmicity, rate and depth of respiration are controlled by the respiratory centre with its numerous inputs to ensure that appropriate alveolar ventilation is achieved with minimal energy cost [1].

## Minute ventilation

The minute ventilation, the volume of gas moved into ( $\dot{V}_I$ ) or out of ( $\dot{V}_E$ ) the lungs in 1 min, can be measured by a variety of techniques [2]; in normal resting subjects at sea level it is about 6–10 L/min (measured at body temperature and pressure when saturated with water, BTPS) and is related to body size. Trained athletes can achieve a minute ventilation of up to 200 L/min [3] during exercise but untrained individuals are unlikely to achieve values higher than 100 L/min. The normal frequency of breathing in adults at rest is 8–18 breaths/min and the volume of gas moved in and out of the lungs with each breath, the tidal volume ( $V_T$ ), is therefore about 500 mL.

## Anatomical dead space

Not all of the tidal volume contributes to gas exchange since at the end of inspiration some of it fills the conducting airways (where no gas exchange occurs) and the rest has mixed with the gas occupying the alveoli where gas exchange occurs (Fig. 2.1). The volume of the conducting airways where gas exchange does not occur is called the anatomical dead space and is about 150 mL in an average person. The anatomical dead space is decreased 60% by tracheostomy [4].



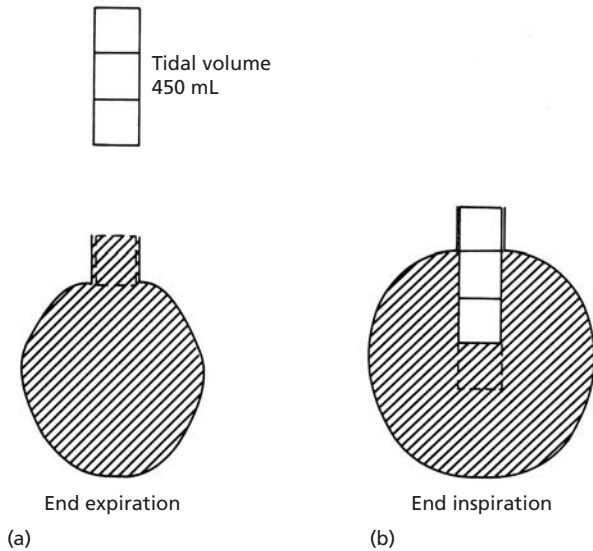


Fig. 2.1 Anatomical dead space. A tube (the conducting airways) leads into a balloon (the alveoli). At the end of expiration (a) the tube is filled with 150 mL of alveolar gas. At the end of inspiration (b), with a tidal volume of 450 mL, the alveoli receive the 150 mL of alveolar gas plus 300 mL of air, and 150 mL of air then occupies the conducting airways. Each block then represents 150 mL. (Modified from Comroe *et al.* [5].)

Anatomical dead space is measured by continuous analysis of the nitrogen ( $N_2$ ) concentration in the expired gas and simultaneous measurement of expired volume.  $N_2$  is used because it does not take part in gas exchange. By means of an  $N_2$  meter a single expiration is monitored following a deep breath of  $O_2$  (Fig. 2.2). The first part of the record at the beginning of expiration represents pure dead space gas in which no  $N_2$  is present. This is followed by a short phase of rapidly rising  $N_2$  concentration, where mixed dead space gas and alveolar gas is being expired, and finally by the pure alveolar sample, which reflects the degree of dilution of alveolar  $N_2$  by the  $O_2$ . If no mixing occurred in the airways the rise in  $N_2$  concentration would occur abruptly as a square front and the anatomical dead space would be the amount expired at this point. The theoretical situation of a square front can be determined by the method of Fowler, which divides the rising phase of the curve into two equal parts; this gives the anatomical dead space [5].

The simplified situation illustrated in Fig. 2.1 does not occur in practice for the tidal volume moves with a cone rather than a square front, thus partly explaining the occurrence of gas exchange when the lungs are ventilated at high frequencies and with tidal volumes less than the anatomical dead space (high-frequency ventilation) [6].

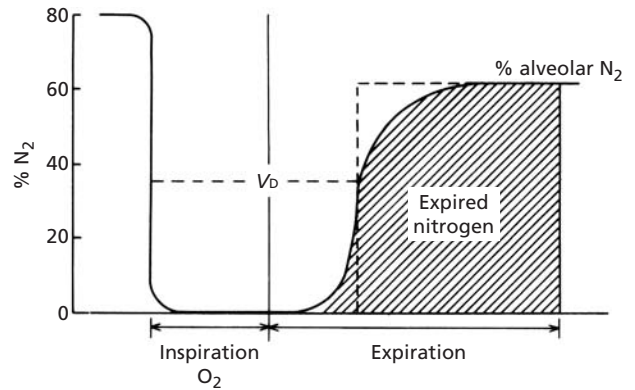


Fig. 2.2 Estimation of dead space by single-breath analysis; see text for explanation. (Modified from Comroe *et al.* [5].)

### Physiological dead space and alveolar ventilation

The physiological dead space ( $V_D$ ) is the volume of gas in the lungs that takes no part in gas exchange. It includes the anatomical dead space and the alveolar dead space, i.e. the volume of gas in alveoli that behaves as if it did not participate in gas exchange. The physiological dead space can be calculated using the Bohr equation [5], where  $P_{ECO_2}$  is the partial pressure of  $CO_2$  in expired gas:

$$V_D = \frac{(P_{ACO_2} - P_{ECO_2}) \times V_T}{P_{ACO_2}} \quad [2.1]$$

assuming that  $P_{ACO_2} = P_{ACO_2}$ . This method simply requires analysis of expired air and of a sample of arterial blood. The ratio of dead space to tidal volume in a physically normal human is about 30%; the dead space is increased in relation to anatomical dead space when there are significant volumes of lung with ventilation disproportionately high in relation to perfusion.

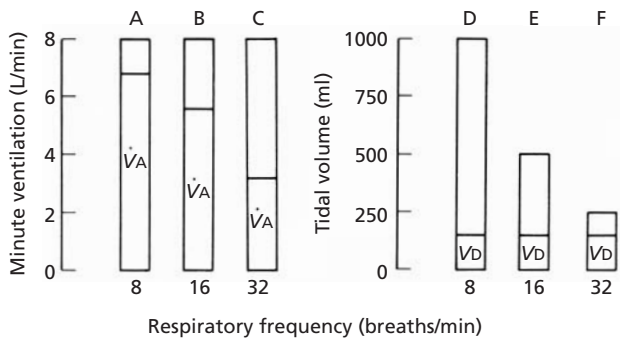
When the physiological dead space is known, the alveolar ventilation ( $\dot{V}_A$ ), i.e. the volume ventilating the gas-exchanging part of the lung, can be calculated. For a given minute ventilation, alveolar ventilation may vary widely depending on the combinations of tidal volume and frequency of breathing employed (Fig. 2.3). Alveolar ventilation may also be derived from knowledge of the concentration of  $CO_2$  in alveolar gas ( $F_{ACO_2}$ ) and the  $CO_2$  output ( $\dot{V}_{CO_2}$ ). Since all the  $CO_2$  in expired gas comes from the alveoli, it follows that  $\dot{V}_{CO_2} = \dot{V}_A \times F_{ACO_2}$ .

This equation can be rewritten in terms of mean alveolar or arterial  $P_{CO_2}$  with the inclusion of a correction factor:

$$\dot{V}_A (\text{BTPS}) = \frac{\dot{V}_{CO_2} (\text{STPD}) \times 0.863}{P_{ACO_2}} \quad [2.2]$$

There is a hyperbolic relationship between alveolar ventilation and  $P_{CO_2}$ , if  $\dot{V}_{CO_2}$  is constant. For example, if  $\dot{V}_A$  doubles,  $P_{ACO_2}$  halves. A decrease in alveolar ventilation causes  $P_{CO_2}$  to rise (as in respiratory failure, see Chapter





**Fig. 2.3** Effect of increasing respiratory frequency at constant minute ventilation (8 L/min) on alveolar ventilation ( $\dot{V}_A$ ). The dead space ( $V_D$ ) is constant and as respiratory frequency increases (D–F) tidal volume falls and a greater proportion of each tidal volume occupies dead space. The resultant changes in alveolar ventilation are shown in (A–C).

24) and an increase in alveolar ventilation causes  $P_{CO_2}$  to fall.

### Alveolar air equation

For practical purposes there are four gases in the alveoli ( $O_2$ ,  $CO_2$ ,  $N_2$ ,  $H_2O$ ) and three in inspired air ( $O_2$ ,  $N_2$ ,  $H_2O$ ). Since neither  $N_2$  nor  $H_2O$  participates in net exchange in the lungs it follows that

$$P_{IO_2} = P_{AO_2} + P_{ACO_2} \text{ or} \quad [2.3]$$

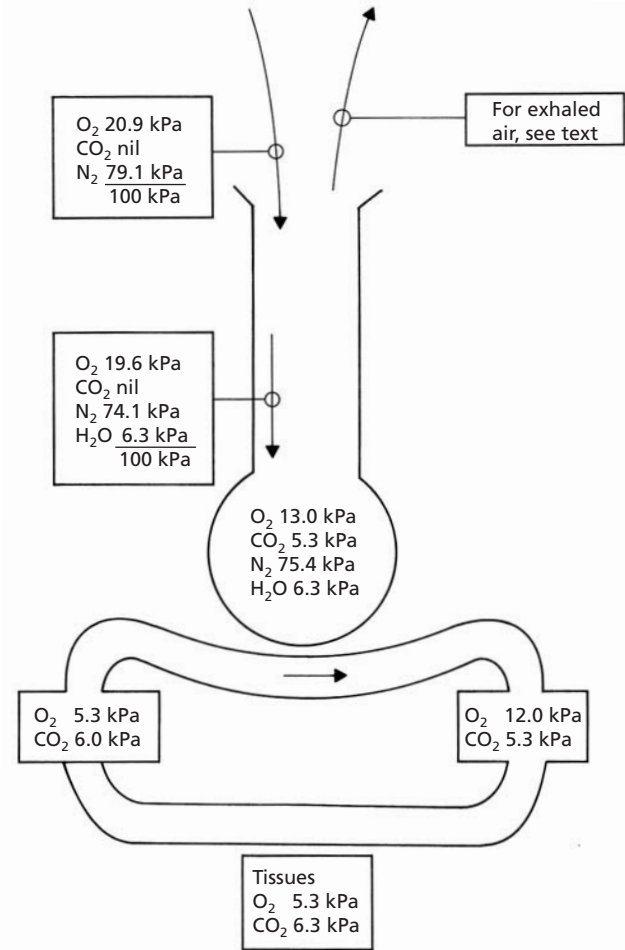
$$P_{AO_2} = P_{IO_2} - P_{ACO_2}$$

This equation is correct if the ratio of  $CO_2$  output/ $O_2$  uptake (respiratory exchange ratio,  $R$ ) equals 1. If  $R$  does not equal 1, then the assumption of constancy of alveolar  $P_{N_2}$  is not justified, for  $O_2$  uptake will exceed  $CO_2$  output with resultant concentration of  $N_2$  molecules in the alveoli and increase in  $P_{O_2}$ . Correction for the known value of  $R$  is then required:

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R} \quad [2.4]$$

Since  $P_{ACO_2} = P_{ACO_2}$  for all practical purposes and  $P_{IO_2}$  is known,  $P_{AO_2}$  can be determined from measurement of arterial blood gas tensions if a value for  $R$  is either assumed or measured.

Since  $P_{AO_2}$  is usually measured at the same time as  $P_{ACO_2}$ , the alveolar–arterial  $P_{O_2}$  difference can be calculated. This is usually less than 2 kPa (15 mmHg) in normal subjects but is increased in disease and serves as a measure of ventilation–perfusion inequality. Determination of the alveolar–arterial  $P_{O_2}$  difference in this way for all blood gas samples is a useful exercise that often serves as a check on the reliability of the sample.



**Fig. 2.4** Approximate partial pressures at various points in the respiratory system (1 kPa = 7.5 mmHg).

### Partial pressures of oxygen and carbon dioxide in the respiratory system

At an atmospheric pressure of 100 kPa (750 mmHg) dry air contains 20.9%  $O_2$ , 0.03%  $CO_2$  and 79.03%  $N_2$  (with minor contributions from other gases), the approximate partial pressures for these gases being 21 kPa (157 mmHg) for  $O_2$ , 0.03 kPa (0.2 mmHg) for  $CO_2$  and 79 kPa (593 mmHg) for  $N_2$ . These partial pressures fall slightly in the airways due to humidification (Fig. 2.4), and  $P_{O_2}$  falls further in the alveoli where  $O_2$  diffuses to pulmonary capillary blood. Since  $O_2$  transport is not perfect in the lungs,  $P_{AO_2}$  is slightly less than  $P_{AO_2}$ ; the  $P_{O_2}$  of blood falls further in the tissues where  $O_2$  is utilized, this change being reflected in the  $P_{O_2}$  of mixed venous blood (Fig. 2.4).

The respiratory control system seems to be set to maintain  $P_{ACO_2}$  at about 5.3 kPa (40 mmHg).  $P_{CO_2}$  is higher in the tissues as a result of metabolic production of  $CO_2$ , which is transported to capillary blood and leads to an increase in the  $P_{CO_2}$  of mixed venous blood. For practical purposes mean alveolar and arterial  $P_{CO_2}$  are identical.

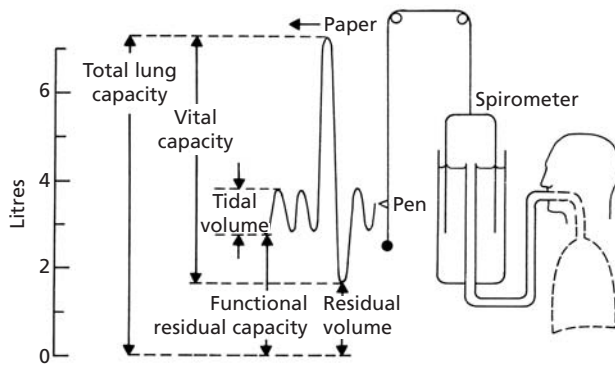


Fig. 2.5 Lung volumes: a water-filled spirometer can be used to provide a trace of lung volumes (see text). The functional residual capacity and residual volume need to be calculated by other methods (see Figs 2.6 & 2.7). (From West [7].)

Finally, the  $P_{O_2}$  and  $P_{CO_2}$  of expired gas reflect expiration of a mixture of inspired air from the dead space and alveolar gas.

### Lung volumes

The static lung volumes can be measured by a simple spirometer (Fig. 2.5). Quiet breathing records the tidal volume ( $V_T$ ), and a maximal inspiration followed by a maximal expiration defines the vital capacity (VC). The inspiratory reserve volume (IRV) and expiratory reserve volume (ERV) can be calculated from such a tracing.

The functional residual capacity (FRC), the volume of gas remaining in the lung at the end of a quiet expiration, and the residual volume (RV), the volume of gas remaining in the lung after a maximal expiration, can be determined by one of two methods. With the helium (He) dilution method [8] the subject is connected, at the end of a quiet expiration, to a closed spirometer containing a known concentration and volume of He, a gas that is almost insoluble in blood. After a period of equilibration, the concentration of He in the lungs and the spirometer stabilizes at a new level and the FRC can be calculated as shown in Fig. 2.6. Alternatively, the FRC can be measured with the subject sitting in a body plethysmograph and attempting to breathe against a closed mouthpiece while the pressures in the mouthpiece and the plethysmograph are recorded (Fig. 2.7). As the subject breathes in, the gas in the lung expands, which increases lung volume and simultaneously decreases plethysmograph volume with a resultant rise in plethysmograph pressure. The FRC is calculated using Boyle's law:

$$P_1 V = P_2 (V + \Delta V) \quad [2.5]$$

where  $P_1$  is resting mouth pressure,  $P_2$  is pressure on inspiration,  $V$  is FRC and  $\Delta V$  is the rise in lung volume on inspiration.  $\Delta V$  can be determined from the increase in plethysmograph pressure based on earlier volume calibra-

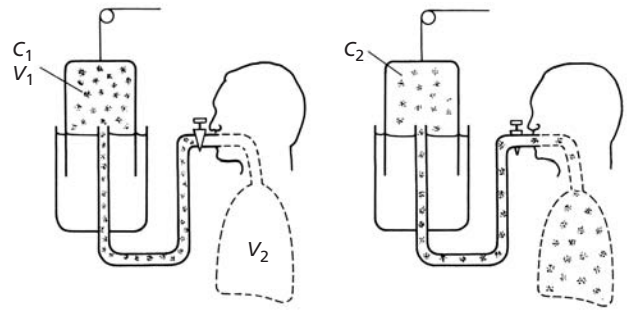


Fig. 2.6 Measurement of functional residual capacity (FRC). Before equilibration a known volume of a known concentration of helium is in the spirometer. After equilibration, when the helium concentration is constant at a new level, the FRC ( $V_2$ ) can be calculated from the following equation:  $C_1 \times V_1 = C_2 \times (V_1 + V_2)$ . (Modified from West [7].)

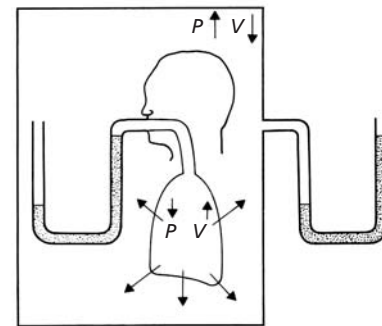


Fig. 2.7 Measurement of functional residual capacity (FRC) using a body plethysmograph. The subject makes an inspiratory effort against a closed airway with a resultant fall in airway pressure, rise in lung volume and rise in the box pressure. FRC can be calculated using Boyle's law (see text). (Modified from West [7].)

tions of the plethysmograph,  $P_1$  and  $P_2$  are both measured and thus  $V$  or FRC can be calculated.

The plethysmographic method measures the total volume of gas being compressed in the lungs and in normal subjects this agrees well with values of FRC determined by He dilution. In some patients, e.g. with lung cysts or emphysema, lung gas may equilibrate poorly with the He in the dilution method ('trapped gas') and then FRC determined in the plethysmograph exceeds that using He dilution. However, if the He equilibrium phase is prolonged, agreement between the two methods improves [9].

When FRC has been determined, it is easy to compute RV and total lung capacity (TLC) (Fig. 2.5). An alternative method of determining TLC is from measurements derived from postero-anterior and lateral chest radiographs [10–12].

## Perfusion: the pulmonary circulation

At rest the right ventricle pumps blood through the pulmonary circulation at a rate of about 5L/min. The mean pulmonary artery pressure is only about 2kPa (15mmHg), and since blood flow = driving pressure / resistance the resistance in the pulmonary circulation is only about one-tenth that of the systemic circulation. The pulmonary circulation has a remarkable reserve capacity, which is due to the great distensibility of the pulmonary vasculature and also to recruitment of capacitance vessels not in use.

## Control of pulmonary circulation

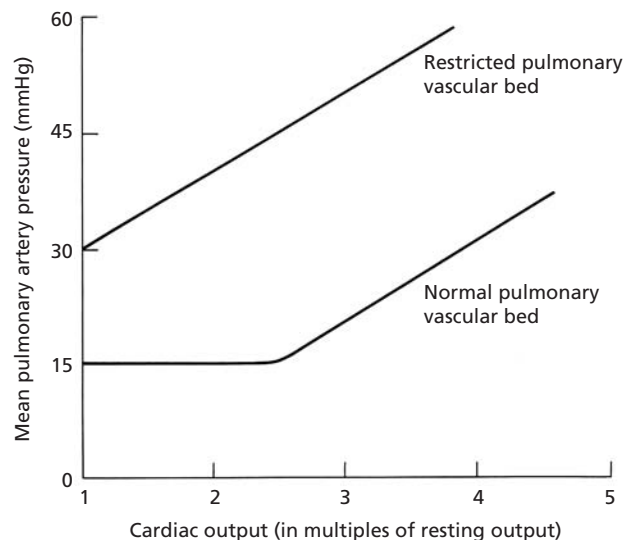
There is no known effective nervous control over pulmonary vascular resistance [13]. However, an efficient regulatory mechanism exists in the normal lung based on the partial pressure of  $O_2$  and  $CO_2$  in the blood. Hypoxia increases pulmonary vascular resistance [14,15], possibly by a direct effect of  $PAO_2$  on pulmonary vessels [16], an observation of major importance in understanding the pathophysiology of respiratory failure. Similarly, a fall in local  $PACO_2$  after obstruction of a pulmonary artery results in a 25% reduction in local ventilation [17], suggesting the existence of a local homeostatic mechanism, based on the prevailing partial pressures of  $O_2$  and  $CO_2$ , that operates to match ventilation and perfusion.

## Variation in pulmonary circulation

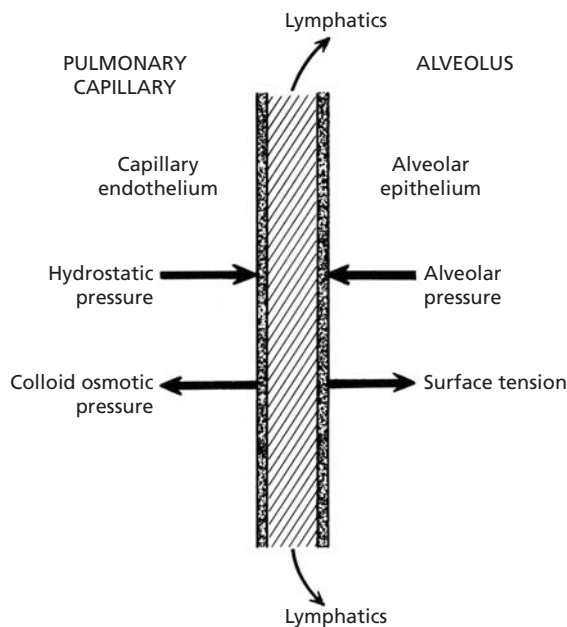
The pulmonary circulation is increased in exercise, thyrotoxicosis, fever, anaemia and left-to-right shunts, and decreased in cardiac failure and right-to-left shunts. The fact that the pulmonary circulation may double without a rise in pulmonary vascular pressure only holds true if the resistance is not increased [18] (Fig. 2.8). Pulmonary vascular resistance may be increased when there is a reduction in the number and calibre of pulmonary vessels, such as may occur in extensive lung resection, multiple embolism, pulmonary vasculitis, primary pulmonary hypertension and, most commonly, the pulmonary attrition associated with chronic bronchitis and emphysema.

## Pulmonary oedema

The pressures operating on a pulmonary capillary are shown in Fig. 2.9. Because pulmonary capillary pressure is low and less than colloid osmotic pressure, fluid tends to be drawn into the capillaries. When pressure rises in the capillaries, as seen in mitral stenosis and left ventricular failure, it may exceed colloid osmotic pressure and lead to transudation of fluid across the capillary membrane into the interstitium and the alveoli, resulting in pulmonary



**Fig. 2.8** Mean pulmonary artery pressure responses to increasing cardiac output. The normal pulmonary vascular bed can tolerate an increase in cardiac output to 250% before pulmonary artery pressure rises. In patients with a restricted pulmonary vascular bed, pulmonary artery pressure rises sharply with even a small increase in cardiac output. (From Robin & Gaudio [18].)



**Fig. 2.9** Forces acting across an alveolar-capillary membrane.

oedema. Not all cases of mitral stenosis with a raised pulmonary artery pressure have pulmonary oedema and this may be due to a compensatory rise in interstitial fluid pressure that prevents transudation from the pulmonary capillaries [19]. Pulmonary oedema may also occur when the permeability of the alveolar capillary membrane is increased, allowing the passage of protein-rich material

into the interstitium and alveolar spaces, as occurs in adult respiratory distress syndrome [20–23].

### Measurement of pulmonary blood flow

Pulmonary blood flow [24] can be measured by the direct Fick method, using the following equation:

$$\text{Cardiac output or blood flow (L/min)} = \frac{\text{O}_2 \text{ uptake (mL/min)}}{\text{arterial-venous O}_2 \text{ difference (mL/L)}} \quad [2.6]$$

Other methods include the indirect Fick method using nitrous oxide [25] and the dye-dilution method [26].

### Distribution of ventilation and perfusion and $\dot{V}_A/\dot{Q}$ relationships

#### Ventilation-perfusion ratios

The commonest cause of failure to oxygenate mixed venous blood adequately is an imbalance between alveolar ventilation ( $\dot{V}_A$ ) and pulmonary capillary blood flow ( $\dot{Q}$ ) [27,28]. Even in normal lungs, ventilation and perfusion are not distributed evenly as a consequence of gravitational effects and the pleural pressure gradient [29,30]. After inhalation of  $^{133}\text{Xe}$  gas, measurement of radioactivity over different regions of the chest demonstrates that, during normal breathing in the erect position, ventilation increases from the apex to the base of the lung [31] (Fig. 2.10). Similarly if  $^{133}\text{Xe}$  is injected into the bloodstream it passes into alveolar gas because of its low solubility in blood and its concentration in the alveoli, which reflects local pulmonary blood flow, can also be measured. Again, blood flow increases from apex to base of the lung (Fig. 2.10), with remarkably little blood flow reaching the apex of the lung [31]. The regional differences in circulation are much more marked than the regional differences in ventilation.

Studies with an isolated lung preparation have resulted in a scheme that satisfactorily explains the distribution of blood flow in the normal lung in the upright position [32] (Fig. 2.11). The lung is divided, from the top down, into three zones by the relative magnitudes of the pulmonary arterial, venous and alveolar pressures. In zone I, which extends to 4 cm below the apex, arterial pressure is less than alveolar and there is no flow, presumably because collapsible vessels are directly exposed to alveolar pressure. In zone II, the arterial pressure exceeds alveolar pressure, which in turn exceeds venous pressure. Here the vessels behave as Starling resistors (i.e. collapsible tubes surrounded by a variable pressure chamber) and flow is determined by the difference between arterial pressure (which is increasing down the lung) and alveolar pressure (which is constant). In the bottom zone, zone III, venous pressure exceeds alveolar and flow is determined by the

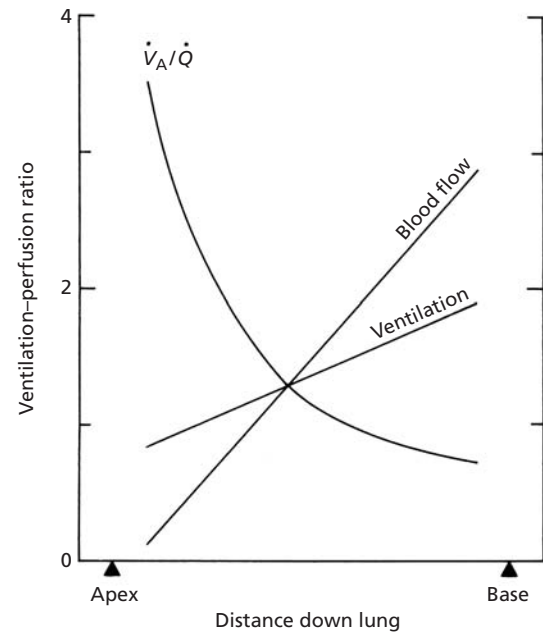
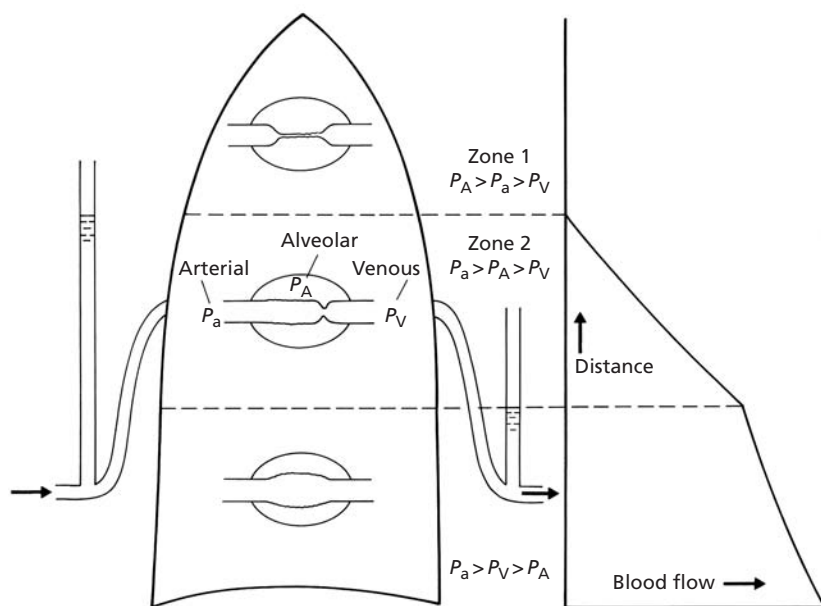


Fig. 2.10 Simplified graph based on  $^{133}\text{Xe}$  studies of ventilation and perfusion showing the relative distribution of ventilation, perfusion and ventilation-perfusion ratios from the apex to the base of the upright lung.

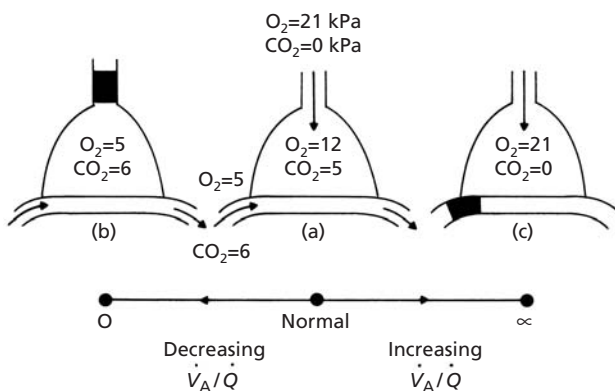
usual arterial-venous pressure difference. Flow increases down this zone because the transmural pressure of the vessels increases, increasing the calibre of the vessels. A fourth zone, at the extreme lung bases, has been shown to have reduced blood flow for reasons not fully understood but possibly due to increased interstitial pressure around small vessels [33,34].

From such studies it is obvious that the ratio of ventilation to perfusion ( $\dot{V}_A/\dot{Q}$  ratio) changes from top to bottom of the lung even in health. The apex is relatively well ventilated with respect to perfusion and has a high  $\dot{V}_A/\dot{Q}$  ratio, whereas the opposite applies to the base of the lung which has a low  $\dot{V}_A/\dot{Q}$  ratio. This well-ordered gradient of  $\dot{V}_A/\dot{Q}$  ratios in the healthy lung maintains normal gas tensions in arterial blood. However, in lung disease disturbance of the normal balance of  $\dot{V}_A/\dot{Q}$  ratios in the lung results in hypoxaemia.

The consequences of abnormal  $\dot{V}_A/\dot{Q}$  ratios can be appreciated by considering the ranges of  $\dot{V}_A/\dot{Q}$  ratios that are possible. Figure 2.12(a) shows a normal alveolus with average  $\text{O}_2$  and  $\text{CO}_2$  tensions. Figure 2.12(b) shows an alveolus receiving no ventilation that has a  $\dot{V}_A/\dot{Q}$  ratio of zero and gas tensions approximating those of mixed venous blood. Figure 2.12(c) shows an alveolus with no perfusion, a  $\dot{V}_A/\dot{Q}$  ratio of infinity and gas tensions similar to those of air. It follows that alveoli in the apex of the normal lung with a high  $\dot{V}_A/\dot{Q}$  ratio have a higher  $P_{\text{O}_2}$  and a lower  $P_{\text{CO}_2}$  than alveoli in the base of the lung where the  $\dot{V}_A/\dot{Q}$  ratio is low (see Fig. 2.10). Since most of the blood



**Fig. 2.11** Topographical distribution of blood flow in the lung; see text for explanation. (From West *et al.* [32] with permission.)



**Fig. 2.12** Effect of changes in the  $\dot{V}_A/\dot{Q}$  ratio on alveolar  $P_{O_2}$  and  $P_{CO_2}$  (see text). 1 kPa = 7.5 mmHg. (Modified from West [35].)

passes through the base of the lung whereas ventilation is more uniform, it follows that there will be a difference between mean alveolar and arterial  $P_{O_2}$ :  $P_{aO_2}$ , determined more by the tensions prevailing in the gas-exchanging units in the bottom of the lung, is 0.6 kPa (4.5 mmHg) lower on average than  $P_{AO_2}$ .

When the number of extreme  $\dot{V}_A/\dot{Q}$  values increases, as in most pulmonary diseases,  $P_{aO_2}$  may fall further. Units with a low  $\dot{V}_A/\dot{Q}$  ratio add less  $O_2$  to the pulmonary capillary blood than normal units; units with a high  $\dot{V}_A/\dot{Q}$  ratio add little more  $O_2$  to blood than normal units, a finding explained by the non-linear shape of the  $O_2$  dissociation curve (see Fig. 2.15). A fall in  $P_{aO_2}$  from normal produces a greater fall in  $O_2$  content than a rise from normal produces an increase. The  $O_2$  content of mixed blood from alveoli with such a range of  $\dot{V}_A/\dot{Q}$  abnormalities tends to reflect the contribution from low  $\dot{V}_A/\dot{Q}$  alveoli, and arterial  $O_2$  content and  $P_{aO_2}$  falls as a result.  $P_{aCO_2}$  should also rise in

such a situation and for similar reasons. However, the central chemoreceptors, which sense  $P_{aCO_2}$ , respond to an increase in  $P_{aCO_2}$  by increasing alveolar ventilation and restoring it to normal.

That  $P_{aCO_2}$  can be restored to normal by an increase in alveolar ventilation while  $P_{aO_2}$  remains low again reflects differences in the  $O_2$  and  $CO_2$  dissociation curves (see Figs 2.15 & 2.19). The latter is linear and therefore a rise in alveolar ventilation increases the  $CO_2$  output of lung units with high as well as low  $\dot{V}_A/\dot{Q}$  ratios. However,  $O_2$  uptake only increases significantly in those units with a low  $\dot{V}_A/\dot{Q}$  ratio, little further increase being possible in those with high  $\dot{V}_A/\dot{Q}$  ratios.

The multiple inert gas technique [36,37] has now made it possible to characterize ventilation-perfusion ratios in more detail in health and disease. A solution containing six inert gases ( $SF_6$ , ethane, cyclopropane, halothane, ether and acetone) is slowly infused into a peripheral vein and, after a steady state of elimination by the lungs has been achieved, the concentrations are measured in the arterial blood and expired gas by gas chromatography. As the gases have different solubilities in blood, they partition themselves between blood and gas according to the  $\dot{V}_A/\dot{Q}$  ratio of the lung unit. It is thus possible to derive a virtually continuous distribution of  $\dot{V}_A/\dot{Q}$  ratios that is consistent with the measured pattern of elimination. Figure 2.13(a) shows such a distribution in a healthy subject, where most of the ventilation and perfusion occurred in lung units with a  $\dot{V}_A/\dot{Q}$  ratio of about 1. In contrast, Fig. 2.13(b) shows the findings in a subject with chronic bronchitis and emphysema in whom large amounts of perfusion occurred in units with a low  $\dot{V}_A/\dot{Q}$  ratio, constituting a *physiological shunt* with resulting hypoxaemia [39]. Similarly, in patients with pulmonary



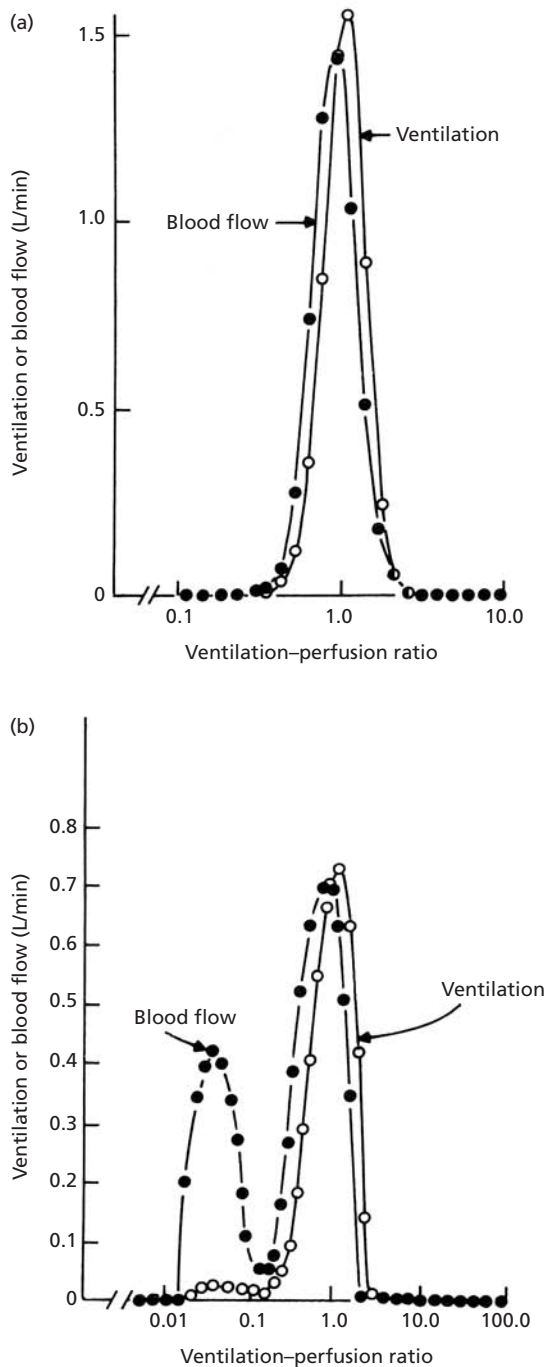


Fig. 2.13 Distribution of ventilation-perfusion ratios measured by the multiple inert gas technique in a normal subject (a) and in a patient with chronic bronchitis and emphysema (b). (From West [38] with permission.)

embolism [40] the associated hypoxaemia can be shown to be due to excessive shunt, although the mechanisms underlying this are unclear. The inert gas elimination technique has now been used to study ventilation-perfusion ratio abnormalities in a range of diseases, including interstitial pulmonary fibrosis [41], asthma [42],

pulmonary vascular diseases [43] and acute respiratory failure [44].

In summary, different  $\dot{V}_A/\dot{Q}$  ratios exist in the normal lung and are reflected in the presence of an alveolar-arterial  $P_{O_2}$  difference. This may be markedly increased in disease. In disease, a large physiological dead space (wasted ventilation) represents an increase in the population of alveoli with high  $\dot{V}_A/\dot{Q}$  ratios; a large physiological shunt represents an increase in the population of alveoli with low  $\dot{V}_A/\dot{Q}$  ratios.

### Measurement of physiological shunt

It is assumed that all of the fall in  $P_{aO_2}$  can be attributed to the addition of mixed venous blood to end-capillary blood. The shunt  $\dot{Q}_s/\dot{Q}_T$  can be calculated using the following equation:

$$\dot{Q}_s/\dot{Q}_T = \frac{C_{CO_2} - C_{aO_2}}{C_{CO_2} - C_{vO_2}} \quad [2.7]$$

where  $C$  represents  $O_2$  content;  $c$ , end-capillary (pulmonary);  $a$ , arterial; and  $v$ , mixed venous. The  $O_2$  content of end-capillary blood is calculated from the  $P_{aO_2}$  and the  $O_2$  dissociation curve [5].

### Causes of hypoxaemia

$\dot{V}_A/\dot{Q}$  abnormality is the commonest cause of hypoxaemia in human lung disease. It must be differentiated from other causes, which include the following.

**1 Hypoventilation:** if alveolar ventilation is halved,  $P_{aCO_2}$  will double. It follows from the alveolar air equation that alveolar and hence arterial  $P_{O_2}$  will fall.

**2 True shunt:** in normal humans, a very small but significant shunt occurs as a result of drainage of part of the bronchial circulation into pulmonary venous blood and also the drainage of coronary venous blood into the left ventricle through the Thebesian veins. In disease, for example pulmonary arteriovenous fistula, larger true shunts may occur and may be revealed by inability to achieve a high arterial  $O_2$  tension when 100%  $O_2$  is breathed, since shunted blood is not exposed to the resulting high  $P_{aO_2}$ .

### Diffusion

#### Factors affecting gaseous diffusion in the lung

By the time inspired gas reaches the alveoli, movement of gas molecules is determined almost entirely by diffusion; this is so efficient that alveolar gas can be considered uniform without the existence of any intra-alveolar gas concentration gradients. Gas transfer across the alveolar wall into the pulmonary capillary involves passage of molecules through the epithelial cell, basement

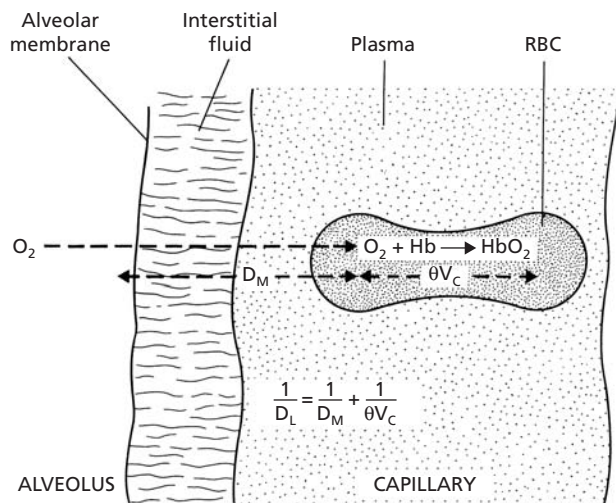


Fig. 2.14 Components of the diffusing capacity of the lung.

membranes, the interstitium and the endothelial cell and thence through plasma and the red cell membrane to the interior of the red cell (Fig. 2.14). The rate of gas transfer in the lung depends on:

- 1 surface area available for transfer;
- 2 thickness of the alveolar–capillary membrane;
- 3 solubility and molecular weight of the gas concerned:  $\text{CO}_2$  has a similar molecular weight to  $\text{O}_2$  but diffuses about 20 times more rapidly because of its high solubility.

The diffusing capacity ( $D_L$ ) for a gas within the lung can be expressed by the following equation:

$$D_L = \frac{\dot{V}_{\text{gas}}}{P_1 - P_2} \quad [2.8]$$

where  $\dot{V}_{\text{gas}}$  is the volume of gas transferred in unit time and  $P_1$  and  $P_2$  are the pressures of gas in alveoli and capillary blood respectively. Thus the diffusing capacity for carbon monoxide (CO) is defined as:

$$D_{\text{LCO}} = \frac{\dot{V}_{\text{CO}}}{P_1 - P_2} \quad [2.9]$$

and since the  $P_{\text{CO}}$  in capillary blood is usually so small that it can be neglected, Eqn 2.9 can be simplified to:

$$D_{\text{LCO}} = \frac{\dot{V}_{\text{CO}}}{P_{\text{ACO}}} \quad [2.10]$$

It is now agreed that the normal alveolar membrane causes no appreciable impediment to  $\text{O}_2$  diffusion from alveoli to blood [45]. Theoretically, diffusion may be influenced by intra-alveolar oedema or exudate, interstitial oedema, exudate or fibrosis, thickening of the alveolar wall, thickening of the capillary membrane or increase of the intracapillary path for  $\text{O}_2$  due to capillary dilatation. Pulmonary diffusing capacity measures the impediment produced by all the factors involved in transfer of  $\text{O}_2$  to the erythrocyte; for the whole lung the  $\dot{V}_A/\dot{Q}$  ratio is probably

the most important factor. In high  $\dot{V}_A/\dot{Q}$  areas, ventilation is wasted and little or no gas is exchanged in spite of an intact transfer surface leading to a decrease in  $D_{\text{LCO}}$  for the lungs as a whole. There are no methods at present available that can distinguish between  $\dot{V}_A/\dot{Q}$  abnormality and impaired diffusion [46] but the general consensus of opinion is that  $\dot{V}_A/\dot{Q}$  disturbances are more important than thickening of the alveolar membrane [47,48].

### Components of $D_{\text{LCO}}$

A significant part of the diffusion pathway lies between the capillary endothelium and the red cell (see Fig. 2.14). An additional factor that influences diffusion of  $\text{O}_2$  is the rate of the chemical reaction that combines  $\text{O}_2$  with haemoglobin within the red cell. The diffusing capacity can thus be considered as having two components, the first reflecting transfer from the alveolus to the interior of the red cell and the second concerned with the combination of  $\text{O}_2$  with haemoglobin [49]. These two components can be expressed as the inverse of their effective diffusing capacities in the following equation:

$$\frac{1}{D_L} = \frac{1}{D_m} + \frac{1}{\Theta V_c} \quad [2.11]$$

where  $D_m$  is the membrane component of resistance to diffusion,  $\Theta$  describes the rate of reaction of  $\text{O}_2$  with haemoglobin and  $V_c$  is the volume of capillary blood.  $\Theta V_c$  is thus the effective diffusion capacity for the rate of reaction of  $\text{O}_2$  with haemoglobin. These two separate components of the resistance to diffusion can be measured by special methods [49] and are approximately equal.

### Significance of changes in $D_{\text{LCO}}$

From Eqn 2.11 it follows that changes in capillary blood volume can influence  $D_L$ , which in consequence is decreased in anaemia and increased in polycythaemia, left-to-right cardiac shunts, exercise and the supine position. A low value for  $D_L$  may also indicate:

- 1 small lungs or lesions reducing lung volumes, e.g. pneumonectomy;
- 2 obstructive lung disease with non-uniform  $\dot{V}_A/\dot{Q}$  distribution;
- 3 emphysema with decrease of total gas-exchanging area;
- 4 interstitial lung disease with altered ventilation, perfusion and probably diffusion in many areas.

$D_L$  is of particular value in defining abnormality and response to treatment in the interstitial lung diseases, which include fibrosing alveolitis, sarcoidosis, asbestosis, farmer's lung, collagen diseases of the lung and polyarteritis nodosa. In some conditions, e.g. sarcoidosis, changes in  $D_L$  may be a more sensitive indicator of response to treatment than radiological changes.  $D_L$  has also been used (after adjustment for the ventilated lung

volume to give the  $K_{CO}$  as a measure of fresh pulmonary haemorrhage in Goodpasture's syndrome, where increases in  $K_{CO}$  are attributed to uptake of CO by sequestered haemoglobin in the lung [50].

### Methods of measuring $D_L$

Ideally, the gas used for estimations of  $D_L$  should be  $O_2$ , and the relevant equation is:

$$D_{LO_2} = \frac{\dot{V}_{O_2}}{P_{AO_2} - P_{CO_2}} \quad [2.12]$$

where  $P_{CO_2}$  is mean pulmonary capillary pressure. Such measurements are possible [51,52], although because of the difficulty in measuring  $P_{CO_2}$  it is more usual in routine practice to measure  $D_{LCO}$  [48,53,54].

CO has a great affinity for haemoglobin (240 times that of  $O_2$ ). At low alveolar pressures of CO only a small proportion of haemoglobin is saturated with CO during passage through the pulmonary capillaries, so that the  $P_{CO}$  in the blood is small relative to the  $P_{CO}$  in the alveoli. The relatively large difference between  $P_{ACO}$  and  $P_{CCO}$  makes the CO method for measuring diffusion capacity more accurate and reproducible than the  $O_2$  method. In essence the techniques employed require measurement of the uptake of CO ( $\dot{V}_{CO}$ ) and  $P_{ACO}$  by means of an infrared analyser,  $P_{CCO}$  is assumed to be zero and the values are entered into Eqn 2.10.

Simultaneous measurement of alveolar volume by He dilution also allows determination of the transfer coefficient ( $D_{LCO}/V_A$ , or  $K_{CO}$ ), which may be a more appropriate indicator of the effectiveness of gas exchange when lung volume has been lost because of either disease or surgery. Although steady-state measurements of  $D_{LCO}$  are possible [55], they are less reproducible than the single-breath method that is currently the procedure of choice.

## Oxygen and carbon dioxide transport in blood

### Oxygen transport

$O_2$  is carried in blood in two forms, dissolved and in combination with haemoglobin.

#### Dissolved oxygen

For every 1 kPa (7.5 mmHg) of partial pressure, 0.023 mL  $O_2$  is dissolved in 1 dL of blood; arterial blood with a  $P_{AO_2}$  of 13 kPa (97.5 mmHg) therefore contains 0.3 mL/dL, a small amount in relation to the volume of  $O_2$  carried by haemoglobin.

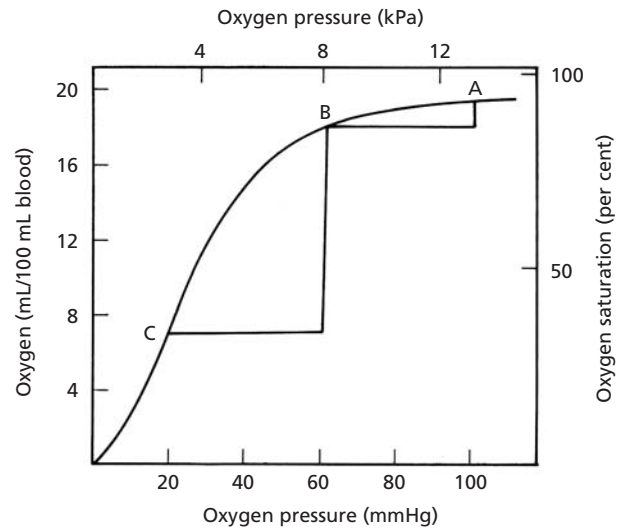


Fig. 2.15 Oxygen dissociation curve: (A, B) a fall in  $P_{AO_2}$  of 5 kPa (40 mmHg) from 13 to 8 kPa (100 to 60 mmHg) produces only a small change in oxygen saturation or content; (B, C) a similar fall in  $P_{AO_2}$  from 8 to 3 kPa (60 to 20 mmHg) produces a much greater change in saturation.

### Bound oxygen: the haemoglobin dissociation curve

The majority of  $O_2$  in the blood is carried bound to haemoglobin, each haemoglobin molecule binding four  $O_2$  molecules. The successive binding of these four  $O_2$  molecules and associated changes in the structure of haemoglobin determine the shape of the haemoglobin dissociation curve (Fig. 2.15), which relates the  $O_2$  content of blood (or percentage saturation of haemoglobin) to the partial pressure of  $O_2$ . In this reaction 1.39 mL of  $O_2$  combines with 1 g of haemoglobin, so that blood with a haemoglobin concentration of 15.2 g/dL that is fully saturated with  $O_2$  contains 21 mL/dL of bound  $O_2$  (cf dissolved  $O_2$ , 0.3 mL/dL).

The shape of the haemoglobin dissociation curve has several important physiological consequences.

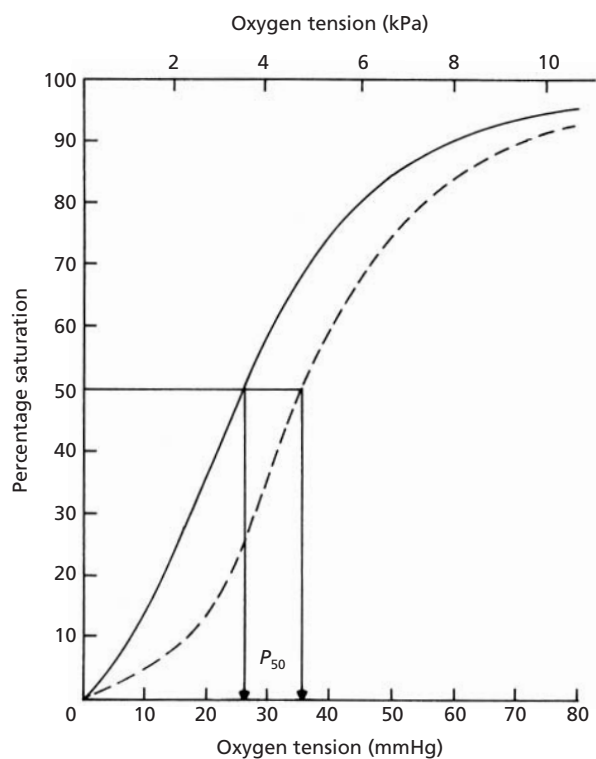
1 At normal  $P_{AO_2}$  haemoglobin is about 95% saturated. It follows that a rise in  $P_{AO_2}$  brought about by hyperventilation or breathing  $O_2$ -rich gas makes little difference to the  $O_2$  content of the blood. Only a small increase in bound  $O_2$  and a partial pressure-dependent rise in dissolved  $O_2$  is possible.

2 A fall in  $P_{AO_2}$  from an initially high level has little effect on the arterial  $O_2$  content or saturation, whereas a similar fall in  $P_{AO_2}$  in the middle range produces striking changes in content or saturation (see Fig. 2.15).

### Factors affecting the position of the haemoglobin dissociation curve

A shift of the  $O_2$  dissociation curve to the right (Fig. 2.16) has consequences for the delivery of  $O_2$  to the tissues





**Fig. 2.16** Effect of a rightward shift of the oxygen dissociation curve on oxygen affinity: for a given  $P_{O_2}$  the haemoglobin is less saturated or the  $P_{O_2}$  at 50% saturation ( $P_{50}$ ) is higher.

where  $P_{O_2}$  is low. The resultant decrease in  $O_2$  affinity of the haemoglobin means that, for a given  $P_{O_2}$ , the haemoglobin is less saturated and has therefore released more of the bound  $O_2$ . Any decrease in  $O_2$  affinity is likely to be beneficial for  $O_2$  delivery to the tissues when  $P_{aO_2}$  is normal since, in this situation at the upper end of the dissociation curve, the reverse effect (that  $O_2$  is also taken up less readily in the lungs) is minimal. However, in hypoxia the decreased  $O_2$  affinity limits the uptake of  $O_2$  in the lungs as much as it enhances delivery to the tissues and no advantage accrues.

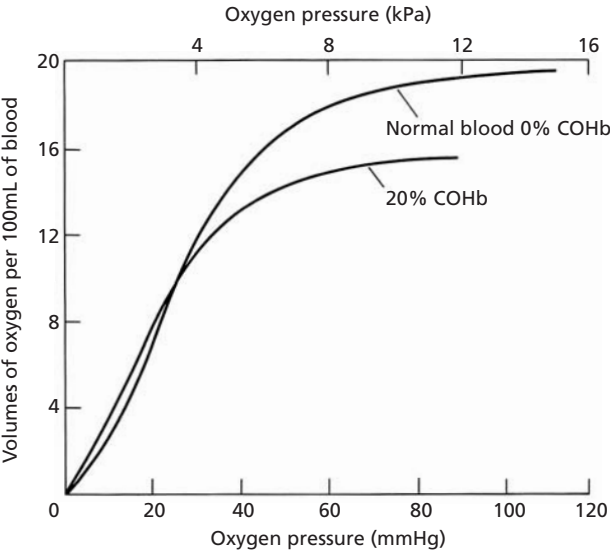
$O_2$  affinity can be determined *in vivo* and *in vitro* by determining the  $P_{50}$  (the  $P_{O_2}$  at which 50% of the haemoglobin is saturated), the normal value for human blood being 3.5 kPa (26 mmHg). The  $P_{50}$  is increased with a rightward shift of the dissociation curve or a decrease in  $O_2$  affinity.

The main factors influencing  $O_2$  affinity are listed in Table 2.1. A rise in hydrogen ion concentration (the Bohr effect), temperature or  $P_{CO_2}$  (independent of pH) and 2,3-diphosphoglycerate (2,3-DPG) [56] all shift the curve to the right and decrease  $O_2$  affinity, favouring the release of  $O_2$  in the tissues. 2,3-DPG is formed as a product of glycolysis in the red cell and its production is increased by a rise in red cell intracellular pH, which increases the activity of phosphofructokinase.  $O_2$  and 2,3-DPG are com-

**Table 2.1** Some factors influencing oxygen affinity. (Modified from Cumming & Semple [58].)

Decrease in $O_2$ affinity (shift in $O_2$ dissociation curve to right)	Increase in $O_2$ affinity (shift in $O_2$ dissociation curve to left)
Rise in $[H^+]$ (fall in pH) $P_{CO_2}$ and temperature	Fall in $[H^+]$ , $P_{CO_2}$ and temperature
Increase in red cell DPG, ADP, ATP and inorganic phosphates	Decrease in red cell DPG, ADP, ATP and inorganic phosphates
Anaemia	Stored (banked) blood
Residence at high altitude	Fetal blood  Rise in red cell carboxyhaemoglobin and methaemoglobin

DPG, 2,3-diphosphoglycerate.



**Fig. 2.17** Normal oxygen dissociation curve compared with the dissociation curve in the presence of 20% carboxyhaemoglobin. (Modified from Cumming & Semple [58].)

petitive binders for deoxyhaemoglobin and a rise in 2,3-DPG therefore displaces  $O_2$  and reduces  $O_2$  affinity.

CO has an affinity for haemoglobin 240 times that of  $O_2$ . Small concentrations of CO in inspired air may therefore produce high levels of carboxyhaemoglobin (COHb). Heavy cigarette smokers may have as much as 20% of their haemoglobin as COHb [57]. This has two consequences (Fig. 2.17):

- 1 20% of the haemoglobin is not available for binding  $O_2$ ;
- 2 the haemoglobin dissociation curve is shifted to the left with a resultant increase in  $O_2$  affinity.

In hypoxic bronchitic patients such levels of COHb have been shown to limit exercise tolerance [59] and this prob-

ably reflects the resulting impaired delivery of  $O_2$  to the tissues.

$O_2$  delivery to the tissues is not solely a function of the  $O_2$  affinity of haemoglobin. Considerable reserves of  $O_2$  exist in blood as reflected in a mixed venous  $P_{O_2}$  of 5 kPa (37.5 mmHg) (see Fig. 2.4). Mixed venous  $P_{O_2}$  can fall further in association with increased  $O_2$  delivery to the tissues. In addition, increases in tissue blood flow, dependent on assorted mechanisms one of which is a fall in tissue  $P_{O_2}$ , may increase  $O_2$  delivery. Where increases in blood flow are limited, as in cardiac disease, changes in  $O_2$  affinity may well be important.

### Carbon dioxide transport

$CO_2$  produced in tissue cell mitochondria passes rapidly into the blood where it is carried in three forms: (i) dissolved  $CO_2$ , (ii) bicarbonate and (iii) in combination with haemoglobin and other plasma proteins as carbamino compounds.

#### Dissolved carbon dioxide

The amount of  $CO_2$  dissolved in blood is proportional to  $P_{CO_2}$  and is determined by the solubility coefficient of  $CO_2$  (0.225 mmol/kPa). Therefore, at a  $P_{CO_2}$  of 6 kPa (45 mmHg),  $6 \times 0.225 = 1.35$  mmol/L of  $CO_2$  will be carried as dissolved  $CO_2$ , constituting about 8% of the total  $CO_2$  transported in blood [60].

#### Bicarbonate

About 81% of  $CO_2$  carried by blood is carried as bicarbonate [60]. When  $CO_2$  passes from plasma to red cells, the reaction  $CO_2 + H_2O \rightarrow H_2CO_3$  is catalysed by the red cell enzyme, carbonic anhydrase. Carbonic acid rapidly dissociates to  $H^+$  and  $HCO_3^-$  (Fig. 2.18);  $H^+$  is bound by haemoglobin, which acts as a base, and more  $HCO_3^-$  is generated to preserve the constancy of the dissociation coefficient (law of mass action). As a result  $HCO_3^-$  within the red cells exceeds that in plasma and  $HCO_3^-$  is exchanged for  $Cl^-$  across the red cell membrane according to the Gibbs–Donnan equilibrium that preserves electrical neutrality.  $H^+$  binding to haemoglobin is facilitated by deoxygenation of haemoglobin in the tissues (the Haldane effect), thus increasing the capacity of venous blood to carry  $CO_2$ . The process shown in Fig. 2.18 as occurring in the tissues occurs equally rapidly in reverse in the lungs, where  $CO_2$  passes from capillary blood to the alveoli.

#### Carbamino compounds

About 11% of total  $CO_2$  carried in blood is in the form of carbamino compounds, which are formed by the combination of  $CO_2$  with terminal amino groups in blood

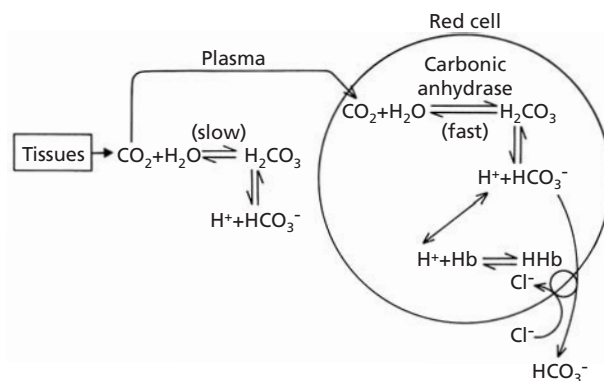


Fig. 2.18 Reactions consequent on the release of carbon dioxide from the tissues to the blood. (From Cumming & Semple [58].)

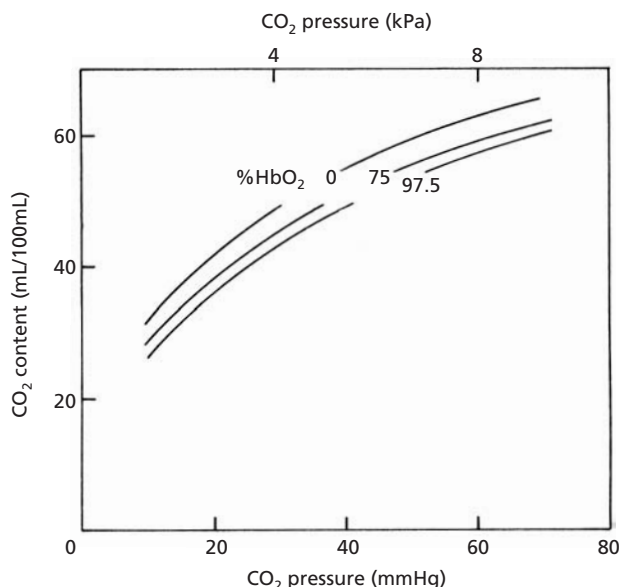


Fig. 2.19 Carbon dioxide dissociation curves for blood of different oxygen saturations. (Modified from West [7].)

protein, the most important of which is haemoglobin, e.g.  $HbNH_2 + CO_2 = HbNHCOOH$ . Reduced haemoglobin can bind more  $CO_2$  than deoxyhaemoglobin so that deoxygenation in the tissue capillaries facilitates  $CO_2$  transport.

#### Carbon dioxide dissociation curve

In comparison with the  $O_2$  dissociation curve, the  $CO_2$  dissociation curve is more linear, i.e. additional  $CO_2$  is carried in blood in proportion to  $P_{CO_2}$  and there is no 'fully saturated' point (Fig. 2.19). More  $CO_2$  is carried by deoxygenated blood for a given  $P_{CO_2}$  as shown in Fig. 2.19.

#### Measurement of blood gas tensions

Clinical estimation of hypoxaemia is rarely accurate and  $O_2$  saturation has to fall below 85% before it can be reliably

appreciated [61], such observations being further confounded by artificial lighting [62].  $O_2$  saturation ( $SaO_2$ ) may be measured by an ear oximeter [63]; this is particularly useful for measuring changes in  $SaO_2$  that may be produced by exercise for example. Transcutaneous monitoring of  $PO_2$  for periods of up to 4 h is possible in infants using a heated polarographic  $O_2$  sensor applied to the skin [64]. Transcutaneous monitoring of  $PCO_2$  has so far proved reliable in a limited number of applications, such as in infants where the duration of application of the sensor is limited to 4 h [65].  $PaO_2$  and  $Paco_2$  are now most commonly measured on samples of arterial blood obtained by puncture of the radial, brachial or femoral arteries and analysed by  $PO_2$ ,  $PCO_2$  and pH electrodes [66], which must be carefully calibrated preferably with tonometered blood [66].

### Acid–base status

The acid–base status of human blood is best considered in the context of the following equation:

$$pH = pK + \log \frac{[HCO_3^-]}{\alpha PCO_2} \quad [2.13]$$

which can be derived from the Henderson–Hasselbalch equation in which  $pK$  is the dissociation constant for carbonic acid and  $\alpha$  is the solubility coefficient of  $CO_2$ . Typical values for this equation are:

$$pH = 6.1 + \log \frac{24}{0.225 \times 5} = 7.40 \quad [2.14]$$

Bicarbonate concentration is chiefly determined by the kidney and the  $PCO_2$  by the lung. Understanding of acid–base disturbance can be helped by the use of an acid–base diagram similar to that shown in Fig. 2.20 [67]. This diagram plots  $Paco_2$  against pH or  $H^+$  concentration; the corresponding  $HCO_3^-$  values, which can be derived from Eqn 2.13, are shown as a fan of isopleths radiating from the origin. The normal range of values is shown by the central square. Five zones are also defined by the 95% confidence limits, representing the five varieties of acid–base disturbance encountered in clinical practice (Fig. 2.20). The limits of these zones were defined by measuring pH and  $Paco_2$  in the following situations.

- 1 Acute respiratory acidosis following acute inhalation of  $CO_2$ -rich gas in normal humans [68].
- 2 Chronic respiratory acidosis in patients with chronic elevation of  $Paco_2$  [69,70].
- 3 Metabolic alkalosis caused by chronic ingestion of sodium bicarbonate [71].
- 4 Respiratory alkalosis in anaesthetized subjects hyperventilated to lower  $Paco_2$  [72].
- 5 Metabolic acidosis in patients with renal failure or diabetic ketoacidosis [73,74].

### Respiratory acidosis

A rise in  $Paco_2$  caused by acute hypoventilation reduces the  $HCO_3^-/PCO_2$  ratio and decreases pH as shown by point 1 in Fig. 2.20; this point lies in the acute respiratory acidosis band. With persistent elevation of  $Paco_2$  the kidneys respond by retaining bicarbonate (over 2–3 days), which tends to restore pH towards normal (point 2 in the chronic respiratory acidosis band in Fig. 2.20). Acute respiratory acidosis may thus be converted, depending on the degree of compensation, to a fully or partially compensated respiratory acidosis.

### Respiratory alkalosis

Hyperventilation, which is seen in many pulmonary diseases, lowers  $Paco_2$ , increases the  $HCO_3^-/Paco_2$  ratio and raises pH (point 3 in Fig. 2.20). If the fall in  $Paco_2$  persists, as it does in high-altitude hyperventilation, renal compensation via excretion of bicarbonate may restore the pH towards normal, i.e. a compensated respiratory alkalosis.

### Metabolic acidosis

Metabolic acidosis is present when a primary fall in  $HCO_3^-$ , such as occurs in renal failure, diabetic ketoacidosis and lactic acidosis, results in a fall in the  $HCO_3^-/Paco_2$  ratio and fall in pH (point 4 in Fig. 2.20). The rise in arterial  $H^+$  stimulates the arterial chemoreceptors, which reflexly increase alveolar ventilation, lower  $Paco_2$  and usually result in partial compensation of the acidosis.

### Metabolic alkalosis

A primary rise in  $HCO_3^-$  may result from excess ingestion of alkalis, diuretic therapy or vomiting of acid gastric juice and is associated with a rise in the  $HCO_3^-/Paco_2$  ratio and pH (point 5 in Fig. 2.20). Respiratory compensation mediated by the central chemoreceptors may occur to a varying degree, giving a full range of compensation from uncompensated to partially or fully compensated metabolic alkalosis.

An example of the use of the acid–base diagram in the assessment of the clinical management of a patient with respiratory disease is shown in Fig. 2.21. A 62-year-old patient with severe chronic bronchitis and emphysema was severely hypoxic ( $PaO_2$  3.7 kPa, 28 mmHg) on admission with an acute exacerbation of his disease. The initial  $Paco_2$  and  $H^+$  values lay between the acute and chronic respiratory acidosis bands (Fig. 2.21). Despite controlled  $O_2$  therapy the  $CO_2$  retention progressed after 24 h so that artificial ventilation was required. This rapidly restored  $Paco_2$  to what was probably his normal level of about 8 kPa (60 mmHg).

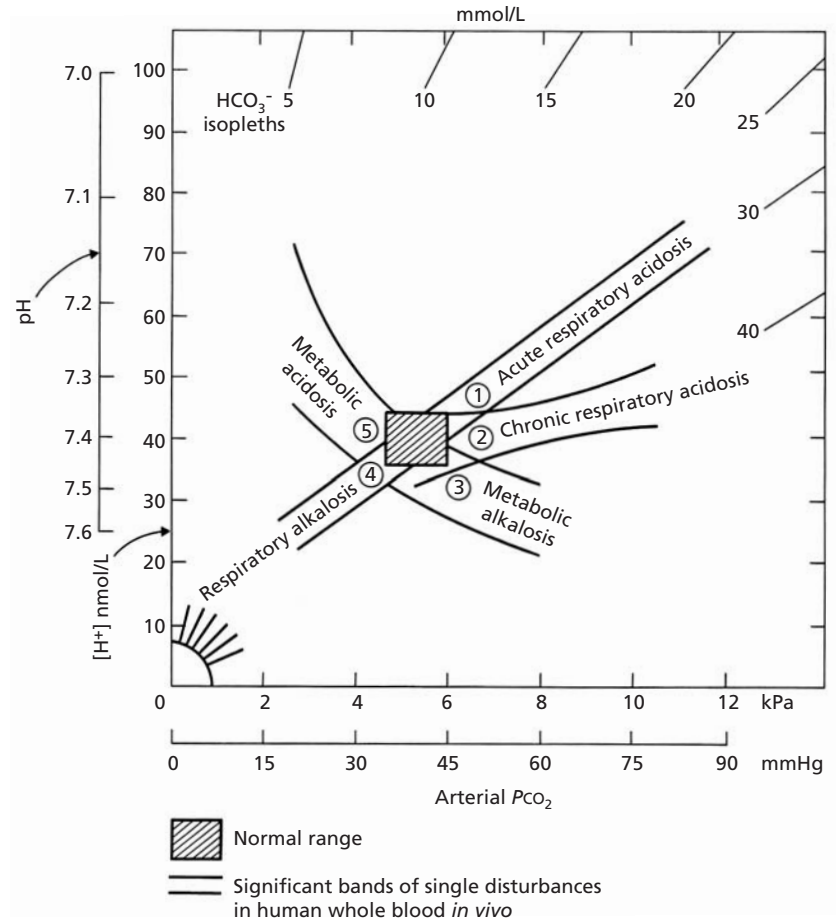


Fig. 2.20 The Flenley acid-base diagram relating arterial hydrogen ion concentration to  $\text{PaCO}_2$  with isopleths of bicarbonate concentration and showing the 95% confidence limits for acid-base disorders derived from published work; for explanation of the numbered points see text. (From Flenley [67].)

## Lung mechanics

During inspiration the respiratory muscles work to overcome the elastic recoil of the lungs and thorax, the frictional resistance due to movement of tissues and the resistance to airflow in airways.

### Elastic properties of the lungs and thorax: compliance

If the thorax is opened, the lungs collapse while the chest wall expands to a value above FRC. In life these tendencies are reflected in the presence of a subatmospheric pressure in the intrapleural space, which can be determined approximately by measuring the pressure in a 10-cm long balloon placed in the mid-oesophagus. Elasticity can be measured as the volume change for a given change in pressure applied to the lungs and chest wall together; this measurement, called compliance, is a measure of the distensibility of the system.

### Measurement of compliance

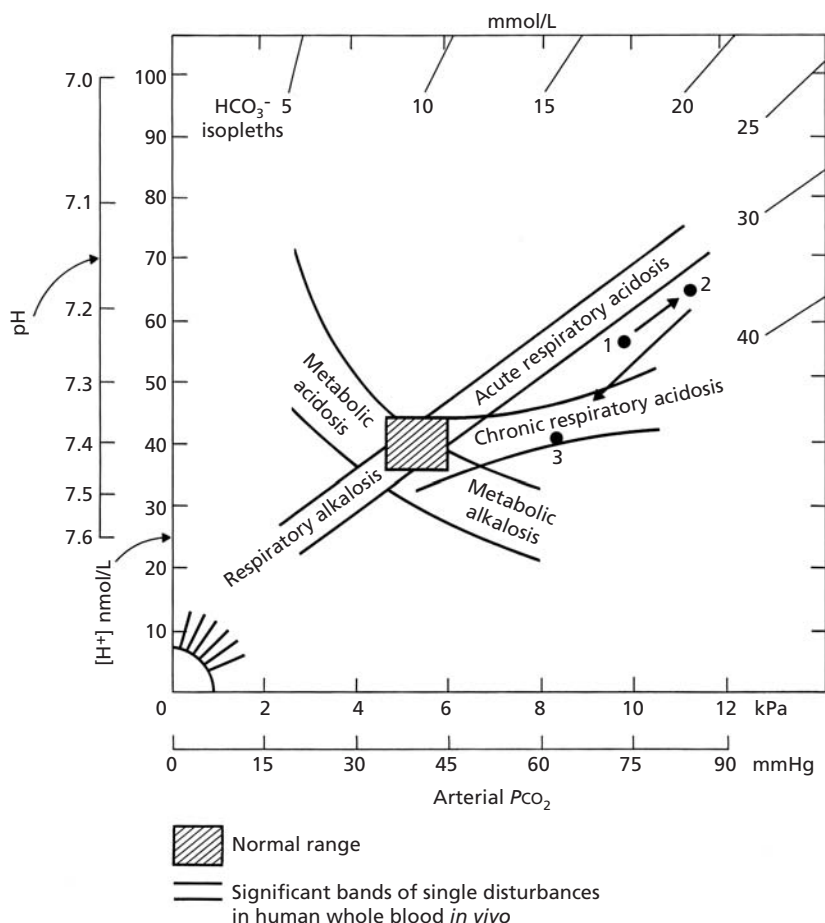
Compliance can be measured under static and dynamic conditions.

### Static compliance

The static compliance of the lungs and chest wall together (total compliance) can be measured by determining the relaxation pressure-volume curve. The subject inspires known volumes from a spirometer and then relaxes with open glottis while airway pressure is measured. The resulting relationship between pressure (atmospheric minus alveolar or airway pressure) and volume is the relaxation pressure-volume curve (Fig. 2.22). If intrathoracic pressure is measured simultaneously, lung compliance alone can be measured (airway pressure – intrapleural pressure) (Fig. 2.22); since these compliances are related as follows

$$\frac{1}{\text{total compliance}} = \frac{1}{\text{lung compliance}} + \frac{1}{\text{chest wall compliance}} \quad [2.15]$$

it is possible to calculate chest wall compliance. The relationships are approximately linear near FRC and normal values are about 0.21 L/cmH<sub>2</sub>O for pulmonary, 0.2 L/cmH<sub>2</sub>O for chest wall and 0.1 L/cmH<sub>2</sub>O for total compliance. Pulmonary static compliance is decreased in



**Fig. 2.21** Serial blood gas values in a middle-aged patient with an acute exacerbation of severe chronic bronchitis on admission (1), 24 h later (2) and after intubation and artificial ventilation (3).

the interstitial lung diseases such as fibrosing alveolitis ('stiff lungs') and increased in emphysema.

### Dynamic compliance

Dynamic compliance of the lung can be measured by plotting intrathoracic pressure against volume on an oscilloscope and drawing a line through the points of no flow (Fig. 2.23). The slope of this line is dynamic compliance, which at normal breathing frequencies is usually identical to the static compliance in normal lungs. In disease dynamic compliance may be lower than static compliance, particularly at high breathing frequencies. This reflects the presence in the lung of units ventilating in parallel at different rates. Units with a low resistance or compliance (fast alveoli) are preferentially ventilated when insufficient time is available for slow alveoli to fill. Measurements of compliance reflect the behaviour of the fast alveoli in this situation and are therefore low. When dynamic compliance decreases, with increasing frequency of breathing, compliance is said to be frequency dependent. Measurement of frequency dependence of compliance has been suggested as a sensitive test for detection of early abnormalities of lung function [75].

### Surfactant

The pressure-volume curve for static points during inflation of the lungs from FRC differs from that on deflation (Fig. 2.24), a finding known as hysteresis that occurs in most elastic materials. However, if the lungs are inflated and deflated with saline, which abolishes surface tension forces, the lungs become more compliant and the hysteresis effect is reduced [76] (Fig. 2.24). The difference between the air and saline pressure-volume curves is now thought to be due at least partly to surfactant, a phospholipid moiety [77] synthesized in the type II pneumocyte, which has the unique property of lowering surface tension in the alveoli where it is produced and thus diminishing the likelihood of alveolar collapse.

Synthesis of surfactant begins at approximately 16–18 weeks of gestation. It is stored in the alveolar cell until 26 weeks when release on to the alveolar surface occurs, although quantities sufficient to prevent the development of hyaline membrane disease are not present until later in gestation [78]. More than 70% of infants born at 29 weeks of gestation develop respiratory distress syndrome compared with only 8–10% of those born at 35 weeks of gestation [79]. Fetal lung maturity can be determined



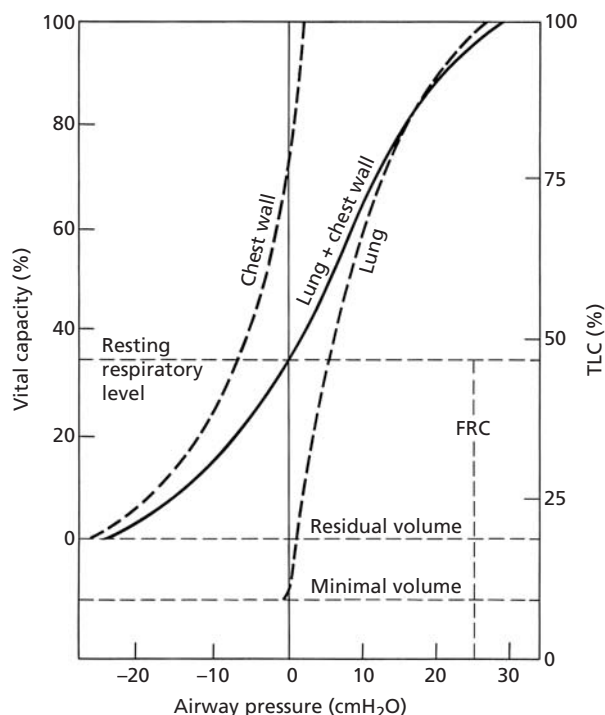


Fig. 2.22 Relaxation pressure-volume curve of the lungs and chest wall shown separately and together. (Modified from West [7].)

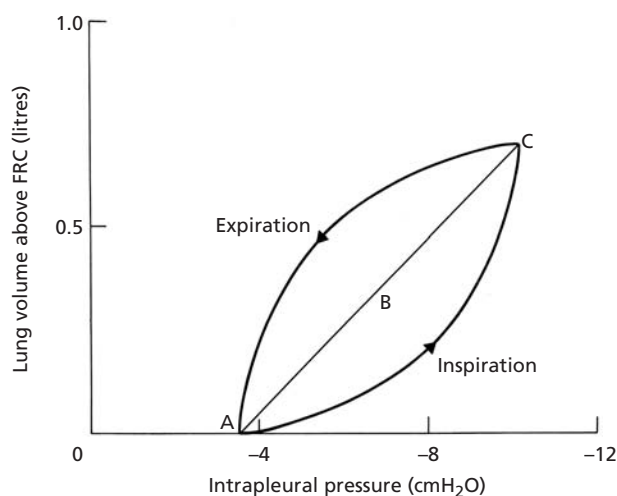


Fig. 2.23 Relationship of lung volume above functional residual capacity to intrapleural pressure during quiet breathing; dynamic compliance is the slope of the line ABC.

antenatally by measurement of the amniotic fluid lecithin/sphingomyelin ratio [80] or the amniotic fluid foam test [81]. Not only are quantitative differences in lung surfactant present in premature babies but qualitative differences are also found. In hyaline membrane disease, surfactant has a relative increase in unsaturated fatty acids (increase in oleic acid and decrease in palmitic

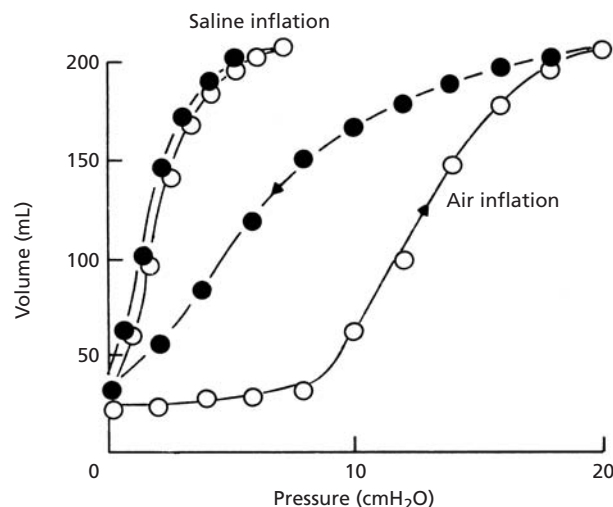


Fig. 2.24 Inflation (open circle) and deflation (black circle) pressure-volume curves of cat lungs with air and saline. (Modified from West [7].)

acid) [82] that returns to normal as recovery occurs. In addition to impairing surface activity, the relative increase in unsaturated fatty acids may increase substrate susceptibility to oxidation by highly toxic endoperoxides. Such endoperoxides may contribute to the pathogenesis of the chronic fibrotic lung disorder termed bronchopulmonary dysplasia, which is seen in some of the infant survivors of hyaline membrane disease [83].

The pathology of hyaline membrane disease in infants, where compliance is low, alveoli are collapsed and fluid transudes into the alveolar spaces, is also seen in the adult respiratory distress syndrome where surfactant deficiency has also been demonstrated [84,85]. Replacement of surfactant by intratracheal instillation appears to be of benefit in hyaline membrane disease [86].

### Airways resistance

Tissue resistance contributes less than 20% of the total resistance to flow in the lungs of a normal subject and although it may be increased in lung disease the majority of the resistance to airflow resides in the airways, the airway resistance (AWR). When flow occurs through a tube, the pressure difference between the ends of the tube is related to flow by a relationship of the form:

$$P = k_1 V + k_2 V^2 \quad [2.16]$$

where the first term indicates a contribution from laminar flow and the second from turbulent flow in the airways. In laminar or streamlined flow, which occurs in the smaller airways in the lung, Poiseuille's equation for flow in straight circular tubes applies:

$$\dot{V} = \frac{\pi P r^4}{8 \eta l} \quad [2.17]$$

where  $P$  is the pressure difference,  $r$  the radius of the tube,  $\eta$  the viscosity of the gas and  $l$  the length of the tube. Since resistance is pressure divided by flow it follows that:

$$R = \frac{8\eta l}{\pi r^4} \quad [2.18]$$

an equation that emphasizes the importance of airway radius: resistance is increased 16-fold if radius is halved.

In turbulent flow, which occurs in larger airways particularly at high flow rates, the pressure difference is proportional to the square of flow and viscosity is no longer important. However, in turbulent flow gas density becomes important and the pressure difference for a given flow is reduced by lowering gas density, e.g. by breathing He/O<sub>2</sub> mixtures. Much of the flow in the lung is probably intermediate or transitional between laminar and fully developed turbulent flow, hence the need to recognize contributions from both to the pressure difference along the airways.

### Sites of airways resistance

By passing catheters into the airways to measure pressure in the lumen it is possible to determine the contribution to total airways resistance from airways of different sizes [87]. Such studies have shown that most of the resistance to airflow arises in medium to large airways in the lung (Fig. 2.25) and that the smaller airways of <2 mm in diameter contribute rather less than 10% to total airways resistance. This would be expected from the differences in total

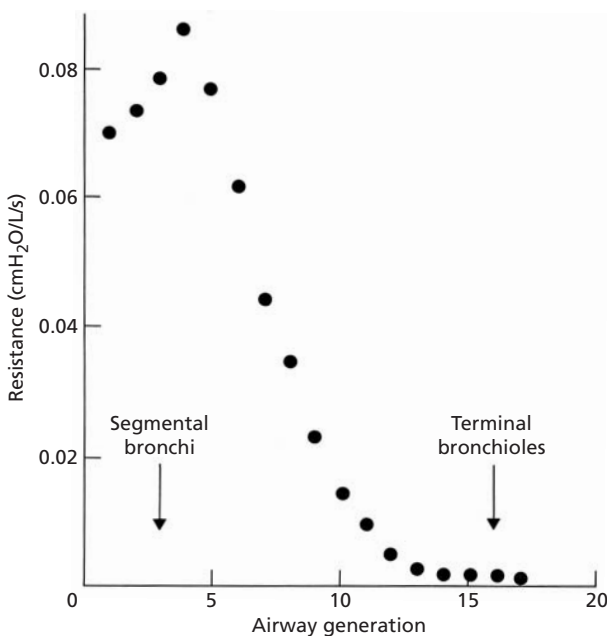


Fig. 2.25 Contribution of different-sized airways to airway resistance: most resistance resides in intermediate-sized bronchi and very little in the small airways. (Modified from West [7].)

cross-sectional area at different levels of the respiratory tract (Fig. 2.26). Disease in small airways may be severe before airways resistance is significantly changed, and hence the development of other tests of 'small airways' function such as He/O<sub>2</sub> flow-volume curves, the maximum mid-expiratory flow rate and frequency dependence of compliance [88,89].

### Factors affecting airways resistance

Airways resistance may be increased because of encroachment on the airway lumen either by mucus or by inflammation or oedema of the airway wall. In asthma or bronchitis and in normal subjects exposed to irritant aerosols [90], bronchial smooth muscle tone is increased with reduction in airway calibre. Mast cell mediators of asthma such as leukotrienes and histamine are not only potent bronchoconstrictors in humans [91] but also increase mucus secretion [92] and cause inflammation [93], with resultant airway narrowing. The airways are also dependent on lung parenchyma for support by traction; thus in emphysema, where parenchyma is destroyed, airways resistance is increased. Finally, airways resistance is dependent on the lung volume at which it is measured, as shown in Fig. 2.27 where resistance and its reciprocal, airways conductance, are plotted against lung volume.

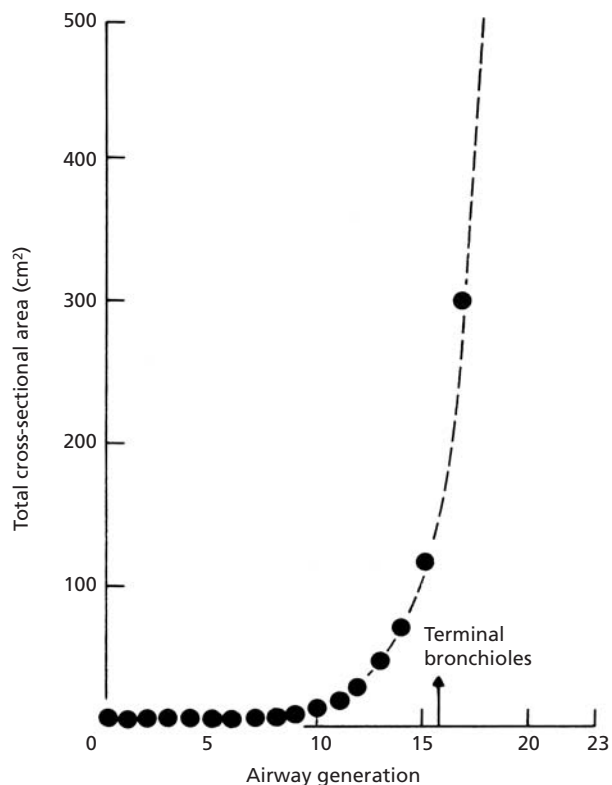


Fig. 2.26 Increase in total cross-sectional area of the airways with succeeding generations of airways. (Modified from West [7].)

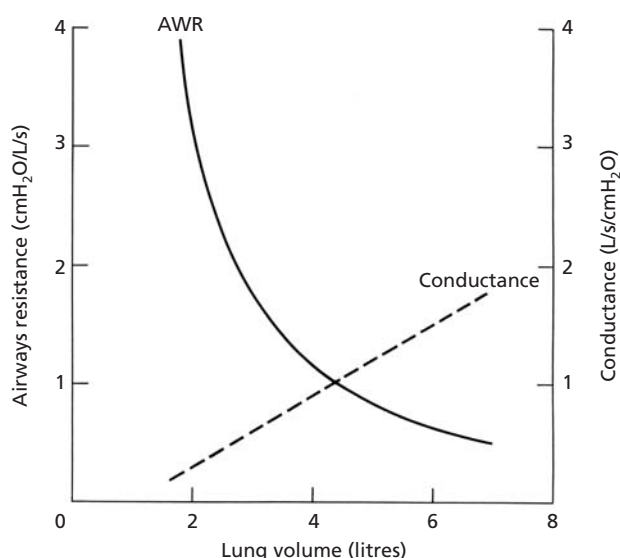


Fig. 2.27 Relationship of airways resistance (AWR) and conductance to lung volume. (Modified from West [7].)

### Measurement of airways resistance

Airways resistance can be calculated from measurements of atmospheric and alveolar pressures and flow. Flow is measured with a pneumotachograph and alveolar pressure with a body plethysmograph using an interrupter technique [94]; normal values are around 1–3 cmH<sub>2</sub>O/L/s with average flow rates. Alternatively, airways resistance can be measured by the simple, non-invasive forced oscillation technique, which does not require the cooperation of the patient [95].

### Other tests for airways obstruction

#### Dynamic lung volumes

A more commonly used index of increased airways resistance or airways obstruction is the forced expiratory volume in 1 s (FEV<sub>1</sub>) and its ratio to the forced vital capacity (FVC). The latter is the volume expired with the greatest force and speed from TLC and the former the volume expired in 1 s during the same manoeuvre (Fig. 2.28). The FEV<sub>1</sub> was initially used as an indirect method of estimating its predecessor as the principal pulmonary function test, the maximal breathing capacity. In normal young and middle-aged adults the FEV<sub>1</sub>/FVC ratio is usually above 75%; in childhood it may be higher, even approaching 100%; while in the elderly values of 70–75% are commonly found. A reduction in the FEV<sub>1</sub>/FVC ratio indicates airways narrowing, the severity of which is best indicated by the absolute value of FEV<sub>1</sub> (Fig. 2.28). Predicted values for these measurements based on height, age and sex have been published by a number of workers [96–99]. An example of the related abnormalities in tests of lung func-

**Table 2.2** Characteristic patterns of disordered respiratory function.

<p><i>Obstructive pattern</i> (e.g. chronic bronchitis and emphysema)</p> <p>Reduced FVC, FEV<sub>1</sub>, MVV and PEFR</p> <p>Relatively greater reduction in FEV<sub>1</sub> than FVC</p> <p>Increased RV and RV/TLC ratio</p> <p>Uneven distribution of inspired gas</p> <p>Increased non-elastic work of breathing</p> <p>Reduced Pao<sub>2</sub> and Sao<sub>2</sub></p> <p>Increased Paco<sub>2</sub></p> <p>Lowered arterial pH during exacerbations</p>	
<p><i>Restrictive pattern</i> (e.g. cryptogenic fibrosing alveolitis)</p> <p>Reduced FVC</p> <p>FEV<sub>1</sub>/FVC ratio normal</p> <p>Slight impairment of gas distribution</p> <p>Increased elastic work of breathing</p> <p>Decreased compliance</p> <p>Decreased DLCO</p> <p>Reduced Pao<sub>2</sub> and Sao<sub>2</sub> (initially only on exertion)</p> <p>Normal or low Paco<sub>2</sub></p> <p>Normal pH</p>	

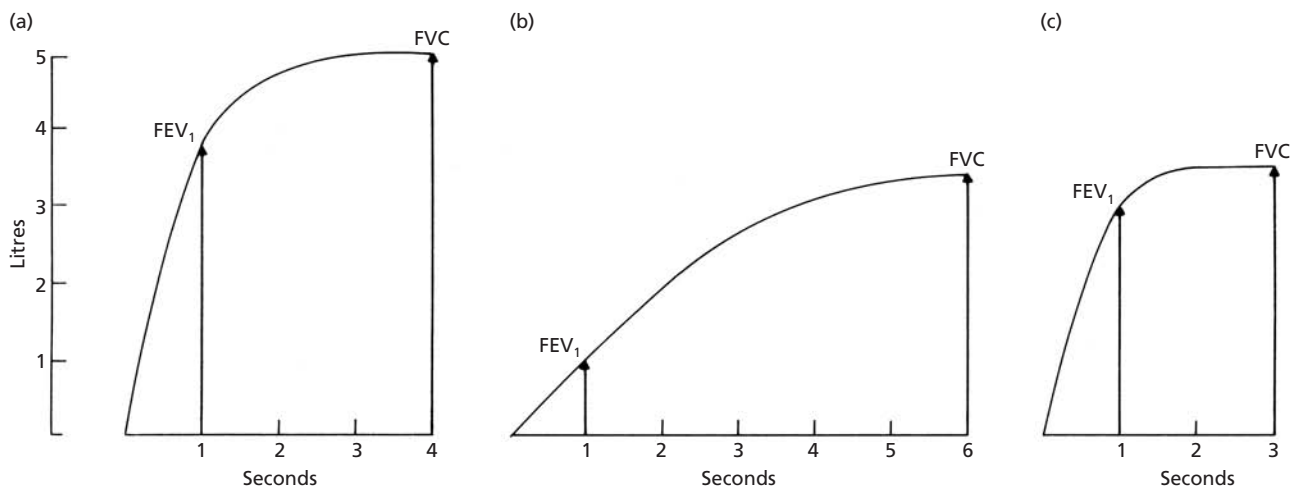
FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; MVV, maximum voluntary ventilation; PEFR, peak expiratory flow rate; RV, residual volume; TLC, total lung capacity.

tion in airways obstruction is given in Table 2.2. Airways obstruction is usually reversible to some extent following administration of a  $\beta$ -adrenergic bronchodilator aerosol, increases of greater than 20% in FEV<sub>1</sub> favouring a diagnosis of asthma rather than chronic bronchitis and emphysema. In restrictive lung diseases, such as fibrosing alveolitis, the FEV<sub>1</sub> and FVC are reduced in parallel (the restrictive pattern) (Fig. 2.28). Other changes in tests of lung function that may be found in restrictive lung disease are also shown in Table 2.2.

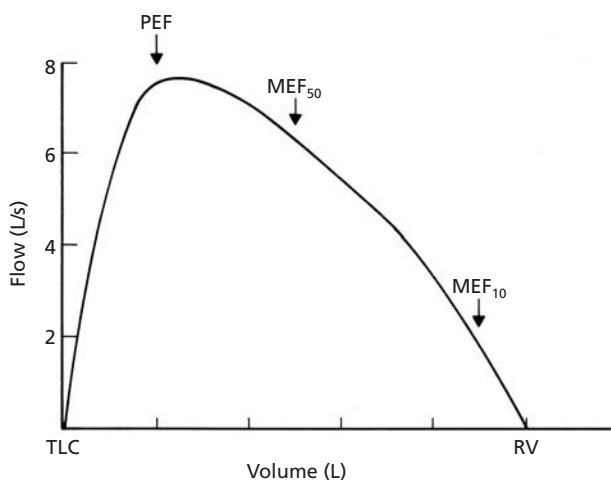
#### Maximum expiratory flow–volume curve

An alternative way of looking at forced expiration is to measure both expiratory flow and the volume expired, and plot flow against volume to give a maximum expiratory flow–volume curve (Fig. 2.29). The maximum flow obtained, also called the peak expiratory flow rate (PEFR), can be measured from such a curve. The peak flow occurs at high lung volumes (Fig. 2.29) and is effort dependent. Flow at lower lung volumes is effort independent, i.e. increases in effort above a certain level produce no further increase in flow due to the presence of dynamic compression of large airways (see below) at lower lung volumes. Thus flow at lower lung volumes depends on the elastic recoil pressure of the lungs and the resistance of the airways upstream or distal to the point at which dynamic compression occurs [100]. Changes in flow on this part of the flow–volume curve therefore represent changes in either the recoil pressure of the lung (e.g. decreased in emphysema) or the resistance of the smaller airways.





**Fig. 2.28** Measurement of forced expiratory volume in 1 s ( $FEV_1$ ) and forced vital capacity (FVC) in (a) a normal subject, (b) a patient with obstructive lung disease and (c) a patient with restrictive lung disease.

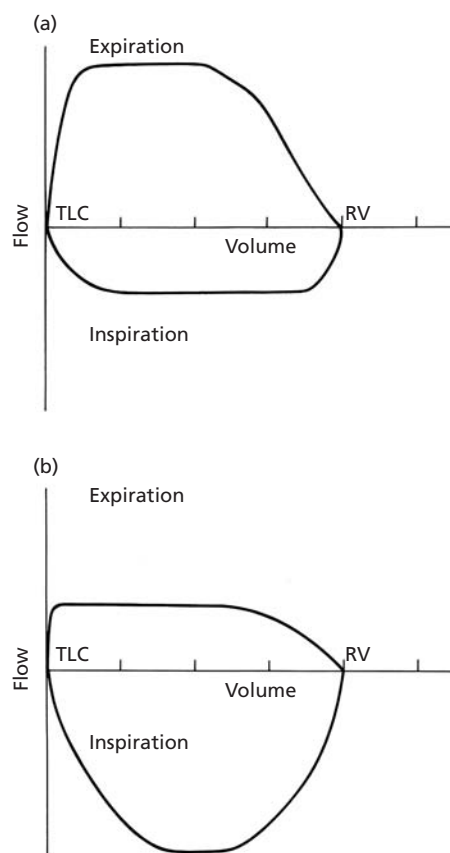


**Fig. 2.29** Maximum expiratory flow-volume (MEFV) curve. The subject expires forcibly from total lung capacity down to residual volume and measured expiratory flow rate is plotted against measured volume. Peak expiratory flow (PEF),  $MEF_{50}$  and  $MEF_{10}$  are indicated by arrows (see text).

Measurements of flow at low lung volumes, e.g. 50, 25 or 10% of VC ( $MEF_{50}$ ,  $MEF_{25}$ ,  $MEF_{10}$ ), are often used as indices of peripheral or small airways resistance and may be less than predicted [101] when the  $FEV_1$  and PEF are normal [102].

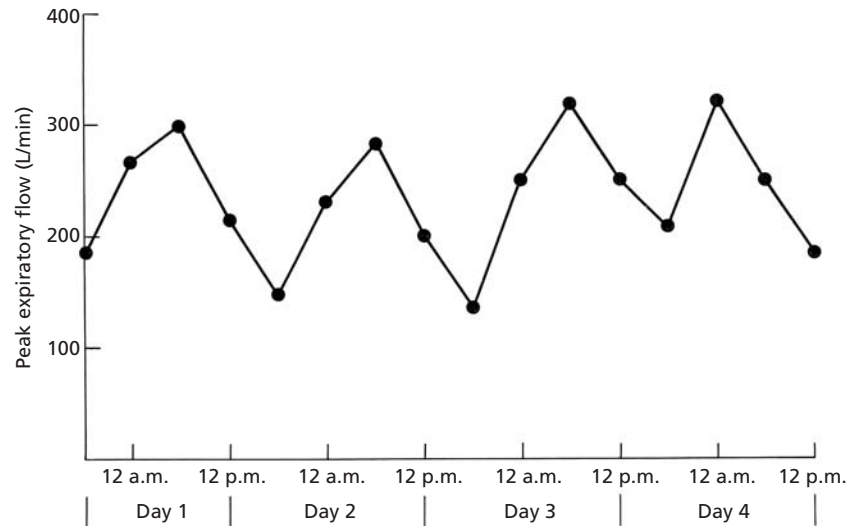
### Upper airways obstruction

In upper airways obstruction, characteristic changes are seen on expiratory and inspiratory flow-volume loops depending on the site of the obstruction (Fig. 2.30). In



**Fig. 2.30** Maximum expiratory and inspiratory flow loops in (a) extrathoracic large airway narrowing and (b) intrathoracic tracheal narrowing.

extrathoracic large airway narrowing, inspiratory flow is impaired more than expiratory and an inspiratory flow plateau is usually seen (Fig. 2.30a). In intrathoracic large airway obstruction, expiratory flow is impaired more than inspiratory flow and an expiratory plateau is usual (Fig. 2.30b).



**Fig. 2.31** Peak expiratory flow chart recorded 6-hourly over 4 days in an asthmatic patient. A marked diurnal variation is seen with the lowest values recorded in the early morning, the 'morning dipper' pattern.

### Peak expiratory flow rate

PEFR may be simply measured using equipment such as the Wright peak expiratory flow meter. The machines are cheap and portable and serve a variety of functions. Variability in PEFR of greater than 15–20% in a single day or from day to day is very suggestive of asthma, as shown in Fig. 2.31 where the 'morning dipper' pattern of variation in airways obstruction is illustrated [103]. Most normal subjects demonstrate less than 10% variation in PEFR over a 24-h period [104]. Similarly, PEFR may be used as an index of response to treatment in asthma, as shown in Fig. 2.32 where serial measurements of PEFR in a patient admitted to hospital with acute severe asthma are recorded. Finally, PEFR is the most convenient measurement for use in the diagnosis of exercise-induced asthma, where a fall in PEFR of greater than 15% following exercise is considered diagnostic (Fig. 2.33).

### Dynamic airways compression

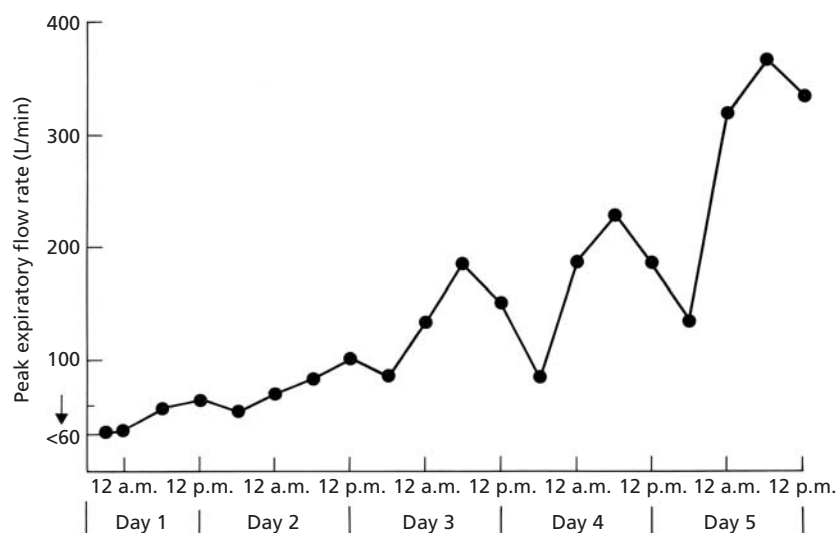
Dynamic airways compression is illustrated in Fig. 2.34, where the driving force of the respiratory muscles is represented by a piston compressing the lungs, shown as a single alveolus and airway within a somewhat expanded pleural space. Figure 2.34(a) shows the static situation with no flow and therefore no pressure gradient in the airways. The intrapleural pressure of  $-10\text{cmH}_2\text{O}$  represents the static recoil pressure of the lungs or the tendency of the lungs to collapse. In forced expiration (Fig. 2.34b) a driving pressure of  $20\text{cmH}_2\text{O}$  raises alveolar pressure to  $20\text{cmH}_2\text{O}$  and intrapleural pressure to  $10\text{cmH}_2\text{O}$ . Flow occurs in the airways where pressure drops from  $20\text{cmH}_2\text{O}$  in the alveolus to  $0\text{cmH}_2\text{O}$  in the mouth. At some point along the airway, airway pressure equals intrapleural pressure and downstream from this equal pressure point (X in Fig. 2.34) airway compression tends to

occur. Compression or collapse is not permanent because transient occlusion of the airway results in a rise in upstream airway pressure to alveolar pressure as soon as flow is abolished, with prompt resumption of flow; the airways thus tend to vibrate at the point of dynamic compression. Since the elastic recoil pressure of the lungs decreases with decreasing lung volume (Fig. 2.35), the collapse point moves distally (or upstream) to the smaller airways as forced expiration proceeds.

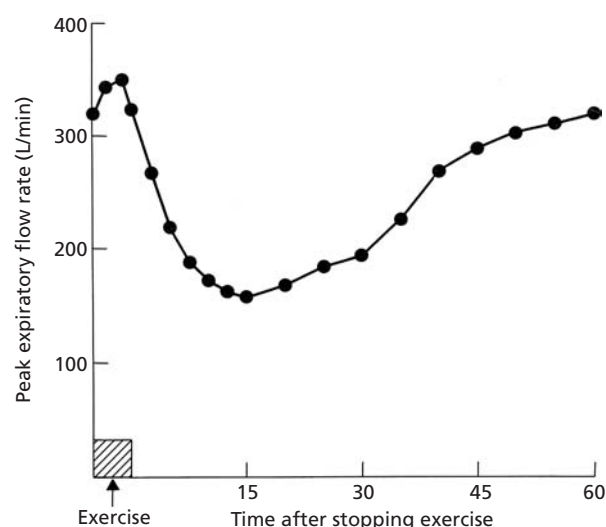
### Helium breathing

Flow in the larger airways is turbulent but is laminar in the smaller airways where the total cross-sectional area is increased. The smaller airways contribute less than 20% to airway flow resistance and thus the determination of changes affecting these airways is difficult. One method, as above, is to look at flow at low volumes on an expiratory flow–volume curve. Another is to study the effect of breathing 80% He/20%  $\text{O}_2$  mixtures on the shape of the flow–volume curve.

An 80% He/20%  $\text{O}_2$  mixture is much less dense than air. Where turbulent flow occurs, flow is dependent on gas density whereas laminar flow is unaffected. Therefore in subjects with disease of small airways the flow–volume curve changes less than in normal subjects when He/ $\text{O}_2$  mixtures are breathed (Fig. 2.36). Partial expiratory flow–volume curves, e.g. to 60% VC, may be used to avoid the inhibition of vagal tone that occurs with a full inspiration [105]. Indices that have been used to reflect this He effect are the differences in flow rate at 50% VC ( $\Delta V_{50}$ ) between air and He/ $\text{O}_2$  mixtures and the volume at which the two curves are superimposed (the volume of isoflow) [106]. Using this technique the predominant site of airway obstruction in patients with asthma has been classified as either peripheral or central [107].



**Fig. 2.32** Peak expiratory flow rate (PEFR) of a middle-aged patient recovering (with treatment) from acute severe asthma. Note the initially very low values ( $<60$  L/min), the very slow rate of recovery and the emergence of the 'morning dipper' pattern as PEFR improves.

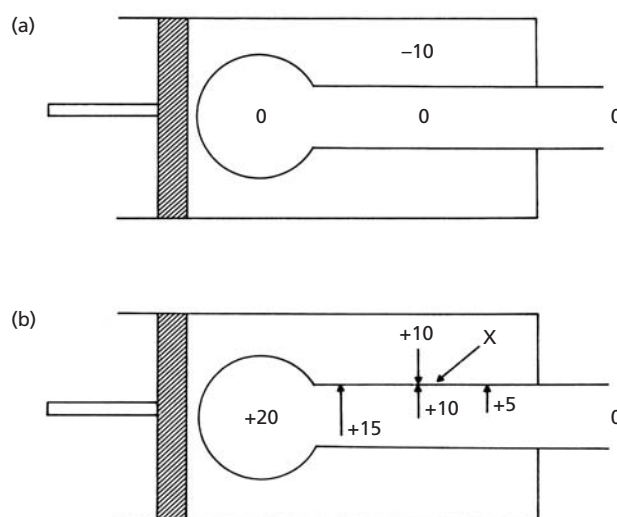


**Fig. 2.33** Serial peak expiratory flow rate measurements taken during 6 min of stair-running exercise and for 1 h in a 14-year-old asthmatic boy to illustrate the time-course of exercise-induced asthma.

### Closing volume

The closing volume is defined as the lung volume at which airways begin to close in the dependent zones of the lungs [108]; this is the volume of gas that can be breathed out to RV after the onset of airway closure. The total volume of gas within the lung at the onset of airway closure is the closing capacity (which equals closing volume + RV).

When a healthy subject in the upright position takes a deep breath from RV, gas initially goes predominantly to the upper zones of the lungs. During the subsequent expiration these zones empty last, i.e. 'first in, last out' [109,110]. This phenomenon may be attributed to airway closure in the dependent lung zones at low lung volumes, i.e. near RV, as the pleural pressure rises above the



**Fig. 2.34** Dynamic compression of airways on forced expiration: intrapleural, alveolar and airway pressures while resting at FRC (a) and during forced expiration (b). Pressures expressed as cmH<sub>2</sub>O; see text. (Modified from Bouhuys [101].)

critical closing pressure of the airways. Early in inspiration from RV, therefore, the 'closed' dependent lung zones do not receive an inspired bolus, which goes predominantly to the upper zones and these consequently have a higher concentration of any tracer gas added to the inspired air.

The test involves the inspiration of a bolus of marker gas from RV to TLC at a rate of less than 0.5 L/s and the subsequent monitoring of the concentration of marker gas during slow exhalation to RV, the concentration being displayed against a simultaneous measure of expired gas volume on an *x-y* recorder. An abrupt change in concentration of marker gas is observed towards the end of expiration and this marks the point from which closing volume is measured (Fig. 2.37). In sitting, normal young subjects

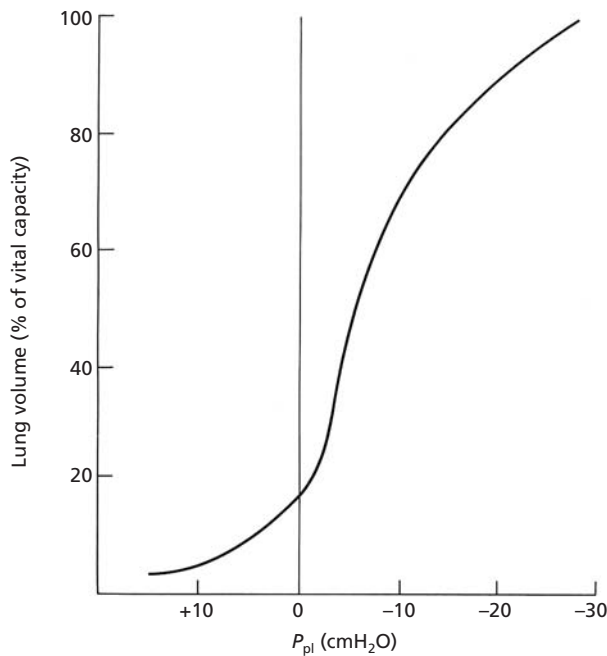
airway closure in the dependent lung zones occurs at lung volumes below about 40% TLC [108].

Loss of elastic recoil of the lung due to ageing means that closure occurs at progressively higher lung volumes, which may encroach on tidal volume breathing. Obesity, ascites and pregnancy, by reducing lung volume, may also cause airway closure during tidal volume breathing. Closing volume may also be increased in chronic bronchi-

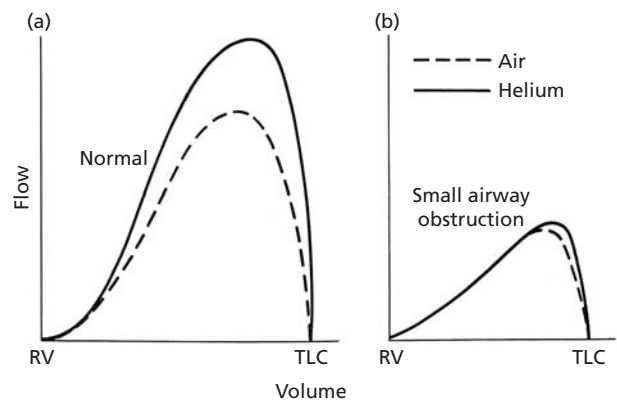
tis, asthma [111], increased left atrial pressure (as in mitral stenosis and left ventricular failure) and reduced plasma osmotic pressure (as in cirrhosis). Increased left atrial pressure or reduced osmotic pressure presumably act by causing a cuff of fluid to surround the terminal airways. These effects on closing volume may offer an explanation for the 'bronchitic' features of mitral stenosis, which may disappear after valvotomy, and for the 'asthmatic' component that dominates the early clinical picture of pulmonary oedema.

### Work of breathing

The work done to move the lungs and thoracic cage can be expressed by the product of pressure and volume changes

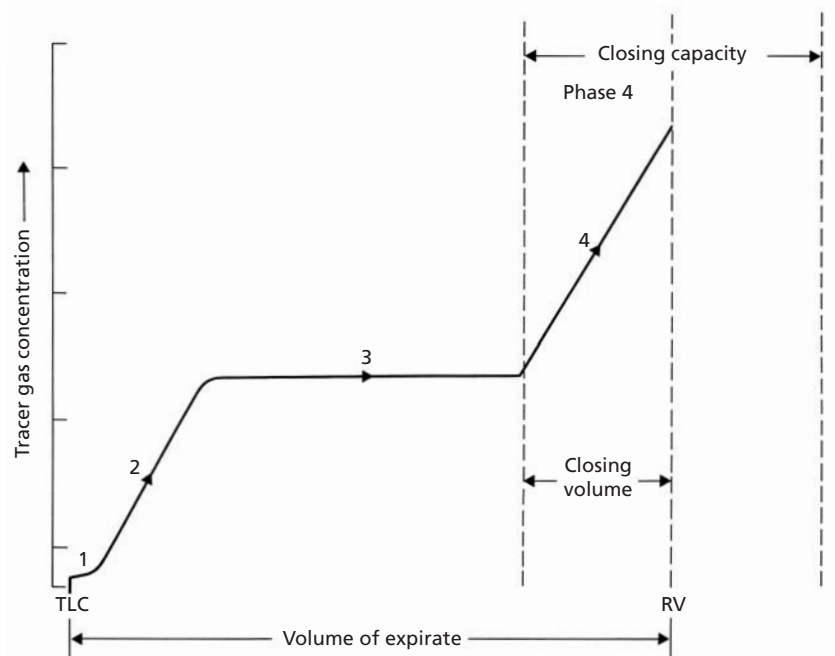


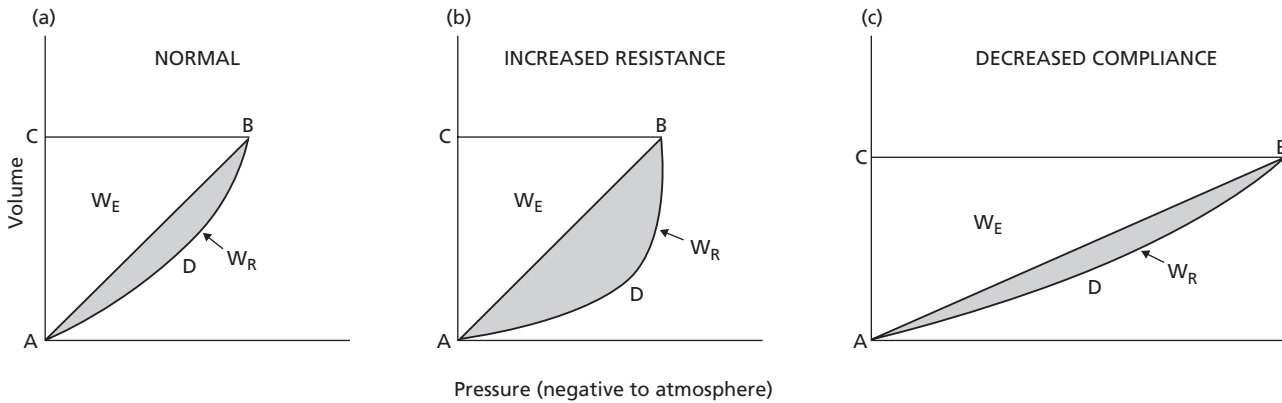
**Fig. 2.35** Static recoil curve of the lungs: intrapleural pressure is more negative as lung volume increases.



**Fig. 2.36** Flow-volume curves breathing air (broken line) and 80% helium/20% oxygen (solid line) in (a) a normal subject and (b) a patient with airways obstruction predominating in small airways.

**Fig. 2.37** Diagrammatic representation of the components of the closing volume. There are four phases: phase 1 is caused by the emptying of the dead space of apparatus and upper airways; phase 2 shows the rise in concentration of marker gas as alveolar emptying begins; phase 3 is the 'alveolar plateau', due to the mixing of marker gas and air from all regions of the lungs; and phase 4 shows the terminal rise in marker gas concentration when emptying ceases from the lower zones where marker gas concentrations are lower. See text for definitions.





**Fig. 2.38** Lung pressure–volume loops in (a) normal lung, (b) increased airways resistance and (c) decreased lung compliance showing the relative effects of work done against elastic ( $W_E$ ) and resistance ( $W_R$ ) forces; see text for explanation.

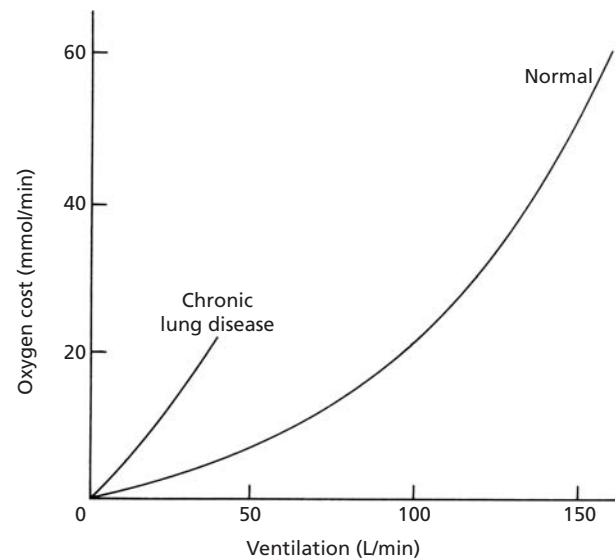
during inspiration and expiration and can be illustrated by pressure–volume curves (Fig. 2.38a), where intrathoracic pressure is plotted against lung volume. Areas in such a diagram represent products of volume and pressure and therefore work. The slope of the line AB represents compliance and the area ABC the elastic work done. On inspiration, work is done to overcome tissue and airways resistance as represented by area ABD. When airways resistance increases, the loop widens (Fig. 2.38b) and the area representing work done against resistance increases. Similarly, if compliance is low (Fig. 2.38c) work done against elastic forces, represented by area ABC, is increased.

### Metabolic cost of breathing

The energy requirements for ventilation of the lungs can be determined by measuring the increase in  $O_2$  consumption that results from a given increase in ventilation during, for example, voluntary hyperventilation. At rest in health, the  $O_2$  cost of breathing is about 2% of the total  $O_2$  consumption and this increases at increasing levels of ventilation (Fig. 2.39). In disease, the  $O_2$  cost of breathing may be considerably increased as a result of the increase in mechanical work required to move the lungs (Fig. 2.39), and a situation may arise where the  $O_2$  cost of increased ventilation encroaches upon the extra  $O_2$  absorbed from the lungs as a result of the increased ventilation, so contributing to respiratory failure.

### Respiratory muscle weakness and fatigue

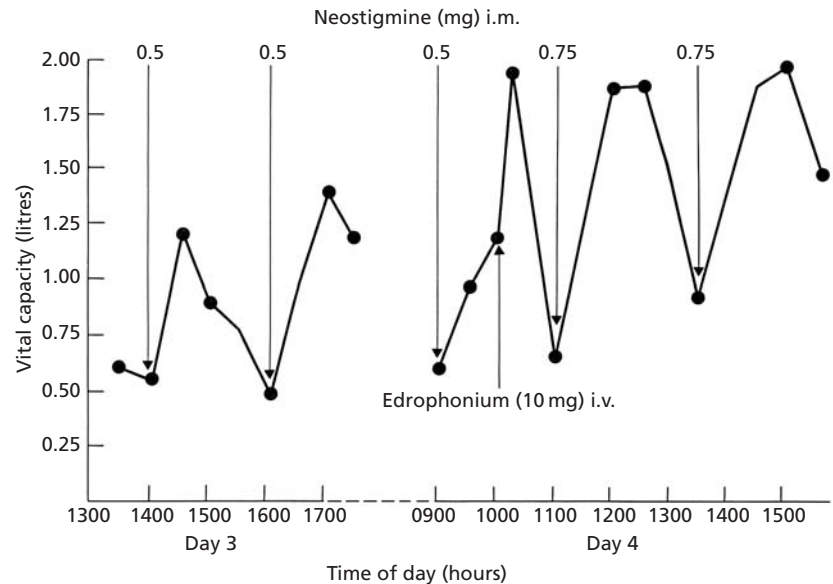
The important respiratory muscles are the diaphragm, intercostal muscles and muscles of the abdominal wall. Unilateral paralysis of the diaphragm is common, easily



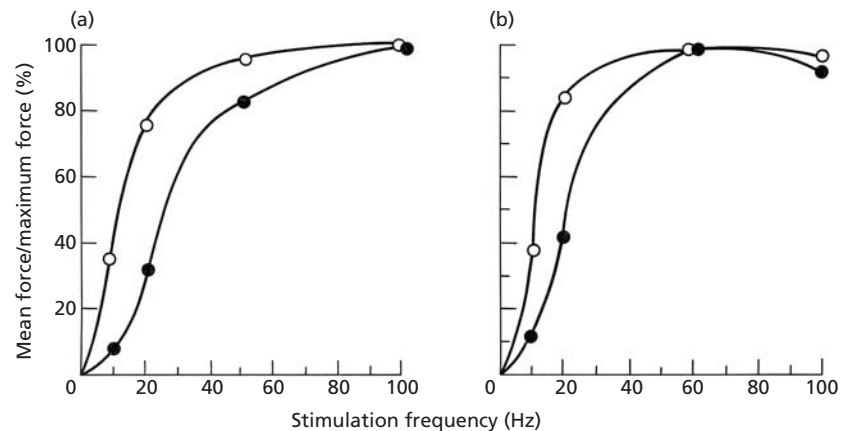
**Fig. 2.39** Energy cost of breathing for different levels of pulmonary ventilation in a normal subject and a patient with chronic lung disease. (From Cotes [1].)

suspected on chest radiography and confirmed by fluoroscopy; it usually causes little clinical or physiological abnormality. However, bilateral paralysis or weakness of the diaphragm [112], which may be seen in motoneurone disease, myopathies, myasthenia, polyneuritis, following trauma and in systemic lupus, results in striking orthopnoea and paradoxical inward movement of the abdominal wall during inspiration. Global weakness of the respiratory muscles may occur in motoneurone disease, myasthenia or Guillain–Barré syndrome.

Measurement of the maximal mouth pressure generated by a patient inspiring against an obstruction from RV or expiring against an obstruction from TLC is a useful index of inspiratory or expiratory muscle weakness. Generated pressures of 80 cmH<sub>2</sub>O should be achieved by normal subjects. Where muscle weakness is established and may be progressive, serial measurements of VC are invaluable indications of deterioration and the need for assisted ventilation (Fig. 2.40).



**Fig. 2.40** Serial measurements of vital capacity in a patient with myasthenia gravis: the improvement in vital capacity following neostigmine and edrophonium are well shown. (From Harrison *et al.* [113].)



**Fig. 2.41** Examples of low-frequency fatigue induced in the sternomastoid muscle showing force generated in response to stimulation before (open circle;) and after (black circle;) (a) inspiratory loading and (b) sustained maximum voluntary ventilation. (Modified from Moxham *et al.* [114].)

Fatigue of skeletal muscles may result from repeated high-load muscle contractions and can be demonstrated by the change in shape of the stimulation frequency–force curve. Of particular interest is low-frequency fatigue, which results in a reduction of force generated at low stimulation frequencies and which can persist for hours (Fig. 2.41). Since the firing frequency of motoneurons during everyday activities is low (5–30 Hz), this form of fatigue is of particular physiological importance.

In normal subjects, inspiratory loading and sustained maximal voluntary ventilation can produce low-frequency fatigue of the sternomastoid and the diaphragm [114,115]. In patients with chronic airflow obstruction, sustained maximal voluntary ventilation causes marked low-frequency fatigue of the sternomastoid muscle [116] and presumably also of the diaphragm. Such fatigue may be of considerable clinical importance in view of the stresses imposed upon the respiratory muscles by pulmonary disease. The finding of reduced ventilatory responses to

inhaled  $\text{CO}_2$  caused by fatigue of the respiratory muscles supports this suggestion [117].

Simple tests for detecting respiratory muscle fatigue are not available at present. However, in situations where low-frequency fatigue is likely to occur due to markedly increased work of breathing, therapy should be directed to reducing the work of breathing. The bronchodilator aminophylline may have the independent effect of improving the force-generating properties of the diaphragm in normal humans [118]. Finally, an important contribution of assisted ventilation may be that it rests the respiratory muscles long enough for low-frequency fatigue to resolve.

### Inhalation challenge tests

Specific bronchial challenge testing, e.g. with allergens causing acute asthma, has been used for many years as a research rather than a clinical investigation. Its use should



continue to be restricted to major centres with the necessary expertise, not least because the procedures may be hazardous in inexperienced hands [119].

In contrast, non-specific bronchial challenge testing is being increasingly and probably excessively used in the diagnosis and assessment of patients with asthma or airways disease. Asthmatic subjects are more sensitive than non-asthmatic subjects to the bronchoconstrictor effects of a wide range of chemical agents. This 'reactivity' can be formally assessed by measuring the effect of inhaling increasing doses of bronchoconstrictor agonists, such as histamine or methacholine, on pulmonary function, for example  $FEV_1$ . The most commonly used standardized technique was described by Cockcroft *et al.* [120] and involves delivering nebulized histamine or methacholine in doubling doses each given during 2 min of tidal breathing with measurement of  $FEV_1$  between doses. The test is stopped when there is either a 20% or greater fall in  $FEV_1$  or when the highest concentration of agonist is reached. The level of non-specific reactivity is calculated as the concentration of inhaled agonist that results in a 20% fall in  $FEV_1$  ( $PC_{20}$ ). The  $PC_{20}$  for histamine is usually lower than 8 mg/mL in asthmatic patients and may be as low as 0.1 mg/mL in severe asthma. Normal subjects usually have  $PC_{20}$  values greater than 16 mg/mL; patients with chronic bronchitis, bronchiectasis and other airway diseases may have intermediate values.

Occasionally, determination of non-specific bronchial reactivity will be of supportive diagnostic value, for example in cases of asthmatic cough in patients with normal pulmonary function. The test has no demonstrable contribution to make to the management of patients who are already known to have asthma.

## Control of breathing

### Central nervous mechanisms

The organization of the central nervous control mechanisms for ventilation is still being extensively investigated [121]. Animal studies have shown that there are cells in the pons and medulla that discharge in phase with expiration and inspiration, as well as cells which discharge during the switch from one state to the other, so-called phase-spanning cells [122,123]. Inspiratory phase-spanning and expiratory cells, which are found in the rostral pons in the pneumotaxic centre, are believed to influence the timing of respiration by providing an input to rhythmically discharging cells at another site. The apneustic centre, caudal to the pneumotaxic centre in the pons, was originally defined when ablation of the latter in the presence of sectioned vagi resulted in apneustic, or gasping, inspiration in anaesthetized cats. However, in awake cats normal rhythmic respiration occurs even in the absence of the pneumotaxic centre and vagal input, indicating that only

an intact pons and lower medulla are necessary for normal respiratory rhythm [124]. Following pontomedullary section, rhythmic respiration is again found, indicating that rhythm generation originates in the medulla or medullary centres.

In the medulla, two major groups of cells active in phase with respiration have been identified. The dorsal respiratory group, located on the ventrolateral nucleus of the tractus solitarius, contains predominantly inspiratory cells and projects to inspiratory motoneurons in the spinal cord. The ventral respiratory group, associated with the nucleus ambiguus and the nucleus retroambiguus, contains both inspiratory and expiratory cells and projects to inspiratory and expiratory motoneurons in the spinal cord [125]. The rhythmicity of respiration is believed to depend upon inhibitory and excitatory interactions between these various respiratory cells in the medulla. Many other factors influence their activity, including neural inputs from higher centres, chemoreceptors and the vagus nerve.

The brainstem control mechanisms can be considered as an involuntary system designed to regulate ventilation so that  $Paco_2$  is kept constant. Voluntary respiratory activities, such as talking, singing and playing a wind instrument, are possible because the cerebral cortex can temporarily override these mechanisms.

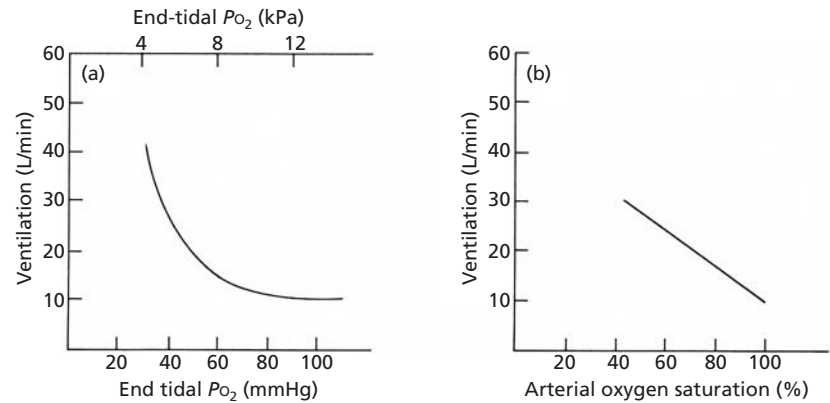
### Higher centres

Electrical stimulation of the cerebral cortex has shown that most areas are inhibitory to respiration, although some motor and premotor areas may be excitatory. Cortical impulses interact with the medullary neuronal network and also descend directly to the spinal cord via the corticobulbar and corticospinal pathways to mediate voluntary respiratory activities.

### Chemoreceptors

#### Carotid chemoreceptors

The carotid bodies, which are situated at the bifurcation of the common carotid arteries, have the highest blood flow per gram of tissue of any organ in the body and are thus uniquely qualified to 'taste' the chemical composition of arterial blood. By altering the chemical composition of arterial blood in an isolated carotid body in animals it has been established that hypoxaemia, hypercapnia and acidosis can increase carotid body nerve discharge and reflexly increase ventilation via an action on the medullary centres [126,127]. The principal stimulus appears to be a fall in  $Pao_2$ ; following bilateral carotid body resection in humans the increase in ventilation caused by hypoxia is abolished, whereas only about 20% of the increase in ventilation due to hypercapnia is abolished [128]. The carotid



**Fig. 2.42** Relationship between pulmonary ventilation and (a) end-tidal  $P_{O_2}$  and (b) arterial oxygen saturation when isocapnic progressive hypoxia is induced over a period of 15 min.

body response to hypoxia is increased in hypercapnia [126].

The ventilatory response to hypoxia in normal humans can be measured by recording ventilation while  $P_{aO_2}$  is reduced by the addition of  $N_2$  to inspired air,  $CO_2$  also being added as required to offset the resulting fall in  $P_{aCO_2}$  [129]. The degree of hypoxia can be measured either as end-tidal (approximately alveolar)  $P_{O_2}$  measured at the mouth with an  $O_2$  analyser or as  $Sa_{O_2}$  measured with an ear oximeter. Typical normal relationships between ventilation,  $P_{O_2}$  and  $Sa_{O_2}$  are shown in Fig. 2.42. The relationship between ventilation and  $P_{O_2}$  is curvilinear, greater increases in ventilation resulting from a fixed fall in  $P_{O_2}$  at lower  $P_{O_2}$  values; the ventilation/ $Sa_{O_2}$  relationship is linear, a logical consequence of the shape of the haemoglobin dissociation curve.

Using methods such as this, a range of normal values for the ventilatory response to hypoxia have been established [130]. The hypoxic drive diminishes with age [131] and has a genetic component [132]. Impaired hypoxic responsiveness has been implicated in chronic mountain sickness [133], the obesity alveolar hypoventilation syndrome [134] and possibly in the pathogenesis of some cases of the 'blue and bloated' syndrome in chronic bronchitis [135]. However, most patients with severe hypercapnic respiratory failure are dependent on their hypoxic drive to continue breathing. Abolition of this drive by inappropriate increases in  $P_{aO_2}$  resulting from  $O_2$  therapy may result in death from  $CO_2$  narcosis secondary to the resulting hypoventilation [136].

### Central chemoreceptors

The  $P_{CO_2}$  of arterial blood is regulated within very narrow limits in humans both at rest and during exercise. Studies in animals have revealed areas on the ventral surface of the medulla that, when stimulated by applications of  $CO_2$  or  $H^+$ -rich fluid or by appropriate changes in the bathing cerebrospinal fluid (CSF), produce an increase in ventilation [137]. These areas, which are remote from the phasi-

cally firing respiratory cells of the medulla, have been designated the central chemoreceptors and are influenced by changes in  $P_{CO_2}$  and  $H^+$  concentration of both arterial blood and CSF. They probably mediate 80% of the increase in ventilation that results from an increase in  $P_{aCO_2}$ .

$CO_2$  diffuses rapidly across the blood-brain barrier from blood to CSF; since CSF is relatively unbuffered compared with blood, an increase in  $P_{CO_2}$  results in a greater decrease in CSF than arterial pH. The resultant hyperventilation lowers  $P_{CO_2}$  and restores arterial and CSF pH towards normal. Studies in animals where  $CO_2$  has been totally removed from blood perfusing the brain have shown that even in the awake animal prolonged apnoea results, suggesting that the medullary centres are dependent on a tonic input from the central chemoreceptors to maintain rhythmic respiration [138].

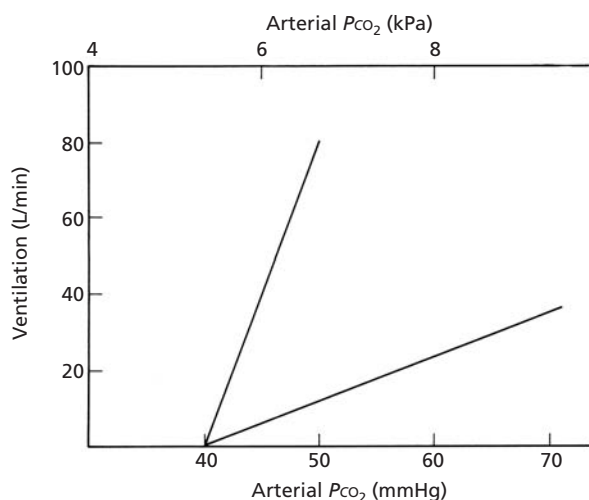
The sensitivity of the central chemoreceptors to increases in  $P_{CO_2}$  can be assessed by measuring the increase in ventilation that results when  $P_{CO_2}$  is increased by adding  $CO_2$  to inspired gas [139], while  $P_{O_2}$  is maintained above 30 kPa (225 mmHg) to abolish the peripheral chemoreceptor contribution [140]. Figure 2.43 shows the range of normal ventilatory responses to  $CO_2$ . The response decreases with age [131] and has a genetic component [132]. The ventilatory response to  $CO_2$  may be decreased by tranquillizer, sedative or narcotic drugs to such an extent that  $CO_2$  retention occurs [141]. Finally, the  $CO_2$  response is diminished in severe chronic airways obstruction, where the increased work of breathing as well as a true fall in central chemoreceptor sensitivity are probably both factors [142].

### Vagal reflexes

#### Pulmonary stretch receptors

There are three reflexes thought to be mediated by stretch receptors located in the bronchi and bronchioles: the inflation reflex (Hering-Breuer reflex), the deflation reflex and the paradoxical reflex of Head.





**Fig. 2.43** Relationship between ventilation and  $P_{aCO_2}$  during carbon dioxide rebreathing in hyperoxia: the two lines represent the extremes of the normal range of response.

### *Inflation reflex*

In 1868 Hering [143] and Breuer [144] showed that maintained inflation of the lungs decreased the frequency of inspiratory efforts in anaesthetized animals and that maintained collapse had the reverse effect. Vagotomy prevents these responses, proving that they are reflex. The vagal afferent input inhibits the discharge of the inspiratory cells of the dorsal respiratory group and hence inspiration. The reflex is present in the human newborn [145] but can only be demonstrated in adults under anaesthesia and only then when inflation volumes of over 800 mL are used [146]. Since this volume exceeds the usual tidal volume at rest, this reflex is not a factor in ordinary quiet breathing.

### *Deflation reflex*

Deflation of the lungs stimulates breathing in animals by a reflex action mediated by stretch receptors [147]. The reflex is unlikely to be active in ordinary breathing but may stimulate the rate and force of inspiration in pneumothorax or atelectasis.

### *Head's paradoxical reflex*

In 1889, Head [148] showed that inflation of the lungs of rabbits when the vagus nerve was partially blocked (during recovery from freezing) gave no inflation reflex but instead resulted in a prolonged and vigorous contraction of the diaphragm. Two observations have suggested possible physiological roles for this paradoxical reflex. The occasional deep breaths that punctuate ordinary quiet breathing [149], which are believed to prevent the microatelectasis that would otherwise occur, disappear

after vagotomy and it has been suggested that they may be due to the paradoxical reflex [150]. Cross and his colleagues [145] observed gasps when the lungs of newborn babies were inflated during the first 5 days. They have suggested that the mechanism is analogous to the paradoxical reflex and that it may promote aeration of the neonatal lung.

### **J receptors**

The prime physiological stimulus to the juxtapulmonary capillary or J receptors is pulmonary congestion, i.e. increase in pulmonary capillary pressure [151,152]. J receptors are responsible for rapid shallow breathing when stimulated by pulmonary congestion and oedema, microembolism and inhalation of certain chemical substances [153]. Other reflex effects of J receptor stimulation are hypotension, bradycardia and marked expiratory narrowing of the larynx. The latter occurs typically in newborn infants with respiratory distress and may explain the expiratory grunting that characterizes the condition.

### **Pulmonary irritant receptors**

Receptors lying in the bronchial epithelium have been shown in animals to discharge in response to irritant gases (smoke,  $SO_2$ , etc.), lung collapse and a variety of other pulmonary insults resulting in reflex bronchoconstriction [154,155] and hyperventilation. Stimulation of these receptors may cause acute asthmatic attacks in susceptible individuals.

### **Cough receptors**

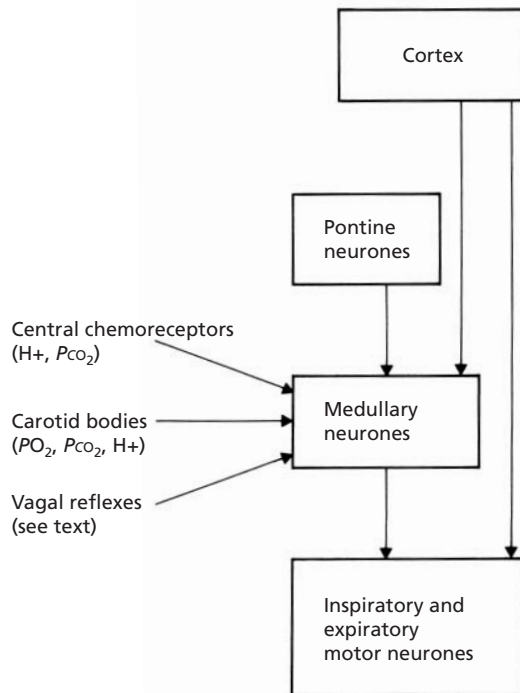
Receptors lying in the large airways are responsible for the cough reflex, which results in an expulsive cough in response to airway irritation [156]. Cough consists of an inspiration followed by expiration against a closed glottis, with a resultant rise in intrathoracic pressure. On opening the glottis, gas flow is accelerated to a high velocity in the airways with consequent expulsion of mucus and the offending irritant [157].

Figure 2.44 summarizes the factors that operate to determine the level of pulmonary ventilation.

## **Defences of the respiratory tract**

### **Upper respiratory tract**

Each day 10000–20000 L of air, which may vary in temperature, humidity and content of particulate matter and noxious gases, pass into the respiratory tract and are subjected to considerable processing by the upper respiratory tract before entering the lungs. The nose is the first line of



**Fig. 2.44** Synthesis of factors influencing and controlling pulmonary ventilation.

defence in the respiratory tract and has a number of important functions.

#### Air conduction

Adults preferentially breathe through the nose unless there is obstruction, e.g. nasal polyps or mucosal oedema; in infants nasal breathing is compulsory except when crying [158]. During quiet breathing the resistance of the nasal passages (most of which resides in the anterior 2–3 cm of the nose [159]) is approximately 50% of the entire respiratory tract resistance to airflow, while during mouth breathing the upper respiratory tract constitutes only 20% of the total respiratory tract resistance [159]. With each inspiration some air from the paranasal sinuses joins the nasal airstream and the reverse occurs on expiration [160].

#### Defence

There is a high impaction rate of particles greater than  $5\mu\text{m}$  in size, particularly in the anterior part of the nose and in the nasopharynx [161]; very small particles ( $<0.01\mu\text{m}$ ) also settle out by diffusion in the nasopharynx [162]. The nasal mucociliary mechanism propels mucus and deposited particles posteriorly to the pharynx where they are disposed of by swallowing. The transit time for the nasal mucociliary escalator in normal subjects varies from 4 to 30 min, with a mean transport time of 5.3 mm/min

(range 0.5–23.6 mm/min) [163] as determined by the saccharin test [164] or transport of radioactive particles [163]. The mucus secreted in the nose may contain specific secretory IgA antibody [165], as well as other non-specific antibacterial substances.

#### Air conditioning

The nasal mucosa operates a countercurrent heating and humidification system to ensure that air reaching the alveoli is saturated with water and close to body temperature, much of the heat and water added on inspiration being recovered on expiration [166]. The large cross-sectional area and narrowness of the nose ensure maximum contact between air and mucosal surfaces, aided by the low linear velocity of air and the mixing effects of turbulence [166]. The extensive mucosal capillary beds and the presence of erectile vessels are presumably of major importance in regulating the amount and water content of surface fluids, these mechanisms being under autonomic control although the reflex arcs are unknown [166]. Over a wide range of temperatures of inspired air, the nasal air conditioning mechanism achieves a temperature of 28–32°C in the nasopharynx that further increases towards body temperature in the bronchial tree [166]. Mouth breathing is less effective at increasing the temperature of inspired air [166].

#### Lower respiratory tract

##### Mucociliary escalator

The mucociliary escalator is the primary pulmonary mechanism for clearing airway surfaces of foreign materials. Each ciliated epithelial cell bears approximately 200 cilia beating about 1000 times per minute (slower in peripheral airways [167]) in the low-viscosity fluid that covers the epithelium. Scanning electron microscopy demonstrates that discrete flakes or droplets, rather than a blanket, of mucus are transported on the low-viscosity layer [168].

Airway secretions consist of a gel of mucus or glycoproteins dispersed in a continuous sol phase [169]. The volume of airway secretions represents a balance between secretion and reabsorption [170] and in normal laryngectomized patients may be as little as 10 mL daily [171]. Secretion may be increased, e.g. in chronic bronchitis or asthma, either reflexly or via the action of mediators such as the leukotrienes and histamine, which are potent secretagogues [172].

Tracheal mucus velocity can be assessed in humans by measuring the linear velocity of radio-opaque Teflon discs insufflated into the trachea through a fiberoptic bronchoscope; values of about 20 mm/min have been recorded in normal humans [173]. Tracheal mucus velocity is

decreased in smokers and patients with chronic bronchitis and asthma. The decrease seen in asthmatic subjects deteriorates further on antigen challenge, an effect reversed by the slow-reacting substance antagonist FPL55712, suggesting that anaphylactically released leukotrienes may be responsible [174].

The importance of this air-conditioning mechanism is emphasized by the frequent complications seen with endotracheal intubation or tracheostomy if the inspired air is not adequately humidified. Drying of the respiratory mucosa compromises mucociliary transport and predisposes to infection. Nevertheless, the tracheobronchial mucosa is capable of adaptation to a situation in which the warming and humidifying functions of the nose are absent. Patients with total laryngectomy breathe directly in and out of the trachea, and although there is an initial period of adjustment there appears to be little final inconvenience [175].

### Cough reflex

Cough may be consciously or reflexly induced. The reflex is due to stimulation of receptors in the epipharynx, larynx or large airways and is conducted in myelinated fibres [156]. The cough reflex exists as both a protective and a clearance mechanism for disposing of excessive secretions from the airways. Coughing starts with a brief inspiration of air larger than tidal volume followed by glottic closure for about 0.2s, which allows pressure to build up in the abdominal, pleural and alveolar spaces to about 6.6–13.3kPa (50–100mmHg) by an expiratory effort. Active opening of the glottis [157] is followed by accelerating expiratory flow at the mouth that reaches a peak of as much as 12L/s within 30–50ms [157] and terminates usually 0.5s later with glottic closure. The coughing sequence may be repeated rapidly several times, progressing through the lung volumes to RV and successively collapsing more and more of the intrathoracic airways [176].

### Alveolar macrophages

The alveolar macrophages are the sentinels of the alveoli and the probable explanation for the usual sterility of the alveolar surface [177]. These large (approximately 20µm) cells are found free in the alveolar spaces and are believed to be derived, at least partly, from bone marrow mononuclear phagocyte precursors [178–181] and possibly also from local proliferation [182] within the interstitium [183] with subsequent migration to alveolar spaces.

Alveolar macrophages ingest particulate matter after opsonization with C3b or IgG via the macrophage membrane receptors for C3b and the Fc portion of IgG [184]. Alveolar macrophages also ingest bacteria, fungi and viruses [185,186] and this ingestion is optimal following

opsonization by immunoglobulin or complement [187]. Following ingestion of particulate matter or organisms, alveolar macrophages become activated, as shown by increased O<sub>2</sub> uptake [188], more rapid glucose utilization [185,188], increased superoxide production [188] and release of the macrophage chemotactic factor for neutrophils [189]. Activated macrophages have an increased content of lysosomal enzymes [190] and are better microbial killers, presumably through fusion of phagosomes with the bactericidal enzymes present in lysosomes to form phagolysosomes [191].

Alveolar macrophages comprise the majority (>90%) of the cells obtained by the technique of bronchoalveolar lavage via the fiberoptic bronchoscope [192], greater numbers being obtained from smoker's lungs. The alveolar macrophages of smokers are activated, as evidenced by increased numbers of lysosomes, phagolysosomes, endoplasmic reticulum, ribosomes and Golgi vesicles [193,194], presumably secondary to the injection of the particulate matter of cigarette smoke.

Alveolar macrophages are found in sputum and the majority are probably cleared from the alveoli by migration to, and transport up, the mucociliary system. Some possibly migrate to the interstitium and may be cleared by the lymphatic system [191].

### Immunological defence mechanisms

See Chapter 4.

## Other aspects of pulmonary function

### Pulmonary function during exercise

Exercise stresses both the pulmonary and cardiovascular components of the O<sub>2</sub> transport system and responses to exercise are often used in the evaluation of patients with pulmonary disease, particularly in the elucidation of the symptom of dyspnoea [195–199]. Exercise is usually performed on a treadmill or a bicycle ergometer, with the subject being exposed to progressively increasing workloads (e.g. 100kPa·m/min increments every minute on a bicycle ergometer). In normal young subjects exercise continues until exhaustion, but in patients and those over 40 years old exercise is usually stopped when the heart rate reaches 85% of the maximum predicted for age [200]. In a simple exercise test measurements are made before, and at intervals during, exercise of minute ventilation, respiratory rate and tidal volume, cardiac frequency, O<sub>2</sub> uptake, CO<sub>2</sub> output and an index of oxygenation, which is usually O<sub>2</sub> saturation measured by an ear oximeter [63], although arterial blood samples may also be taken.

With increasing workload, or in metabolic terms O<sub>2</sub> uptake, minute ventilation increases linearly until anaerobic sources begin to contribute to the energy supply at

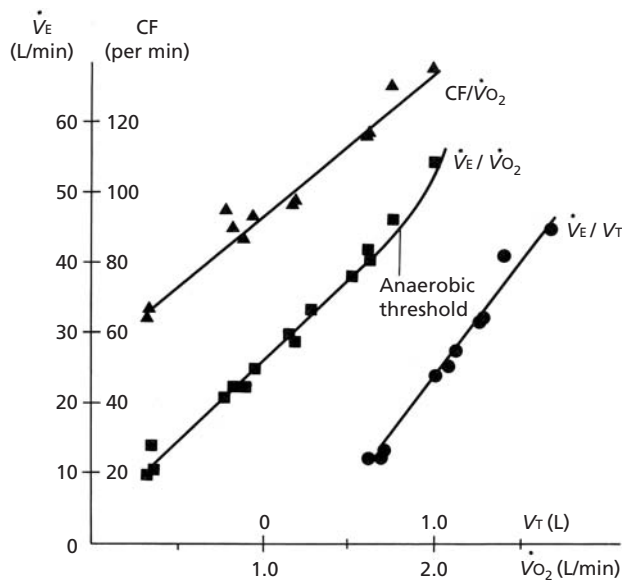


Fig. 2.45 Relationship in a normal subject of cardiac frequency (CF) and ventilation ( $\dot{V}_E$ ) on oxygen uptake ( $\dot{V}_{O_2}$ ) and of ventilation on tidal volume ( $V_T$ ). (From Cotes [204].)

about 50–60% of maximal  $O_2$  uptake, the anaerobic threshold [201]. Above the anaerobic threshold the lactic acid produced by anaerobic metabolism provides an added drive to breathing and ventilation increases more steeply with increasing work rate or  $O_2$  uptake (Fig. 2.45). Tidal volume increases linearly with  $O_2$  uptake until a maximum value is reached above which further increases in minute ventilation are only possible by increasing respiratory rate [202]. Similarly, heart rate increases linearly with  $O_2$  uptake to a maximum dependent on the subject's age [200] (Fig. 2.45). In normal subjects hypoxaemia does not occur even at strenuous levels of exercise [203].

Normal ranges for the cardiovascular and ventilatory responses to exercise have been defined. Since maximal exercise studies are not desirable in patients, a number of simple indices derived from submaximal exercise studies can be used to describe exercise responses [204]: (i) minute ventilation; (ii) cardiac frequency at specified submaximal  $O_2$  uptake, usually 1.0 or 1.5 L/min; and (iii) tidal volume at a fixed level of minute ventilation, usually 30 L/min.

Patients with respiratory disease alone stop exercising at a heart rate below the maximum predicted for their age, since the factor limiting exercise in both obstructive and restrictive disease is the ventilatory capacity [205,206]. The ventilatory response to exercise is therefore greater than predicted while the cardiac response is normal. Where the heart is also compromised, as in recurrent pulmonary embolism or left heart failure, both ventilatory and cardiac responses to exercise exceed predicted values.

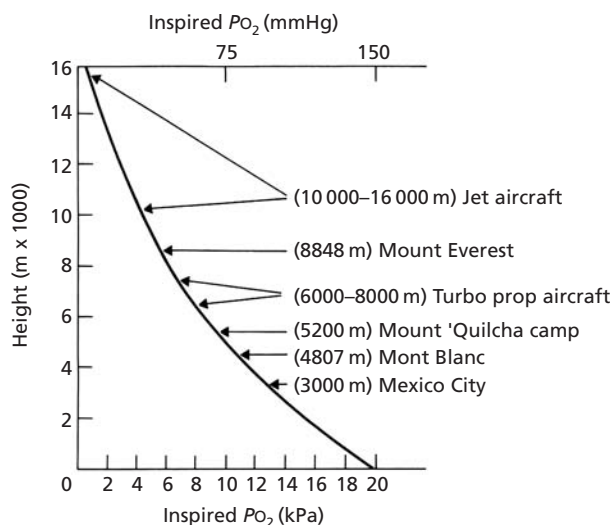
A simple test of exercise capacity is the 12-min walking distance, i.e. the distance walked in 12 min on the flat; the only apparatus required for this test is a clock and a corridor [207]. The test has the advantage that it is based on a universally familiar activity (not everyone cycles) and allows subjects to adjust their pace during the test. In patients with airways obstruction or restrictive lung disease, the 12-min walking distance correlates significantly with the response to a standard questionnaire scaling subjective impressions of exertion and with patients' assessment of their own performance using an  $O_2$  cost diagram [207]. The 12-min walking distance correlates better with FVC than  $FEV_1$  in both obstructive and restrictive disease and correlates well with  $DL_{CO}$  in those with pulmonary infiltration. The measurement of 12-min walking distance has since been applied successfully in assessing the value of bronchodilator therapy in patients with chronic bronchitis and emphysema [208,209]. More recently, it has been found that the 6-min walking distance is as useful an index as the 12-min walking distance [210].

### High-altitude physiology

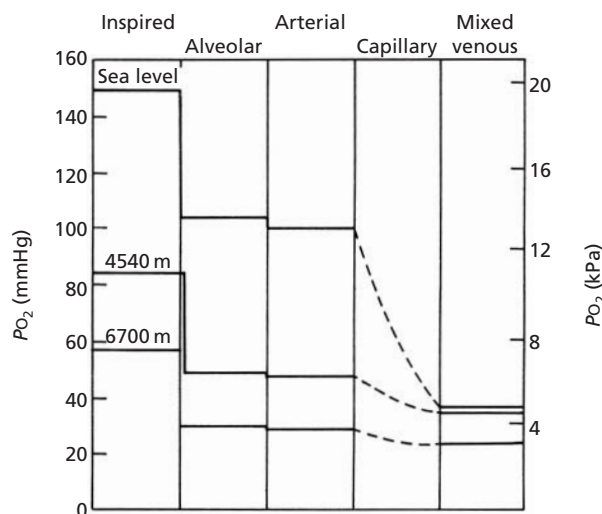
The main factor determining physiological adaptation to high altitude is hypoxia [211,212]. With decreasing atmospheric pressure, the prevailing partial pressure of  $O_2$  also falls (Fig. 2.46); as a consequence the partial pressures of  $O_2$  in the  $O_2$  cascade also fall (Fig. 2.47). The adaptive physiological changes in native-born high-altitude dwellers (natural acclimatization) are complex and range from changes in ventilatory response, haemoglobin and rates of blood flow to carotid body hyperplasia, altered myocardial metabolism, pulmonary arterial hypertension and changes in the rate of body growth. Although Mt Everest (8848 m) has been climbed without supplemental  $O_2$ , there does appear to be a finite level of altitude above which permanent residence is not possible. Andean humans have survived by natural acclimatization at 4200–4500 m for 10000 years but people wintering in the Himalayas at 5700 m have progressively lost weight despite adequate caloric intake. In addition to the adaptive physiological changes seen at high altitude, pathological conditions due to hypoxia also occur and these principally affect the cardiopulmonary system.

### Ventilatory adaptations

Exposure to high-altitude hypoxia increases minute ventilation and lowers  $P_{ACO_2}$ , an effect reversed by giving  $O_2$ . However, after a few days at high altitude there is a further increase in ventilation that is not abolished by  $O_2$  therapy. The resultant respiratory alkalosis is soon compensated for by renal excretion of bicarbonate. This is associated with an increase in the ventilatory response to inhaled



**Fig. 2.46** Inspired oxygen pressures at various heights above sea level. (From Heath & Williams [211].)



**Fig. 2.47** Mean oxygen pressure gradients from inspired air to mixed venous blood in subjects native to sea level and 4540 m and in climbers at 6700 m. The oxygen cascade at high altitude is much less steep than at sea level. In spite of a much lower inspired  $PO_2$  the final  $PO_2$  achieved in mixed venous blood is not much lower at high altitude than at sea level. (Modified from Heath & Williams [211].)

$CO_2$  [213]. The conventional explanation for the maintained hyperventilation is as follows. Altitude hypoxia causes hyperventilation with a resultant decrease in arterial and CSF  $P_{CO_2}$ . The rise in CSF pH that follows minimizes the initial hyperventilation until CSF pH is restored to normal over 5–10 days by active transport of  $HCO_3^-$  out of the CSF. The hyperventilation is then established and, since CSF  $HCO_3^-$  has fallen, small increases in  $P_{CO_2}$  now produce larger decreases in CSF pH with attendant hyperventilation, i.e. an increased ventilatory response to

inhaled  $CO_2$ . However, measurements of CSF pH during acclimatization and deacclimatization do not fit with the above hypothesis and it would appear that other, as yet unknown, factors may be responsible for ventilatory acclimatization [214,215].

The amount of increase in ventilation and decrease in  $P_{CO_2}$  varies with altitude and with time at a given altitude. Andean Indians and Himalayan Sherpas ventilate less than acclimatized lowlanders. This is probably due to their marked carotid chemoreceptor insensitivity to hypoxia [216,217], which may result from exposure to a low ambient  $PO_2$  in the early years of life [218]. Arterial blood gas measurements, minute ventilation and FVC measured at rest in Operation Everest II, a decompression chamber study [212], are shown in Table 2.3. At 8848 m, the height of Mt Everest,  $P_{aO_2}$  was only 4.0 kPa (30 mmHg) at rest and hyperventilation lowered  $P_{aCO_2}$  to 1.5 kPa (11 mmHg) and raised arterial pH to 7.56. FVC fell with increasing altitude, a phenomenon attributed to increased central blood volume and interstitial oedema.

### Haematological adaptations

Both native-born and long-term residents at altitude develop an absolute polycythaemia associated with an increase in the number of red blood cells and in haemoglobin, resulting in an increased transport capacity for  $O_2$ . The haematocrit appears to correlate best with  $SAO_2$ , which of course is dependent on the ambient  $PO_2$ . The polycythaemia is due to an increase in circulating erythropoietin [219] and takes months to develop fully. In spite of the decreased saturation, a given volume of arterial blood in natives resident at high altitudes contains a greater amount of  $O_2$  than is found in controls at sea level. It has also been shown that the affinity of haemoglobin for  $O_2$  is decreased at high altitude so that the  $O_2$  dissociation curve at a given pH is displaced to the right, thus facilitating the release of  $O_2$  to the tissues. This change in affinity is due to increased production in the red cell of 2,3-DPG, which decreases the  $O_2$  affinity of haemoglobin and moves the  $O_2$  dissociation curve to the right [220].

### Circulatory adaptations

Rapid movement to high altitude results in tachycardia. With acclimatization, both the heart rate and resting cardiac output become normal. For reasons that are unknown the stroke volume and cardiac output are reduced during exercise and this applies to acclimatized residents as well as newcomers [212,221–223].

The natives of high altitudes show a moderate degree of pulmonary hypertension that does not correlate well with age or haematocrit and tends to increase abruptly with exercise or further hypoxia. The hypertension cannot be explained on the basis of increased pulmonary blood



**Table 2.3** Resting measurements at several barometric pressures in Operation Everest II [212].

Barometric pressure (kPa)	Altitude (m)	$P_{aO_2}$ (KPa)	$P_{aCO_2}$ (KPa)	Arterial pH	$\dot{V}_E$ (L/min)	FVC (%)
101 (760)*	0	13.7	4.5	7.43	11	100
57 (429)	4800	6.3	3.3	7.46	15	96
46 (347)	6300	5.2	2.6	7.50	21	92
37.5 (282)	8100	4.6	1.6	7.53	37	87
33.5 (252)	8848	4.0	1.5	7.56	42	86

\*, values in parentheses represent mmHg.  
FVC, forced vital capacity.

volume, although this probably occurs to some degree at altitude, and results partly from increased precapillary vascular resistance due to pulmonary arterial constriction caused by hypoxia.  $O_2$  given for short periods reduces the pulmonary hypertension at altitude but the pulmonary artery pressure never reaches sea-level values. This has been explained by a fixed, high pulmonary vascular resistance due to medial smooth muscle hypertrophy in the pulmonary arterial tree. It seems probable that involution of the smooth muscle of the fetal pulmonary vasculature does not occur at altitude because of hypoxia.

Studies of the elastic configuration of the larger pulmonary arteries have been helpful in elucidating the natural course of high-altitude pulmonary hypertension. At sea level the pulmonary trunk of the newborn contains long, parallel, tightly packed elastic fibres as in the aorta. As age progresses the elastic content of the pulmonary trunk decreases [223]. In high-altitude natives, this regression of elastic fibres in the larger pulmonary arteries does not occur and has been found to persist in subjects born at high altitudes who have subsequently lived for several years at sea level. This is in contrast to the medial muscle hypertrophy, which is known to remit, along with the pulmonary hypertension, after prolonged stay at sea level. The persistent elastic configuration of the pulmonary trunk is thought to represent a property of the elastic material in the vessel wall of the adult rather than being evidence of pulmonary hypertension [223].

The functional significance of the pulmonary hypertension of altitude is not known. It may simply be the consequence of accommodation to hypoxia in fetal life.

### Other adaptive changes

High altitude has an adverse effect on body weight and growth generally in the laboratory animal and in humans [224], although the effect is very much less on the lungs so that TLC in relation to height or body weight is increased [224,225]. The membrane component of the diffusing capacity ( $D_m$ ) is increased in high-altitude natives [226] but overall diffusing capacity does not appear to increase in lowlanders with acclimatization [227].

The carotid bodies of subjects living at high altitude in

the Andes are larger than those living on the Peruvian coast [228]. Experimental studies have shown that this also occurs in animals and is presumably due to chronic hypoxia [229].

Coronary blood flow per time and per unit mass is lower at high altitude than at sea level in spite of the lower  $P_{aO_2}$ , contrasting with the classical view that hypoxia is a potent vasodilator for coronary vessels. The lower coronary flow is not compensated by an increased haematocrit or arterial oxygenation; the  $O_2$  supply to the heart is simply lower. Nevertheless a high degree of adaptation seems to occur since there is no evidence of insufficient oxygenation of the myocardium,  $O_2$  extraction by the heart is normal and there is no indication of anaerobic metabolism in normal subjects living permanently at high altitude [230]. The  $O_2$  consumption of the heart is lower through some sparing mechanism of the heart cells, as yet not fully understood. The myocardium at altitude is therefore more efficient in that it can work effectively with less  $O_2$ . While using the same substrates to create its energy, the heart at high altitude consumes more carbohydrate, particularly lactate, and this may explain in part the increased efficiency. It is an interesting observation that angina pectoris and myocardial infarction are rare at high altitude [230]. Anatomical differences may contribute since it has been shown that high-altitude natives have more abundant coronary channels than those resident at sea level [231].

Cutaneous blood flow decreases at high altitude, the blood being redistributed as a reservoir of  $O_2$  to the other organs of the body.

### Diseases of altitude

Acute mountain sickness [232] is a condition affecting lowlanders 6–90 h after rapid ascent to altitude. It is characterized by lethargy, insomnia, headache, nausea, vomiting and dyspnoea. In severe forms cyanosis, crepitations in the lungs, papilloedema and other signs of cerebral oedema are also features. The cause is not known for certain but fluid retention probably plays an important role and pretreatment with diuretics, especially acetazolamide, has proved an effective preventive measure [233].

Loss of acclimatization to high altitude may occur acutely, giving rise to high-altitude pulmonary oedema, or chronically, causing chronic mountain sickness.

### Clinical applications of pulmonary function testing

The application of pulmonary function testing in specific clinical conditions is discussed in the appropriate chapters in this book. In general terms chest physicians need not consider themselves underequipped if access to standardized [234–238] measurements of PEFR, dynamic lung volumes ( $FEV_1$ , FVC), static lung volumes and  $DLCO$ , arterial blood gas tensions and exercise testing responses are available.

Most diagnoses in respiratory medicine can be made (or strongly suspected) after talking and listening to the patient; the diagnosis may be confirmed by the findings made on physical examination (see Chapter 6). Pulmonary function tests may be used to confirm or establish the diagnosis or, in the case of potentially progressive disease, to establish baseline pulmonary function with a view to future monitoring. Many of the tests outlined earlier in this chapter are described solely to enhance the reader's understanding of how the respiratory system functions; most of them have been used only in research applications. In the clinical situation simple pulmonary function tests may provide an answer to the most commonly asked questions: Does this patient have airways narrowing or obstruction? Does this patient have restrictive lung disease? Why is this patient breathless?

For the assessment of *airways narrowing or obstruction* simple measurements of  $FEV_1$  or FVC (see p. 43) are more than adequate. If asthma is suspected, regular monitoring of PEFR (see p. 45) may reveal significant diurnal variation or association with exercise or occupational exposure. Testing for exercise-induced asthma may be necessary. Measurement of a significantly reduced  $DLCO$  or  $Kco$  suggests emphysema but is unlikely to influence management.

The tradition of separating patients with airways narrowing or obstruction into those with 'reversible' and 'irreversible' airways obstruction on the basis of whether  $FEV_1$  does or does not improve by 10–15% following a bronchodilator should be discarded. Improvement in PEFR or  $FEV_1$  following a bronchodilator, however great or small, is usually an indication that the patient will derive subjective and objective benefit (e.g. improved exercise tolerance, 12-min walking distance, see p. 55)

from such therapy. Large improvements in pulmonary function (>20%) following a bronchodilator suggest a diagnosis of asthma; lesser improvements are more consistent with chronic bronchitis and emphysema with airways obstruction; however, there are no absolute rules in medicine.

Maximal flow–volume curves provide no additional useful information on patients with obstructive airways disease. Their value is in the assessment of central airways narrowing, most commonly due to tumour, where it is unusual for clinical or radiological evidence to be absent at the time of testing.

Although the classical symmetrical reduction in  $FEV_1$  and FVC is likely to be obtained in the patient with *restrictive lung disease*, confirmation of the reduced static lung volumes and diminished  $DLCO$  is essential. Resting oxygenation, measured as either  $PaO_2$  or  $SaO_2$ , should also be assessed. Serial estimations of lung volumes and  $DLCO$  are of value in assessing progression of disease and the response, or lack of it, to therapeutic intervention, for example in pulmonary sarcoidosis or cryptogenic fibrosing alveolitis.

The assessment of patients with *breathlessness* presenting to a chest clinic (see Chapter 6) is usually straightforward; on the basis of the history, examination, chest radiology and simple pulmonary function testing most patients prove to have obstructive or restrictive pulmonary diseases [239]. If asthma has been excluded and the chest radiograph, lung volumes and  $DLCO$  are normal, then most primary pulmonary diseases can be excluded as causes of breathlessness although, occasionally, recurrent pulmonary thromboembolism may present in this way (see Chapter 25).

The presence of a restrictive defect as indicated by reduced static lung volumes in the presence of a normal chest radiograph and  $Kco$  suggests the possibility of an extrapulmonary cause such as respiratory muscle weakness. In such cases, determination of maximum inspiratory and expiratory pressures would be appropriate.

It is sometimes difficult to distinguish cardiac from respiratory causes of exertional dyspnoea, particularly in cigarette smokers who may have combined disease. Progressive exercise testing (see p. 54) with determination of the ventilatory and cardiac responses to exercise may provide helpful pointers to the dominant cause of dyspnoea; often the system at fault is only identified by appropriate therapeutic trials.

Finally, a small minority of patients prove to have hyperventilation or related syndromes; these are dealt with in Chapter 48.

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# EPIDEMIOLOGY

ANTHONY SEATON

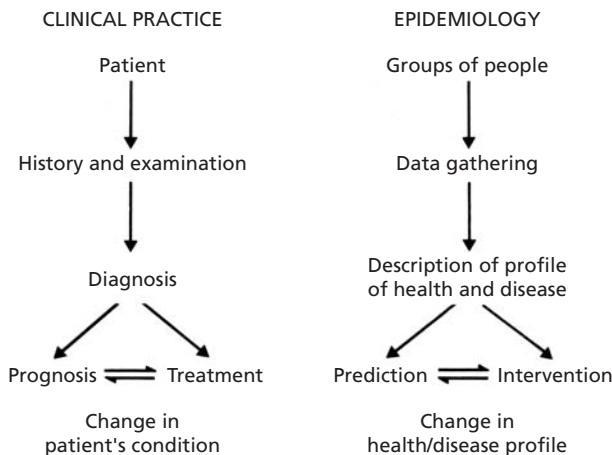
In treating individual patients the clinician has little feel for the overall frequency of disease. Hospital physicians may from time to time become aware of an unusual number of patients with pneumonia or with asthma related to work in a particular factory, but our view of disease is necessarily biased by seeing only a highly selected group of subjects. In clinical practice, therefore, it is usual to spend relatively little time investigating the causes of the diseases one sees, the main concerns being their diagnosis and cure. In order to learn more about the patterns of disease and their causes the physician needs to understand something of epidemiology.

Epidemiology literally means the study of epidemics, a word coined by Hippocrates to describe the concept of the occurrence of disease in patterns, affecting many people at the same times of year (*epi demos*, among the people). As is still the case with much medical research, the study of epidemics has over the centuries been influenced by the fashion of prevailing theories; Galen in the first century AD placed the emphasis on man's constitution, though he recognized that this could be influenced by external factors such as diet or exercise, while Sydenham in the seventeenth century looked upon disease as the body's attempt to expel malign influences, or miasmata, derived from the earth. Such miasmata held sway, with contagion, as suspected causes of disease for almost two centuries after Sydenham, until the gradual appreciation in the nineteenth and twentieth centuries of the importance of microorganisms and pollutants as external, and of genetic factors as constitutional, determinants of disease.

The conflict between apparently rival causes of disease continues, perhaps in a less overt manner, driven by the special interests of research workers. Until quite recently, much research into the causes of disease focused on the pathogenetic mechanisms, for example the immunological, biochemical and molecular reactions occurring when a tissue is injured or as cancer occurs in an organ. Such research clearly has value: in understanding the changes in a cell, it may be possible to modify such changes by treatment or even prevent them by production of a

vaccine. However, the approach has limitations when the ultimate aim is prevention. To take a well-known example, and one that is a classical illustration of the method and purpose of epidemiology, the waves of cholera epidemics in Britain that accompanied the Industrial Revolution were ultimately eliminated by improved hygiene measures derived from the work of John Snow. Snow studied the patterns of these epidemics in London and was able to show greater than fivefold differences in incidence of the disease between populations obtaining their water from different suppliers. He hypothesized that faecal contamination of drinking water was responsible and was subsequently able to test this hypothesis by preventing access to a pump supplying contaminated water to people around the Broad Street area of London and to show that the epidemic then waned. Application of more modern tests to this famous episode might have cast some doubt on the precise causal relationships between removal of the pump handle and decline of the epidemic, but the point was well made: epidemiology has its major application in the prevention of disease.

Since the time of Snow (he published his first work on cholera in 1850, 33 years before *Vibrio* was described by Koch) much has been learnt about the pathogenetic mechanisms of disease. Epidemiology has also spread its wings, and now concerns itself with the overall study of the patterns of health and disease, appropriately in view of the original observations of Hippocrates and Sydenham, rather than confining itself to epidemics of infection. It may be defined as the study of the distribution and determinants of health and disease in groups of people. An important distinction from clinical medicine is thus made: the epidemiologist studies populations, the clinician (*cline*, a bed) studies and treats sick people. However, there is a useful analogy between their activities (Fig. 3.1). The clinician studies a patient, making observations by history-taking and various examinations that properly lead to a diagnosis. This in turn leads to the possibility of both prognosis and treatment, each of which may influence the other. The process is essentially the application of



**Fig. 3.1** Analogy between clinical and epidemiological practice. (Courtesy of Dr Michael Jacobsen.)

deductive logic, a process well known to Sherlock Holmes (whom Sir Arthur Conan Doyle modelled on Dr Benjamin Bell, the Edinburgh surgeon who, among other things, described skin cancer in workers producing paraffin from oil-shale). In this form of reasoning, arguing from the general to the particular, information derived from the general body of medical knowledge is used to draw conclusions about a particular patient. By analogy, but in contrast, the epidemiological process uses inductive logic, arguing from the particular to the general; the epidemiologist studies a group of individuals, gathering data on that group in a systematic way. This allows the description of a profile of health and disease in the group, from which it may be possible to make predictions as to what might happen if certain determinants of health or disease were altered (e.g. if people were prevented from drinking contaminated water). It may also be possible to make recommendations for intervention that could lead to improvements in the health of the group. Thus epidemiology, like clinical medicine, may have as its objective not only description of the pattern of a disease but also its amelioration, but in groups rather than individuals.

## Some principles in planning an epidemiological study

### What is the question?

The stimulus to make observations on groups of people has usually come from observations on individuals by astute clinicians, although recently concern about occupational and environmental pollutants has led increasingly to questions about the safety of substances being asked by non-medical people. The first step in an epidemiological study is to rephrase the often rather ill-defined question in terms that are answerable by the application of this discipline. For example, the clinician may notice a lot of cough

and wheeze in wool-workers and ask if the wool causes asthma. This may easily be answered in a clinical sense by a challenge test in the particular individual, but the epidemiological question requires a different approach. An appropriate investigation may set out to answer the question: What, if any, relationship exists between certain respiratory symptoms and measurements of exposure to wool dust? Or again, the clinician may think there are radiological changes on the chest films of some workers exposed to polyvinylchloride (PVC) dust and ask if PVC exposure causes pneumoconiosis. The epidemiologist might ask: Is there a relationship between exposure to PVC dust and small opacities on the chest radiograph? Note the transformation; the clinician thinks in terms of diseases and their causes, while the epidemiologist thinks in terms of relationships between possible determinants of disease and measurable manifestations of that disease.

Of course, the simple epidemiological question may not be sufficient to satisfy the clinician. To pursue the examples above, one may wish to know about the functional effects of wool dust on the lungs or of radiological changes in workers exposed to PVC. These give rise to additional or subsidiary questions: Is there a relationship between exposure to wool dust and certain measurements of lung function? Do workers with radiological changes have different lung function from other workers without radiological changes? The principle is to write down a short list of simple questions. Much bad epidemiology, in avoiding the discipline of clarity in defining objectives, results in the accumulation of a mass of data from which no useful conclusions can be drawn.

### Keep it simple

In investigating a patient, it is commonplace to perform many complex tests and ask a multitude of questions, analysis of which within the doctor's brain can lead to a diagnosis. The instinct of the clinician embarking upon an epidemiological study is therefore to obtain a lot of information on every individual. However, the complexities of gathering and analysing many pieces of information from hundreds or even thousands of subjects make it desirable that the data obtained are those most directly related to the questions being addressed. Moreover, it is essential that information obtained from groups of people is obtained from each individual in a standardized manner. Every questionnaire administered and every test carried out must be assessed with regard to its repeatability and reliability; clearly the more information obtained, the more scope there is for problems with repeatability and the more care and effort is required to ensure consistency. Another important problem with epidemiological studies is their cost, which is related largely to the salaries of the people carrying out the study. The more complex the study, the greater the cost.

### Define the population

Since the epidemiologist studies groups of people, it is essential that the group to be selected is clearly defined. For example, a carelessly designed study of death from coronary artery disease might mistakenly conclude that the condition is related to coal-mining as the result of investigating the causes of death and occupations of people subjected to autopsy in a mining area such as South Wales. However, examination of the population, in this case those undergoing autopsies, would show that a disproportionately large number of individuals in South Wales are coal-miners, where the law relating to industrial injuries benefit ensures that most miners have autopsies. The flaw in such a study would be a lack of information about the denominator, the autopsy population. In planning an epidemiological study, it is essential to consider first the population at risk. This may be the population of a whole nation or some subdivision by age or geography, the workforce of an industry or a factory, the patients attending a hospital or all those undergoing an autopsy. Each of these groups is selected in some way (even a national population is a mixture of different racial or tribal types) and an awareness of factors influencing this selection bias is important when conclusions are drawn from the study.

The *target population* for a study might be defined as that group whose pattern of health and sickness the investigator wishes to define. This may be too large a group to study, in which case a *study population* might be identified; for example, rather than studying all wool-workers, those employed in a representative selection of factories might be chosen. This may of course introduce some bias, if it happened that particularly dusty or non-dusty factories were chosen, so considerable care needs to be exercised in selecting such a study population. If this group is again too large to examine, a *study sample* might be selected, by a randomized method that can if necessary be stratified to ensure sufficient representation of appropriate age or ethnic groups, ranges of exposure to respiratory hazards, and so on.

### Use an appropriate study design

Perhaps the single most important piece of advice to a clinician planning an epidemiological investigation is to involve a statistician in the design of the study. Most doctors are aware of the frustration at being asked to advise on the care of a patient when delays and errors of management have led to an irretrievable situation. Statisticians might be expected to have similar feelings when asked to analyse the results of a study planned either without a clear concept of the questions to be answered or using a design inappropriate to their solution. Decision on study design stems from clarity in defining the questions,

and several broad types of epidemiological study are discussed below.

In general, a desire to establish the *prevalence rate* of a condition, i.e. the proportion of people in a population at any one time with the disease or symptom of interest, may be satisfied by carrying out a *cross-sectional study*. The *incidence rate* of a condition, i.e. the proportion of people in a population developing a disease or symptom over a defined period, is measured by a *longitudinal (or cohort) study*. A properly controlled cross-sectional study may give clues about the aetiology of disease, for example the finding of a high prevalence of bronchitis in certain polluted towns or of an increased prevalence of asthma in circuit board manufacturers. Such clues may then require specific follow-up studies to test the hypotheses derived from them. Two types of study might be considered: (i) a *case-control study*, in which individuals suffering from the condition of interest are compared with control subjects, either healthy or suffering from unrelated disease; or (ii) a longitudinal study, in which the incidence of the condition in a cohort is measured in relation either to the exposure of individuals in the cohort to the aetiological factor in question or to some planned intervention.

### Standardize the methods

Data gathered in an epidemiological study are obtained from many different people, often by several different observers, and seriously misleading results may be obtained if these data are not gathered in a carefully standardized manner. As a result, bias, which can be systematic or selective, may occur. For example, in a study relating ventilatory function to exposure to respirable quartz dust, failure to standardize the end-point in measurement of vital capacity (possibly also with inadequate calibration of the spirometer) led to a serious underestimate of the subjects' lung function and hence to probable overestimates of the toxic effects of dust [1,2]. In the epidemiology of respiratory disease, the methods most commonly requiring standardization are those used to obtain data by questionnaire, the testing of lung function and chest radiology. These matters are discussed in more detail later. In addition, if documentary data are to be used it is necessary to assure oneself that they have been recorded in a standardized manner and to be aware of possible biases. For example, in mortality studies the data on cause of death are recorded and coded by the Registrars General in the UK in a carefully standardized manner, but depend on the often idiosyncratic diagnoses of individual doctors. Thus in spite of the care taken in coding, there may be regional or temporal differences due to diagnostic fashion. Other matters requiring standardization in respiratory epidemiology might be the recording of certain physical signs, such as lung crepitations or finger clubbing, the taking of an occupational history, or the



estimation of individual and group exposures to airborne dusts.

## Some definitions

### Problems in study design

#### Error

The word 'error' means a mistake in normal usage but has a more specialized meaning in epidemiology: it may be *random*, when it describes the chance divergence from the true value of a result obtained in the study of a population sample because of individual variation and sampling and measurement errors; or it may be *systematic*, when it is known as bias.

#### Bias

Bias is present when the results vary in a systematic manner from the true value; avoidance of bias is probably the major problem in design of an epidemiological study. The two most important sources of bias are in selection of the group for study, *selection bias*, and in making measurements, *measurement bias*. The former occurs when there is a systematic difference between the group selected for study and the population they are taken to represent or the control group. An obvious example would be when people are asked to volunteer for a study, since those willing to take part are likely to be motivated differently and to have different characteristics from those who do not. Similarly, in a random population sample, if a proportion fail to participate because they are feeling too ill or too well, selection bias can occur. More subtly, a cross-sectional study of an industrial population might achieve a high participation rate yet bias occurs because ill people had migrated out of the population or had never been fit enough to be employed, leaving only the most healthy to be studied. This phenomenon is commonly called the *healthy worker effect*. Measurement bias occurs as a consequence of inaccurate measurement, as in the example of spirometry quoted above or when, for example, different chest-film readers have different criteria for the description of radiological opacities. A special sort of measurement bias is called *recall bias*, which occurs particularly in case-control studies where the conditions under which retrospective information is obtained may mean that cases suffering from some disease may recall possible causative factors more easily than can controls without the disease. Some ingenuity in study design is required to avoid falling into such traps.

#### Confounding

Confounding occurs when there are two or more risk factors for an outcome and their effects have not been sep-

arated. For example, in a study of the effects of air pollution on health it has been suggested that prolonged residence in polluted cities is associated with increased risks of cardiopulmonary diseases. Any such study needs to take account of the fact that people resident in such cities are not only exposed to more pollution but, in general, may also be poorer, may be exposed to more toxic fumes at work, may eat a less healthy diet and may smoke more cigarettes than residents of less-polluted cities. These factors, among others such as age and gender distribution, are potential confounders. In a study of the association between exposure and disease a confounder may be defined as a factor associated with both the exposure and the disease being studied. If it is unequally distributed between exposure groups, it may cause any relationships to be wrongly attributed, obscured or altered.

### Descriptions of health/disease profiles

#### Prevalence rate

The prevalence rate is the number of people with the defined condition at one time, or over a short period, expressed as a proportion of the number in the population at risk at that time.

#### Incidence rate

The incidence rate is the number of people developing the condition of interest anew over a defined period expressed as a proportion of those at risk over that period. In this case the denominator is the sum of the lengths of time over which each individual in the study remains free of disease. A somewhat simpler description is the *cumulative incidence rate*, where the denominator is the number of people without the disease at the start of the defined period of study.

#### Mortality rates

The *crude mortality rate* is the number of people dying over a specified period expressed as a proportion of the average number at risk of death over the same period. This index does not take account of such determinants of mortality as the age and social structure of the population, and a more useful means of expressing death rates is by calculating age-, social class- and gender-specific mortality rates. For example, an age-specific rate would be the number of deaths occurring in a defined age group over a given period expressed as a proportion of the total numbers in that age group over that period.

A *proportionate mortality rate* is sometimes used as a simple index of mortality from different diseases. This is the number of people dying from a particular disease over a defined period expressed as a proportion of the total



number of deaths over the same period. It may indicate a disproportionately high risk of death from particular causes in the defined population.

Since most studies of mortality require comparisons between a population thought to be at increased risk and one that might be regarded as being at normal risk, it is usually necessary to compare the study population with a much larger group, typically the national population or even a standard world or European population. At this level there will be systematic differences in age structure, as well as, usually, differences in terms of gender and social status. Such studies require standardization, i.e. expression as the rates that would have been present had the two populations had the same structure. A *standardized mortality rate* (SMR) is the number of deaths in a defined population, adjusted for its age and sex distribution, over a given period expressed as a proportion of that in the standard reference population. Such rates may also be applied to specific diseases, for example SMRs for different types of cancer, and a similar term may also be applied to incidence of disease (SIR), appropriate reference data being available from cancer registries.

### Exposure and dose

The value of studies intended to demonstrate possible causative relationships is greatly enhanced if some measurements of exposure to the putative causative factors are made, since it may then be possible to demonstrate a relationship between exposure and risk of the disease in question. In general it is only possible to make an estimate of *exposure* rather than measure the actual *dose* that individuals in the study have received. Exposure may be expressed with varying degrees of accuracy and may be current, cumulative or historical. The simplest measure of *current exposure* is derived from estimates of, say, dustiness or pollution on a relative scale; however, most studies of workplace exposure now make use of personal or area air sampling over one or several shifts, while in studies of air pollution the recordings made by area samplers are commonly used as a surrogate for exposures of individuals in the population. Such measurements can be used to calculate the approximate dose to the lungs from a knowledge of the size distribution of the airborne particles and the breathing rates of the subjects, although these complex calculations are rarely made. *Cumulative exposure* of individuals is usually calculated as the sum of the products of time spent in particular jobs or areas and the average concentrations of airborne substances in those areas at the relevant times. Such estimates are only possible when measurements of substances have been made systematically in the past or as part of a carefully planned prospective study, but when they have been obtained they have provided powerful data on which to base preventive standards. In some cases it has proved possible to estimate *his-*

*torical exposure* from a study of records of past occupational hygiene monitoring, employment records and reconstruction of past industrial processes. Such estimates have the potential to strengthen conclusions drawn in studies of workplace carcinogens, where the relevant exposure may have occurred many decades previously.

## Epidemiological study designs

A descriptive study is the simplest type of design, intended to delineate the pattern of health and ill-health in a population without attempting to investigate possible causes. Routinely collected data on mortality and as part of the UK General Household Survey are of this type, as are the data gathered in the UK Survey of Work-Related and Occupational Diseases (SWORD) [3]. Such information is valuable because it allows the generation of hypotheses and measures change over time, and may form the basis for further types of epidemiological study [4].

### Ecological study

An ecological study is one in which correlations are sought between patterns of ill-health and other data usually collected for other purposes, such as meteorological conditions, social conditions, and so on. This type of design has been used in many studies of air pollution [5], as well as in the early studies that related changes in asthma mortality to sales of bronchodilator drugs [6] and in those that related mortality from mesothelioma to importation of asbestos [7]. This type of study is particularly useful as a generator of hypotheses, although it may also be used to obtain indirect, but not direct, evidence relating to the testing of a hypothesis.

### Cross-sectional study

A cross-sectional study is designed to measure the prevalence of a condition in a population. It may do this at one particular time, as a census counts the population on one day in the year, or over a defined period. The information obtained in the study may be sufficient to study interrelationships between disease and possible causative factors and thus to provide data of value in prevention. Such studies necessarily have their limitations: they are of little value for studying rare conditions or acute episodes of disease; they are very dependent on good response rates; and they are usually quite expensive, requiring much time in identifying, tracing and examining the sample. Nevertheless, since they are relatively straightforward in design and may also serve as useful starting points for either longitudinal or case-control studies, they are among the most frequently performed types of study.

A cross-sectional study aimed at investigating causes of

disease will include controls. However, the difference between these controls and those in a case-control study should be noted. In the latter, controls are individuals without the disease or symptom in question, while in the former they are subjects unexposed to the putative cause. Many cross-sectional studies use internal controls, i.e. the study population will include people with a broad range of exposures to the factor under investigation, from none to a great deal. Other studies may require separately selected controls, though care should be taken that they are appropriately matched for possible confounding factors such as age, social class, gender and perhaps domestic circumstances.

Cross-sectional studies might be used to determine the prevalence of asthma in a community, the relationship of evidence of respiratory disease to exposure to an industrial pollutant or the influence of work on asthma and of asthma on work. Such examples are discussed in the next section in order to illustrate some of the problems.

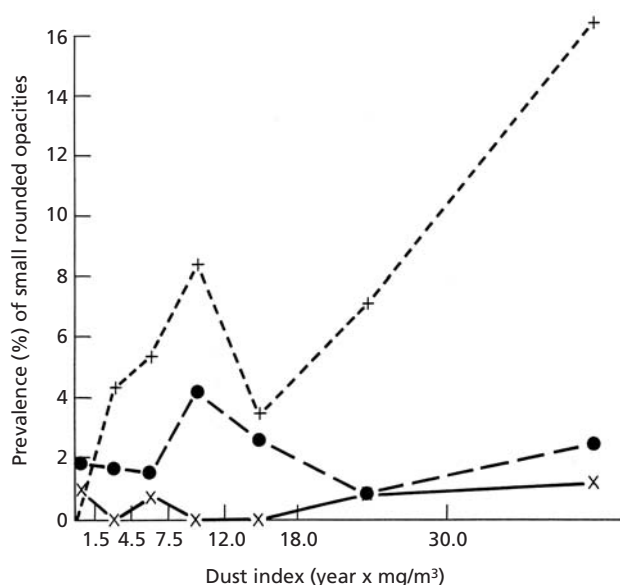
### Examples of cross-sectional studies

A physician became convinced that many patients with asthma among the elderly were being misdiagnosed as having chronic bronchitis. In order to make a point, for educational purposes, about the prevalence of asthma in elderly people and also to determine how many patients were undiagnosed, he decided to perform a cross-sectional study [8]. The target population in this case could easily be defined as all people over the age of 70, but to make the project manageable the study population was confined to those living in one town. Access to the register of voters allowed a random sample of 1 in 8 to be taken. The main problem of such studies is deciding upon a definition of the disease in question, in this case asthma. A wide choice is available: it could be an appropriate history, positive answers to certain questions, the demonstration of reversible airflow obstruction or some combination. Whatever is chosen (and it may be decided to have several separate definitions) it is important to ensure that the data are collected in an unbiased and repeatable manner. In this case, several definitions were investigated and it was shown that a history of having suffered from 'doctor-diagnosed asthma' at some time occurred in 6.5% of the old people studied, in 3% of whom it was currently present. Half of those with clinical asthma were unaware that they had the disease. A second problem in such studies is ensuring that the maximum possible number of subjects selected attend the survey. Ideally all should be seen but this is almost never possible. In this example, 86% of the study sample were seen, the others not taking part because they did not want to, were too ill or were unable to cooperate. This level of response was not unexpected in such a survey, even though attempts were made to increase it by carrying out the investigations where neces-

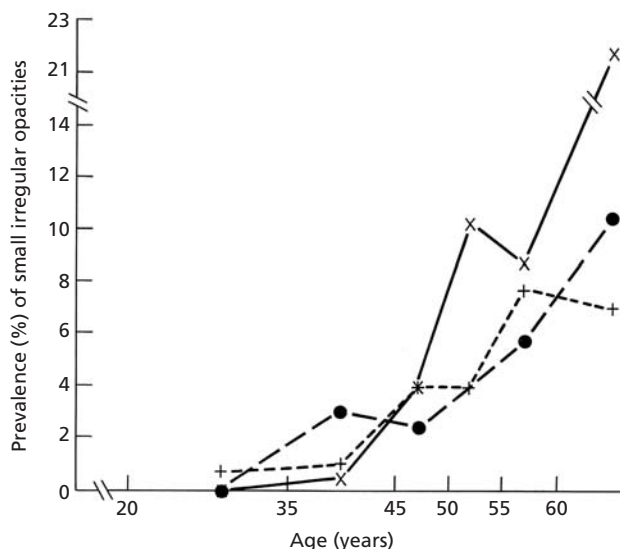
sary in the subjects' homes and in a local community hospital. It could of course lead to bias if a disproportionate number of the non-attenders are suffering from the condition in question and so steps need to be taken to obtain some information on their health; in this case a history of asthma was sought from their general practitioners' records.

A cross-sectional study may be used to investigate hypotheses of causation, either when a disease or abnormality is recognized and one wishes to investigate its relationship to a possible cause or when an environmental pollutant is present and it is desirable to find out if it causes any adverse effects. An example of the former approach occurred when a physician recognized some rather minor nodular shadows on the radiographs of workers producing PVC. Were these related to the exposure? A cross-sectional study was planned to examine the current workforce of the factory together with a sample of ex-workers [9]. The latter were included in order to avoid the bias implicit in studying the current workers, who can be regarded as a survivor population, perhaps of relatively healthy men; this is the so-called healthy worker effect [10]. As part of the study, detailed measurements were made of the workers' current exposures to PVC dust of respirable size and careful occupational histories were recorded from all participants. These allowed estimates to be made of lifetime exposures to the dust. As mentioned in the section on case-control studies, steps had to be taken to have the radiographs read in a standard manner and a panel of three doctors carried this out using International Labour Office (ILO) standard films for comparison (see p. 78). One of the three readers detected a relationship between dust exposure and the presence of small rounded opacities, at category 0/1 (Fig. 3.2). Other investigations in this study led to the description of a relationship between dust exposure and decline in ventilatory capacity, having allowed for the effects of age and cigarettes, and between age and prevalence of irregular opacities (Fig. 3.3). The value of such a study is that it gives quantitative information on the relationships between dust exposure and harmful effects that can be used by the industry in setting preventive dust standards.

Conversely, doctors are frequently asked whether something causes disease. For example, does work with wool cause respiratory disease? If the question is a general one, it may be desirable to keep an open mind about the type of effect and study the relationships between dust exposure across a broad range of the industry and symptoms as recorded by questionnaire. A study to investigate this problem selected some 20 factories, ranging from some employing 200 people to others employing a handful [11,12]. The factories were chosen to represent a cross-section of the processes and of the levels of dustiness found in the industry. Thus the target population was wool-workers, the study population was those workers in

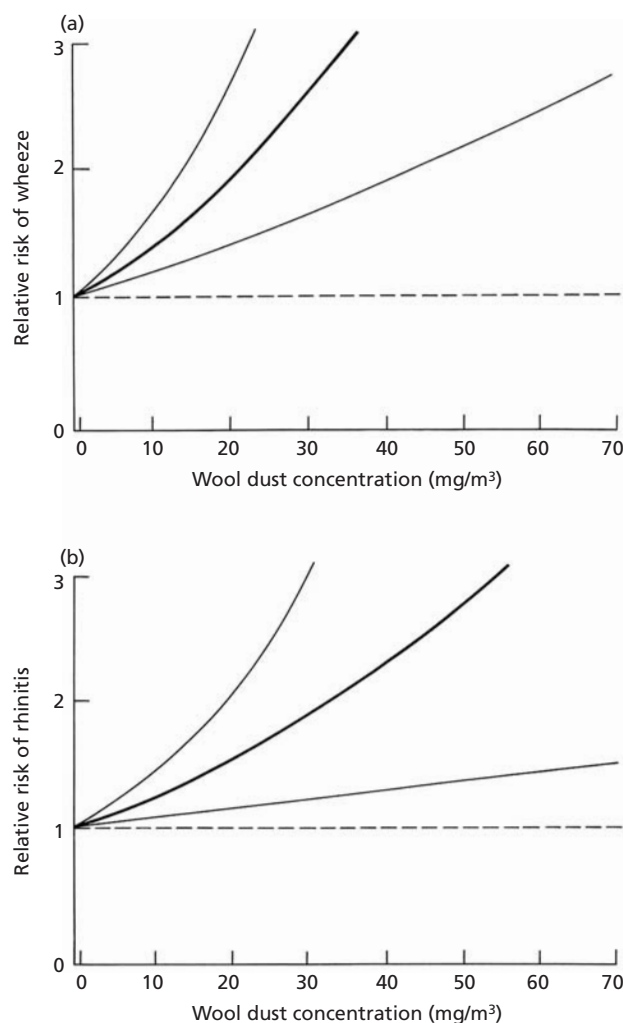


**Fig. 3.2** Prevalence of small rounded opacities (category 0/1 or more) on the chest radiographs of PVC production workers in relation to exposure to respirable dust as recorded by three readers (+; black circle; x) independently. One reader found a relationship between prevalence of opacities and exposure. (From Soutar *et al.* [9].)



**Fig. 3.3** Prevalence of small irregular opacities (category 0/1 or more) on the chest radiographs of PVC workers in relation to their age as recorded by three readers independently. All found an increase in prevalence with age. (From Soutar *et al.* [9].)

the chosen factories and, in this case, it was decided to study as far as possible all such workers, though for practical reasons ex-workers were not included. A questionnaire was designed (see later) to include a broad range of possible symptomatic responses to wool-dust exposure; in this investigation, a substantial minority of the workers



**Fig. 3.4** Estimates with 95% confidence limits of relative risk of (a) wheeze and (b) rhinitis, as recorded by questionnaire, in relation to measured current exposures to dust in woollen mills [11].

studied were not fluent in English so the questionnaire was translated into Urdu, their first language. Tests of logic and reproducibility of the questionnaire in the two languages were carried out before its use in the study. The data were analysed in terms of the relationships between individual symptoms (and groups of symptoms) and current dust exposure and exposure-response relationships were demonstrated with cough, wheeze and rhinitis (Fig. 3.4). Again, the results of this sort of study can be used in debate that leads to the setting of preventive dust standards.

A final example of a cross-sectional study might be to investigate the prevalence of a common disease in relation to one particular cause, for example how much asthma is occupational in aetiology. The same sort of study could be used also to assess the effects of having the disease asthma on employability. Such a study might

sample the population of a town or, better, an area including both town and country with a wide range of industries, and obtain information on symptoms and work by questionnaire.

### Case-control study

A case-control or retrospective study is designed to compare two groups of individuals, one with a particular condition and the other without, with a view to determining whether or not a suspected aetiological factor or response to the disease process is present to excess in the group of cases. For example, the investigator may wish to know whether a particular type of work is important in the aetiology of lung cancer, whether the risks of developing lung cancer are modified by changes in smoking habits or whether subjects with pneumoconiosis have worse lung function than those without. These three examples are used to illustrate some of the problems associated with case-control studies, but to begin with a number of general points about such studies are made.

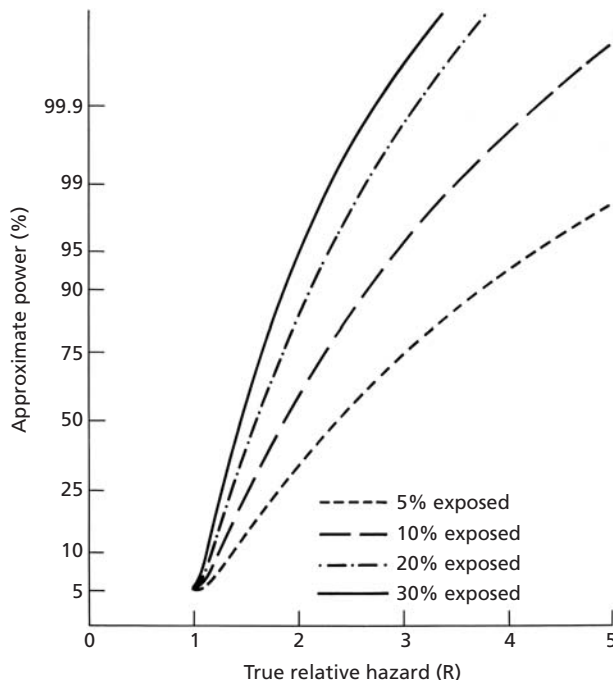
Firstly, as always, the target population must be defined and the cases *and* controls drawn from this or from the study population derived from it, in order to estimate the exposure to the suspected hazard in the unaffected population. For example, in a study of patients derived from a hospital clinic it is important that the controls are derived from the same referral areas. Secondly, it is important to avoid any other bias in selecting the controls, particularly in relation to exposure status. Thirdly, data gathered for investigation of differences between the groups must be obtained in an identical manner from both cases and controls, preferably by someone who is unaware of which group the individuals are in. Such studies are relatively cheap and easy to design and analyse, and are particularly useful for the investigation of possible causative factors in rare diseases. The end-point of a case-control study is the calculation of an *odds ratio*, i.e. the risk of exposure (or other factor studied, such as physiological consequence of the disease) in the cases as a ratio of that in the controls.

### Examples of case-control studies

If the investigator wished to study the relationship between, say, work in the oil-shale industry and lung cancer [13], one approach might be to contrast the occupational histories of all patients presenting with that disease over a defined period with those of patients presenting in the same area or hospital group with other diseases over the same period. Two problems immediately become apparent: first, who should be chosen as controls and, secondly, what numbers of cases need to be studied to give a reasonable chance of finding an effect of shale work (if one exists). The choice of controls is always problematical. Important confounding factors need to be considered;

lung cancer is a disease of older people and of cigarette smokers and so the control group should as far as possible be matched for age and smoking habits. Equally, it should not be chosen from people whose disease might also have been influenced by work in the shale industry, so should not be confined to patients presenting with bronchitis. An appropriate choice of control population might be patients presenting with cardiac disease, or all patients presenting without respiratory disease, in the same hospital and over the same period, if the referral pattern of the controls were similar to that of the cases. Alternatively, controls might be selected from the electoral register or from general practice lists. The control group may then be sampled from one of these populations according to matching criteria defined beforehand.

The second problem, the number of subjects needed, can be examined statistically [14]. It is intuitively obvious that the target population must contain a sufficient proportion of men who worked in the shale industry. The chances of finding an effect will therefore depend on that proportion, on the strength (or weakness) of the effect of shale work in causing lung cancer, and on the time lapse between work in the industry and the time of the study. Given an appropriate interval for cancer to develop, the ability of a study to detect an effect can be summarized as its statistical power and illustrated graphically (Fig. 3.5).



**Fig. 3.5** Estimates of power of a study of 212 subjects with lung cancer and 221 controls to detect an increased relative risk of work in the shale industry. In the study in question, approximately 20% of the study population had some exposure to work in that industry, giving a 90% chance of detecting a doubled risk of lung cancer [13].

The statistical power of a study is defined as the probability of rejecting the null hypothesis when it is wrong. It is particularly dependent upon the size of the population studied, and calculations of the power of detecting differences at different levels of statistical probability should be made before starting any epidemiological study.

Similar methods on a grander scale have been used to study the effects of modifying smoking habits on the risks of developing lung cancer [15]. Cases were defined as patients presenting with lung cancer, proved histologically, at seven groups of European hospitals. Controls were sampled from other patients presenting at the same hospitals with diseases unrelated to smoking, two controls being chosen for each case. Detailed smoking histories were obtained in an unbiased manner from all participants and analyses were confined to those who had smoked at some time. Recruitment of large numbers of subjects allowed detailed examination of the relative risks of developing lung cancer after smoking for different periods and after having given up or reduced for different periods. The information obtained is thus clearly useful in coming to decisions about advising smokers on changing their habits; the risks were related to length of smoking habit, number of cigarettes smoked and, inversely, to duration since stopping. In general, heavy smokers with a prolonged habit have to wait much longer for appreciable reduction in risk than do lighter smokers with a shorter habit.

A third example, more familiar to most respiratory physicians, is the use of case-control methods to determine the functional effects of disease. To return to shale workers, the question arose as to whether shale pneumoconiosis was associated with abnormalities of lung function [16]. Men with pneumoconiosis were to be compared with men without the condition. Again, several potential problems needed to be resolved. How should pneumoconiosis be defined? Who should be used as controls? The satisfactory resolution of these problems has an important influence on the results and their interpretation. In the study referred to, it was decided to define pneumoconiosis in terms of a majority reading of the radiographs by a panel of readers and to select subjects as cases who had readings above a certain ILO category. The controls were, of course, to be selected from the same defined population of shale workers, were to have radiographs agreed as not showing pneumoconiosis, and were to be matched as far as possible on age distribution and occupational histories. This latter decision was made in an attempt to isolate the effects on lung function of the pathological changes of pneumoconiosis from those of exposure to dust and fumes; in other words, abnormal lung function could be due to the disease or could be a separate effect of the factors that caused the disease. The results of the study showed that men with pneumoconiosis had worse lung function than men without, although in the absence of

detailed information on exposures to shale dust and fumes it was not possible to exclude the possibility that this difference was due to their exposures rather than to the pathological process.

These three examples should illustrate the versatility, value and relative simplicity of the case-control approach. Modern statistical techniques are able to take account of imperfect matching and multiple confounding factors, and much valuable information can be obtained in a relatively straightforward way.

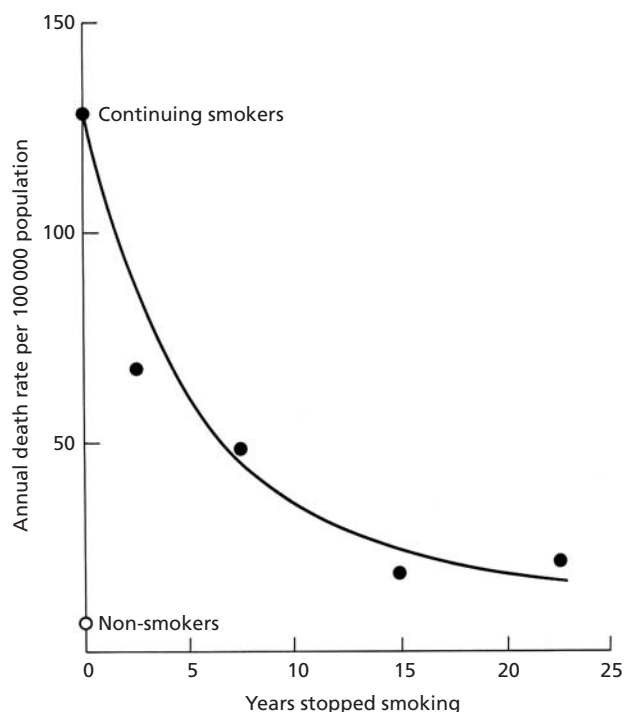
### Longitudinal study

A longitudinal, or cohort, study is designed to measure the incidence of a condition in a population. It therefore has defined starting and finishing points. It may also be used to study the progression of a condition over time. Either of these applications might include measurement of suspected causative factors to relate to the measured responses. Such studies are of necessity complex, time-consuming and expensive, but in return give the most complete information that can be obtained by epidemiology. Among the examples of longitudinal studies most familiar to chest physicians are those carried out to measure the respiratory symptoms and ventilatory function in a group of London engineering and office workers in relation to their smoking habits [17] and those performed to study the mortality patterns of British doctors, also in relation to their smoking habits [18] (Fig. 3.6). Other well-known studies include those intended to follow cohorts of children through periods of their lives in order to elucidate factors important in the development of chronic airflow obstruction [19,20] and those intended to demonstrate relationships between coal-dust exposure and health [21,22].

From what has been said before, some problems of longitudinal studies will be apparent: selection of the cohort, ensuring maximum attendance at survey and ensuring complete follow-up. In particular, there are difficulties in keeping track of participants in a prolonged study that requires their regular attendance for survey, and such drop-out rates may have an important influence on the results. This is less of a problem in mortality studies, where the end-point to be measured, death, requires only ascertainment at a central registry. Nevertheless, keeping full information on the whereabouts of a mortality study population and determining the vital status of all individuals at the chosen end-point of the study have their problems.

### Examples of longitudinal studies

Three applications of longitudinal studies are illustrated: measuring mortality, measuring decline in lung function and measuring the incidence of disease.



**Fig. 3.6** Standardized death rates from lung cancer for cigarette smokers, ex-smokers for various periods, and non-smokers. (Based on Doll & Hill [18].)

### Mortality studies

In principle, measurement of mortality is relatively simple. A cohort is identified (this is usually done retrospectively by using records or census information applying to some time in the past) and followed forwards in time until a proportion has died. The causes of death are obtained from death certificates. The results may be expressed quite simply as the crude mortality rate (numbers dead divided by number in the cohort), either for the whole period of the study or on an annual basis. Use of data on cause of death allows calculation of crude cause-specific mortality rates, and these expressed as a fraction of all deaths give a proportional mortality ratio. However, this sort of information is of relatively little use, as death rates are clearly influenced by many factors that may be present in the cohort and that may cause it to differ from other populations. More useful information requires some form of standardization, particularly for the age structure of the cohort in relation to the age structure of a comparison group, for example adjusting for a disproportionately large number of older subjects who might therefore have been expected to die sooner than younger ones.

To pursue the example mentioned previously of shale workers, it was suggested on the basis of clinical observations that this group of men might be at increased risk of death from cancer [23]. It proved possible to identify a cohort consisting of all men registered in the shale indus-

**Table 3.1** Estimated risks of death of shale workers from various causes relative to those of the general population of Scotland.

Cause	Relative risk	No. of deaths
All deaths	1.00 (0.95–1.07)	1066
Cancers		
Stomach	0.92 (0.60–1.41)	21
Colon	0.58 (0.31–1.07)	10
Rectum	1.16 (0.66–2.04)	12
Lung	0.86 (0.70–1.07)	84
Skin	4.83 (2.18–10.94)	6
Kidney	1.00 (0.37–2.66)	4
Bladder	0.84 (0.42–1.67)	8
Lymphatic	0.88 (0.47–1.63)	10
Circulatory disease	1.05 (0.97–1.13)	610
Ischaemic heart disease	1.00 (0.90–1.12)	352
Bronchitis/emphysema	1.02 (0.80–1.31)	63

Numbers in parentheses represent 95% confidence intervals.

try's provident fund between 1950 and 1960. Fortunately the fund records provided information on the workers' occupations in the industry, so it was possible to investigate mortality in relation to different jobs [13]. Tracing of vital status by local searches and enquiry of appropriate records allowed identification of over 96% of the cohort. The workers were all male and from Scotland and it was thought appropriate that their mortality rates should be compared with those of all Scottish males and with those of all males from the same region of Scotland. Standardized for age, these comparisons give rise to a figure for each cause of death that relates the observed risks of death among members of the shale cohort to those of the reference population, the relative hazard or (multiplied by 100) the SMR (Table 3.1). Such calculations, although giving one figure for each cause, need to be qualified by a statement which describes the statistical confidence that the mortality of the cohort does or does not differ from that of the reference population. This is conventionally done by describing the 95% confidence intervals, i.e. the range of SMRs within which there is a 95% likelihood that the true, but unknown, ratio really lies. Table 3.1 shows that although the SMR for death from carcinoma of the rectum was 116%, this could have been as low as 66% or as high as 204%; in other words, an increased risk could not be demonstrated with 95% confidence. It can be seen that only death from skin cancer appeared to be a special risk for workers in this industry.

In the same study, further analyses allowed examination of the effects of different occupations within the cohort on mortality from different causes but were unable to demonstrate any clear-cut relationships. In contrast, in a study of coal-miners, where the actual exposures of the individuals in the cohort to coal dust had been measured



prospectively, it had been possible to demonstrate clear-cut relationships between dust exposure and mortality from respiratory diseases [22]. Clearly the value of a longitudinal study is greatly enhanced if it includes systematic measurement of factors, such as cigarette smoking or dust exposure, that might be important determinants of fatal disease.

### *Decline in lung function*

As stated before, all epidemiological studies require rigorous standardization of methods. Particular problems arise with longitudinal studies where different investigators may be used at different times, and measures to ensure quality control are essential. These and other important methodological problems are discussed in the account of a study of respiratory health in London workers [17]. The interested reader is recommended to consult this book.

Another study has addressed the problem of decline in ventilatory function of coal-miners in relation to various possible determinants including dust exposure. This research included prospective measurements of dust exposure and 4–5-yearly measurement of ventilatory capacity in a large cohort of coal-miners [21]. In addition, respiratory symptoms and smoking habits were recorded by questionnaire and chest radiographs were taken. One analysis investigated decline in forced expiratory volume in 1 s ( $FEV_1$ ) over an 11-year period in a subgroup of the cohort and was able to relate decline to age, smoking habits and dust exposure [24] (Fig. 3.7). An important feature of this study was the loss of men from the original cohort in the course of the 11 years; the possible effects of this loss on the results were discussed in the paper but were nevertheless the subject of some lively correspondence in the journal subsequently, illustrating the uncer-

tainties surrounding conclusions from epidemiological studies [25–30].

### *Incidence of disease*

A cross-sectional study, as discussed above, may allow useful conclusions to be drawn about relationships between provoking factors and disease. However, these conclusions may be much affected by the absence of people who may, by dying or falling ill and thus leaving the workforce, have shown the most marked effects. Or, possibly, fitter people may have been best able to leave for better or healthier jobs. Longitudinal study of a cohort of subjects may overcome this problem, but only if a very high proportion are able to be kept in view. Mortality studies, discussed above, use death as their end-point. Morbidity studies require regular examination of the cohort to detect the disease of interest, which must therefore be one that, having occurred, persists. Clarity of definition of the end-point is essential, and this may not be easy as disease usually occurs not as a sudden event but as a gradual change on a continuum from health. For example, it might be desirable to measure (to pursue the coal-mining theme) the incidence of progressive massive fibrosis in miners. Such information would of course be of little practical value in the absence of information on the dust exposures causing the condition. Any such study should therefore ideally measure dust exposures of the individuals prospectively from the day they enter the industry and take regular radiographs in order to detect the disease at the earliest stage. Such a study would be impracticable, although close approximations have been made. The best known of these, from which several of these examples have been taken, is the British coal industry's pneumoconiosis research, in which a sample of some

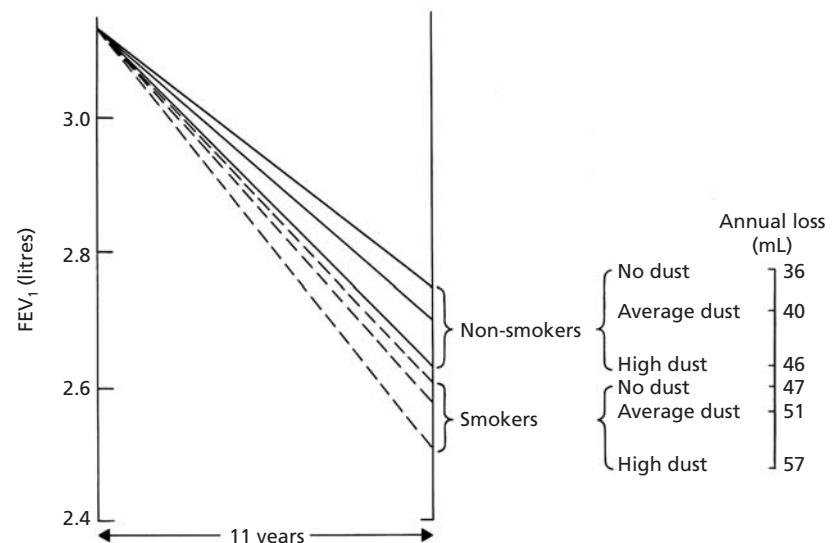
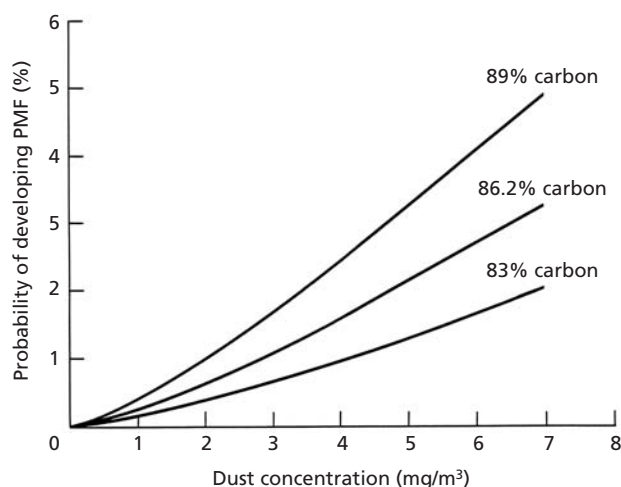


Fig. 3.7 Estimates of decline in forced expiratory volume in 1 s ( $FEV_1$ ) over an 11-year period in a population of coal-miners in relation to time, smoking habit and dust exposure. (Derived from Love & Miller [24].)

50 000 miners was followed prospectively by questionnaire, spirometry and chest radiography every 5 years [21]. Prospective measurements of exposure to respirable dust were made on the basis of sampling for occupational groups and detailed occupational histories, and were added to careful estimates of past exposure. Because of the complexities inherent in analysis of such a large study, various subsamples have been examined and the risks of progressive massive fibrosis in these groups estimated. One such analysis concerned the risks after leaving the industry and showed, *inter alia*, that over an 11-year period after leaving a miner with category 1 simple pneumoconiosis has a 17% chance of developing massive fibrosis [31] (Table 3.2). More importantly, another study has shown the risks of massive fibrosis in currently working men in relation to dust exposure, information that can be used for preventive standard setting [32] (Fig. 3.8). All these conclusions are dependent on the definition of the end-point. In the former study this was a majority reading of massive fibrosis by a panel of five readers, of whom one was medically qualified. Subsequent review of the films by an experienced physician resulted in agreement in 82% of cases. In the latter study, it was a clinical reading of massive fibrosis by one or more experienced physicians. Further discussion of the effects of multiple



**Fig. 3.8** Estimated risks of developing massive fibrosis in coal-miners exposed for 35 years to dusts of differing carbon contents in relation to average level of dust exposure.

Category of pneumoconiosis prior to leaving industry (ILO)	0	1	2	3	All
Incidence over 11 years (%)	3.7	16.8	20.5	47.1	8.2
No. of men	859	185	132	17	1193

ILO, International Labour Office.

readings can be found in a third paper on this subject, in which readings were made by a large panel of specialized physicians [33].

An application of longitudinal studies of topical interest might be to assess the incidence of asthma in a workforce. The two difficulties mentioned above, of definition and of drop-out, are particular problems here. Asthma is hard to define epidemiologically, whether in terms of symptoms or in terms of variability in function, and sufferers from work-induced asthma have an understandable tendency to seek employment elsewhere. Judging from cross-sectional studies in which attempts have been made to follow up ex-workers, this loss of affected individuals may be a substantial one in, for example, industries involving exposure to colophony [34,35].

In designing a longitudinal study of occupational asthma a definition would first have to be agreed; this might be achieved by questionnaire supplemented by readings of peak flow rate. The population would have to be identified and their (and management's) agreement sought. An initial survey would establish the prevalence of current asthma and all such individuals would of course be excluded from the prospective study of incidence. However, they might be followed up in order to study the influence of change of job on their disease. An appropriate follow-up interval would then be determined and special efforts made to ensure that leavers would be included in subsequent surveys. Steps would have to be taken to avoid possible bias due, for example, to knowledge among the workforce of the possibility of compensation claims. Finally, environmental monitoring would need to be carried out in such a way that incidence could be related ultimately to exposure, and to take account of changes in levels resulting from improved industrial hygiene. Two such studies along these lines have reported relationships between exposure to flour and laboratory rat allergen and the risks of developing respiratory sensitization [36,37].

### Mixed studies

The main types of epidemiological study can of course be combined, and this often proves an attractive and efficient method of studying a problem. For example, both descriptive and cross-sectional studies may provide useful starting points for a prospective study of mortality or disease incidence, and may also be used as methods of identifying

**Table 3.2** Incidence of massive fibrosis per 100 men over an 11-year period in ex-miners by category of pneumoconiosis at time of leaving the industry.

subjects for a case-control study. The latter design is often described as a 'nested' case-control study.

### Experimental studies

All physicians are familiar with the randomized controlled trial, introduced in the early investigations of the treatment of tuberculosis and now the foundation of 'evidence-based medicine'. This is a particular application of epidemiology in which patients are allocated randomly to alternative interventions, usually with pharmaceuticals, in order to compare different clinical responses and rates of side-effects. In such studies, ethical aspects are of paramount importance to the design. Experimental studies may be very large, as in some of the multicentre investigations of new cardiac drugs, and may be applied to the investigation of other interventions such as vaccination and dietary alteration in field and community studies.

### Standardized methods in the epidemiology of respiratory disease

The tools of epidemiology are standardized methods for examining individuals in the populations being studied. Such methods must be capable of producing the same results when applied to the same individual on different occasions both by the same observer and by different observers, i.e. intraobserver and interobserver error must be small, the results of the examination being said to be repeatable. In addition, the method should have been validated or be capable of validation, in that studies should show that the results of using it relate to some standard measurements of illness or its determinants. For example, a questionnaire on dyspnoea might be validated by reference to measurements of exercise tolerance or lung function and a questionnaire on cough might be validated by direct observation of the coughing habits or sputum production of individuals. More commonly in epidemiology, however, validation is made indirectly. For example, a method of reading radiographs could be validated by showing that category of change relates to measurements of exposure to dust; or a questionnaire on symptoms could be validated by showing that severity of the symptoms relates to smoking habits. Finally, in terms of validation, a useful test for detecting illness is both sensitive and specific, i.e. it detects most cases of the illness (producing few false-negative results) and it picks out predominantly individuals with the condition (making few false-positive diagnoses). Table 3.3 illustrates some commonly used terms.

In addition to the above criteria, which of course apply equally to clinical, epidemiological or screening methods, three others are important in epidemiology: the method should be acceptable to the subjects and therefore not provoke a reduced rate of participation; it should be

**Table 3.3** Validation of a test.

Study method	Reference test result		Totals
	Positive	Negative	
Positive	True positives (a)	False positives (b)	Positives (a+b)
Negative	False negatives (c)	True negatives (d)	Negatives (c+d)
Totals	True positives (a+c)	True negatives (b+d)	

Sensitivity of study method =  $a / (a + c)$   
 Specificity of study method =  $d / (b + d)$   
 Systematic error (ratio of study method positives to 'true' positives) =  $(a + b) / (a + c)$   
 Predictive value (proportion of study method positives that are 'truly' positive) =  $a / (a + b)$

simple, so that the operator and the subject are both able to perform it; and it should be objective and not subject to bias as a result of poor cooperation or knowledge of expected result.

### Questionnaires

Each individual question in a questionnaire can be subjected to the above criteria and used in epidemiological analyses. In designing a questionnaire, the principles outlined at the start of this chapter should be taken into account, and in general it is wise to use a tested, reproducible and validated questionnaire rather than start from scratch. Fortunately the British Medical Research Council has published both short and longer versions of one such questionnaire for the study of respiratory symptoms [38,39] and this forms the basis of most subsequent questionnaires, two of which are those published by the European Coal and Steel Community and the American Thoracic Society [40,41]. For international comparisons, validated translations of the questionnaire are necessary and here the European one may be of particular value.

These questionnaires deal with the common symptoms of cough, sputum production, breathlessness and wheeze, and enquire also about previous respiratory health. They include questions on smoking that allow estimates to be made of pack-year cigarette use. They may be complemented by questions on occupational history; these should obtain a chronological account of all jobs done since leaving school and are best taken by someone familiar with the occupational environments in question. In any study of occupational factors in disease, investigation of that environment by an occupational hygienist and classification of the various jobs in terms of suspected respiratory hazard is an essential preliminary.

The above-mentioned questionnaires are excellent tools for the study of what might be termed irritative

bronchopulmonary reactions, such as chronic bronchitis, industrial fibroses and so on, and were not specifically designed to study hypersensitivity reactions, such as asthma and allergic alveolitis. Specific questions therefore need to be added for these purposes. In studying asthma, several investigators have found that the best question is a direct enquiry about whether the subject has, or has had, asthma. The difficulty stems from the fact that clinical asthma is the end of a continuum of bronchial reactivity that manifests itself in a number of different ways. Logically, therefore, it would seem sensible in investigating 'asthma' epidemiologically to study the presence of various complexes of individual symptoms in relation to either some standard, such as measurements of variability of function or histamine responsiveness [42,43], or to some suspected determinant, such as exposure to dust or fume [44]. One such questionnaire has been devised to study the relationships between respiratory symptoms and response to dust in the wool industry [11]. Although rather longer than it might ideally be (it takes about 15 min to administer), it has been shown to be reproducible, valid in terms of demonstrating relationships between symptoms and dust exposures, and to perform equally well in translation into Urdu. It includes questions designed to quantify variability of symptoms, aimed at measuring the most important feature of clinical asthma, and intended to assess relationships between symptoms and work. These latter questions have been designed in a way to minimize bias, by avoiding the suggestion that symptoms and work may be related (e.g. Is your cough worse at work?). Another questionnaire found useful by the author was designed to assess the variability of airflow limitation by asking questions about exercise tolerance when the subject's chest is at its best and worst [45], deriving a score that related to serial measurements of peak flow rate.

The advantages of a standardized questionnaire are that results obtained with it can be compared directly between, for example, different countries, areas or industries. This presupposes that the questionnaire is administered in a standardized manner, without prompting or helping the subject other than by repeating the question. From this it follows that the questions must be designed in such a way as to make it likely that the subjects will be able to answer with a simple 'yes', 'no' or a number. In embarking on a survey, the clerks administering the questionnaire must be carefully trained; instructions for the use of standard questionnaires have been published by the Medical Research Council, the European Coal and Steel Community and the American Thoracic Society [39–41]. Useful information may be obtained relatively inexpensively by means of self-administered questionnaires. These of necessity should be extremely simple to understand and complete. Their length is inversely related to the likelihood that they will be returned. The use of postal questionnaires always requires some form of back-up; it is usual to send a second

request to those who do not return the questionnaire first time and then, if necessary, to follow this up with a visit by the researcher. With appropriate checks on identity of responder, it is also possible to carry out questionnaire surveys by telephone, although here any bias arising from factors such as relative wealth associated with possession of the telephone need to be taken into account.

### Physical examination

There is no reason why elements of physical examination should not be used in epidemiological studies of lung disease, as the recording of blood pressure has been used in cardiovascular epidemiology. However, relatively little use has been made of this, perhaps reflecting the lack of value of most signs as indicators of disease. Repetitive crackles have been used in studies of asbestosis [46] and some studies of crackles and wheezes have been carried out in PVC workers [47]. The clinical measurement of forced expiratory time has been assessed in terms of its reproducibility and validity [48]. Any use of physical examination in epidemiology requires careful standardization of methodology together with some preliminary assessment of its reliability.

### Lung function testing

In contrast to physical examination, lung function testing has formed an important part of most epidemiological studies of respiratory disease. Again, the criteria of simplicity, acceptability, reproducibility, objectivity, specificity and sensitivity need to be taken into account when choosing a test. It is important to realize that these criteria may be met to different degrees in field studies and in the laboratory. Most studies have used simple measurements of spirometry (FEV<sub>1</sub> and forced vital capacity) as these are particularly robust tests. However, studies of diseases causing fibrosis, such as allergic alveolitis or asbestosis, may require measurements of lung volumes, diffusing capacity or even exercise testing. In the investigation of early evidence of bronchial disease it might be desirable to use tests of 'small airways' function. The reproducibility of various tests of lung function in the laboratory and in the field is illustrated in Table 3.4 [49]. This table illustrates, *inter alia*, the unacceptably high variability of the tests of so-called small airways function, i.e. maximal flow at 50% of vital capacity and closing volume. In general, other tests show relatively low variability, at least in the hands of the authors of that paper, though results in the field are usually slightly more variable than those in the laboratory.

A particular problem in epidemiology is the measurement of variability of airflow obstruction in the assessment of asthma. Several methods have been used, of which the simplest in concept is measurement of peak flow rate at frequent intervals over a period of days or

**Table 3.4** Reproducibility of selected lung function tests in the laboratory and in the field. (From Love *et al.* [49].)

Variable		Subject numbers	First test		Second test		Variation between tests	
			Mean	SD	Mean	SD	SD	Cov (%)*
FEV <sub>1</sub> (L)	Lab	14	4.36	0.61	4.37	0.67	0.14	3.2
	Field	38	3.69	0.97	3.65	0.93	0.19	5.1
FVC (L)	Lab	16	5.55	0.68	5.51	0.75	0.14	2.6
	Field	35	4.68	0.82	4.69	0.84	0.17	3.7
TLC (L)	Lab	40	7.38	1.00	7.26	0.97	0.18	2.4
	Field	38	7.22	1.12	7.28	1.13	0.27	3.7
D <sub>L</sub> CO (ml/min/kPa)	Lab	40	10.65	1.88	10.69	2.06	0.81	7.5
	Field	38	10.45	1.90	10.69	2.14	0.69	6.6
$\dot{V}_{\max/50}$ (L/s)	Lab	16	4.62	0.98	4.54	0.93	0.24	5.3
	Field	38	3.80	1.68	3.78	1.72	0.57	15.1
$\dot{V}_{\max/25}$ (L/s)	Lab	16	1.86	0.59	1.83	0.59	0.22	12.1
	Field	38	1.39	0.84	1.32	0.84	0.26	19.6
CV/VC (%)	Lab	16	12.3	6.2	11.5	6.1	2.44	20.5
	Field	38	15.2	7.52	15.9	8.94	3.76	24.6

\* Cov, coefficient of variation =  $\left( \frac{\text{standard deviation of differences}}{\text{mean of all the tests}} \right)$ .

CV, closing volume; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; VC, vital capacity.

weeks. The difficulties of analysing these multiple data have not been completely resolved, particularly as variability is related to the initial level of flow rate; some summary statistic of variation is commonly used. Other methods of studying variability include the use of simple exercise testing, response to bronchodilators and methods of testing bronchial reactivity to inhaled histamine or methacholine [50–52].

In using lung function tests in epidemiology, there is sometimes debate as to whether results should be expressed directly or as a percentage of a value predicted from a regression equation. If the latter method is used (which has the advantage of comparing the results with some external standard), it is important to ensure that the population from which the predictions were derived was an appropriate one. Often, when comparisons between healthy and ill people are being made, there is no need to introduce this complication and the direct results of the tests should be used. In cross-sectional or longitudinal studies, the results from the epidemiological population can be used in multiple regression analyses to develop predicted values for the population in relation to age, height, smoking and so on. If a reference population is required, appropriate equations have been published [53,54]. When using these, it is important to take account of the racial composition of the population, as values differ somewhat, not unexpectedly, in different racial groups [55–57].

### Chest radiography

The chest radiograph has been and remains as important

an epidemiological tool as lung function tests. The taking and reporting of a chest radiograph are relatively complex processes, but use of standardized radiographic technique coupled with the use of standard films for comparison with those under examination have allowed these processes to be widely and effectively applied to epidemiology. These standard techniques and films have been published by the ILO, most recently in the 1980 revision [58]. The booklet accompanying the films describes the methods to be used, which are summarized briefly here.

### ILO classification

The classification is strictly one for epidemiological investigation of the pneumoconioses, although it may be used for other pulmonary fibroses that cause similar appearances. The shadows are categorized as small or large opacities. The former are subdivided into rounded or irregular opacities, each being subclassified on the basis of predominant size. Rounded shadows are denoted p, q and r, while irregular ones are called s, i or u (Table 3.5). Profusion is assessed, again by comparison with standard films on a broad scale of 0 (least) to 3 (most). The broad categories are subdivided (Table 3.6) on the basis of whether the film is thought to be, say, category 1 but category 0 was seriously considered (1/0), or category 1 but category 2 was considered (1/2), into a 12-point classification. The classification also requires description of the lung zones affected and the presence of large opacities, which are classified as A, B or C in ascending order of size. In addition there are methods for recording size and type of pleural plaques, diffuse thickening and calcification. Symbols are provided for

recording other features, such as tuberculosis, emphysema, bullae, tumours, and so on. Comment is also required on film quality. Thus a complete classification would include film quality, presence, site and category of small shadows, predominant types of small shadows (either one or two), presence and extent of pleural shadows and any other features. If shadows consistent with massive fibrosis are present, they should be staged as A (greater than 1 cm and up to 5 cm in maximum diameter), B (above 5 cm but less than the volume of the equivalent of the right upper zone) or C (greater than B). If multiple lesions greater than 1 cm are present, their maximum diameters are summed.

Use of the ILO classification

A common question asked by the novice reader is: How do I know if the changes are due to pneumoconiosis or some other disease such as tuberculosis? This arises particularly when the reader is responsible for making a clinical decision about the patient as well as producing an epidemiological classification, but also arises as part of the decision as to whether or not to assign a film a pneumoconiosis classification. It is useful to separate the clinical and epidemiological roles clearly, and the author teaches new readers to imagine that they have two hats, one labelled ‘clinician’ and the other ‘epidemiologist’, only one of which may be worn at one time. The following sequence of decisions is suggested.

- 1 Read the film wearing the clinical hat and report any significant abnormality. This diagnosis would normally lead to further clinical investigations by the doctor or a colleague.
- 2 Put on the epidemiologist’s hat and start epidemiological classification by asking if any of the appearances

Table 3.5 International Labour Office classification of small opacities: the predominant types should always be determined by reference to the standard films.

Rounded
p: up to 1.5 mm diameter
q: 1.5–3 mm diameter
r: 3–10 mm diameter
Irregular
s: up to 1.5 mm in width
i: 1.5–3 mm in width
u: 3–10 mm in width

could be due to pneumoconiosis; if so, classify. Note that there is a very wide range of appearances of pneumoconioses and one should err on the side of including doubtful films.

- 3 Record film quality and do not classify if this is very poor.
- 4 Classify acceptable films according to the ILO protocol.
- 5 Make any clinical comments, for example doubts about the pathological nature of the shadows classified, so that these may be taken into account in the analyses.

The reader should sit in a darkened room and use a uniformly bright viewing box with space for at least three films. The film to be classified should be compared with whichever standard film or films is thought to be closest in appearance. It is wise to keep a standard 0/0 film on the viewing box throughout in order to keep in sight what a normal film looks like; this avoids underclassifying films with early changes. Attempts to keep the classification in one’s head result in excessive use of the middle category (1/1, 2/2 or 3/3) and increase interobserver differences [59]. The results should be recorded on standard preprinted forms in the same order as specified by the ILO booklet. In any epidemiological reading exercise, it is important that doctors forget their medical qualification (and with it their natural inclination to *interpret* the shadows) and simply record what they see. Indeed, it is perfectly possible to train non-medical people to read films very adequately for epidemiological purposes [60,61]. Even with careful adherence to the ILO guidelines, there will be differences between different readers. While these can be reduced by special training and feedback of results, they can also be used epidemiologically. For example, some readers may be more sensitive to early changes and may detect relationships between small shadows and age and smoking as well as dust. Other readers may be less sensitive to such changes, but may detect stronger relationships between the shadows and dust exposure. An example of such differences, from a study of the radiographs of shale workers, is given in Table 3.7 [62]. This illustrates the value of independent analyses of the results from each reader separately, rather than (as is often done) the production of some average reading. It can be seen that three of the four readers detected an effect of working in shale mines, though at somewhat different relative risks. All readers detected an effect of age on the prevalence of small opacities (both rounded and irregular were included in this analysis), and in addition two detected an effect of smoking. Interest-

0/–	0/0	0/1	1/0	1/1	1/2	2/1	2/2	2/3	3/2	3/3	3/+
Category 0			Category 1			Category 2			Category 3		

Table 3.6 International Labour Office classification of profusion of small opacities.



**Table 3.7** Analysis of readings of radiographs of shale workers by four separate doctors. Results of multiple regression analysis of relations between readings of 1/0 or more and various possible determinants of those appearances. (From Seaton *et al.* [62].)

Reader	Possible determinant	Relative risk	P
1	Per 10 years in shale mines	1.63	<0.0001
	Per 10 years increase in age	2.16	<0.0003
2	Per 10 years increase in age	1.94	<0.0001
3	Per 10 years increase in age	1.79	<0.0001
	Ex-smoker relative to smoker	0.72	<0.0001
	Non-smoker relative to smoker	0.41	<0.0001
	Per 10 years in shale mines	1.2	<0.01
4	Per 10 years increase in age	1.65	<0.0001
	Ex-smoker relative to smoker	0.77	<0.0004
	Non-smoker relative to smoker	0.39	<0.0004
	Per 10 years in shale mines	1.19	<0.022

ingly, when the analyses were confined to readings of the higher category of 2/1 or greater, only shale mining and age effects were detected.

Epidemiological studies that use only one reader, no matter how eminent, should be treated with considerable suspicion. Indeed, the more distinguished, the less likely is the reader to use standard films and the more likely to interpret rather than record. In reporting studies using the ILO classification, it is useful to record the degree of inter-observer and intraobserver variability in the panel of readers, obtained by recycling a sample of the films among the readers.

An important aspect of epidemiological film reading is the assessment of change in category, either progression or regression. Much has been written of the respective merits of side-by-side comparisons and of independent classifications of individual films from the same subject [63]. Both methods have advantages and disadvantages but either is acceptable epidemiologically so long as an appropriate protocol is followed. In general, more progression will be recorded when films are read side by side and the order of the films is known; this bias should be acknowledged when the study is published.

## Screening for disease

One application of epidemiology is screening for disease, usually in order to detect it at a stage at which intervention could influence its course. This is therefore an adaptation of a prevalence study. The technique has been widely practised by chest physicians, with considerable success, as part of the drive to eliminate tuberculosis; more recently, consideration has been given to population-based screening for lung cancer, while a number of indus-

tries carry out regular screening for occupational diseases such as pneumoconiosis.

Before embarking upon a screening programme, it is important to consider a number of questions related to its value and justification [64].

1 Is the condition important for individuals and the community?

2 Is there effective treatment for the condition?

3 Is the natural history of the condition, particularly its evolution from latent to overt disease, understood?

4 Is there a recognizable latent or early stage?

5 Is there an acceptable and reliable screening test?

6 Are facilities available for further investigation and treatment of people found by screening?

7 Is there an agreed policy on whom to treat?

8 Does early treatment influence the course of the disease favourably?

9 Is the cost of case-finding and management of cases acceptable in relation to the overall cost of healthcare?

10 Do the potential benefits for true positives outweigh the disadvantages of dealing with false positives?

Ideally, the answers to all these questions should be in the affirmative. Two examples may be used to illustrate this: general screening for cystic fibrosis and specific screening of an industrial population for lung cancer. In the first example, with respect to antenatal or early postnatal diagnosis, the answers to questions 1, 3, 4, 7 and 8 are clearly positive. Effective, though not at present curative, treatment is available (question 2) but facilities for providing it are not always readily available (question 6) and the cost of their provision may well not be acceptable in some economies (question 9). The disadvantages that accrue to the parents of individuals in whom false-positive diagnoses have been made can be considerable in terms of producing anxiety and invalidity (question 10), so a very sensitive and specific test is necessary. The use of modern methods of intrauterine diagnosis fulfils these criteria (question 5) [65,66], though the predictive value can only be kept adequately high if the prevalence of the condition in the screened population is high, and this is therefore generally only applied in pregnancies after screening of the parents for heterozygote status. With respect to screening of individuals for carrier status, it is apparent that screening of all pregnant women and their partners has important potential benefits, partly countered by their costs and the anxiety caused in those screened [67,68]. The availability of reliable screening tests for heterozygotes has made this a very widely discussed issue; these matters are considered further in Chapter 30. Prenatal detection of carrier status clearly has ethical and management advantages over detection during pregnancy, although this has important cost implications and may cause problems in terms of causing both anxiety and false reassurance [69,70].

In the case of screening for lung cancer in a workforce with the intention of early detection and surgical cure, the decision may rest on the answers to questions 5 and 10. Sputum cytology may well be an acceptable screening test but its employment on a large scale demands large resources. If the disease is a relatively uncommon one, as lung cancer is in people of working age, and if the incidence is not very greatly increased by the industrial exposure in question, then the predictive value of the test will be relatively low and the problems arising from a relatively high number of false positives (leading to chest radiography, CT scanning, bronchoscopy and possibly thoracotomy) in proportion to the numbers of true positives cured will be disproportionately large. In general, the evidence suggests that population screening for this disease is of little or no benefit in terms of outcome [71]. Care should be exercised in judging papers that investigate this, since it is likely that patients detected during routine periodic screening will have, on average, slower-growing tumours, and the fact that they are detected earlier will mean that they would be expected to survive longer than those detected at a later stage whatever treatment is used.

## Determination of the cause of disease

As stated at the beginning of this chapter, epidemiology may be defined as the study of the distribution and of the determinants of health and disease in groups of people. However, the statistical methods used in epidemiology point to relationships between disease and its determinants rather than to causation of disease. Evidence of association is not necessarily evidence of causation. An investigator who wishes to comment on the cause of a disease should look at all the available evidence in terms of the criteria proposed by Bradford Hill [72].

1 *Strength of the association.* A strong association, one that is highly unlikely to have occurred by chance, suggests a cause-and-effect relationship.

2 *Consistency of the association.* Do all, or most, of the properly conducted studies of this relationship point in the same direction?

3 *Specificity of the association.* Is the disease confined to a particular group exposed to a particular agent?

4 *Relationship in time.* Does the disease follow the exposure after an appropriate time interval?

5 *Biological gradient.* Can the risk of disease be related to exposure to the suspected cause?

6 *Biological plausibility.* Does the relationship make biological sense?

7 *Coherence of the evidence.* Do the observed relationships conflict with what else is known of the natural history and biology of the disease?

8 *Experimental evidence.* Are the observations supported by studies in animals or in the laboratory?

9 *Analogy.* Do the observations accord with other previously described associations in other fields?

These criteria do not all have to be satisfied of course, but each in turn may give further support to a hypothesis of causation. Lung cancer and cigarette smoking, for example, are strongly associated, the risk in smokers being about 10 times that of non-smokers (criterion 1). The association has been shown in a multitude of studies (criterion 2); although the disease is not the only condition of which smokers are at increased risk of dying, the strength of the association is such that the criterion of specificity is satisfied (criterion 3). The temporal relationship between smoking and development of cancer seems appropriate (criterion 4) and a biological gradient has been established (criterion 5). Biological plausibility is strong, in that smoke contains known carcinogens (criterion 6), and the evidence is coherent in that, for example, death rates from cancer have fallen in groups who have reduced their smoking habits (criterion 7). Animal experiments have not been successful in producing experimental evidence in support of the epidemiology (criterion 8) and useful analogies are hardly necessary in the face of such strong evidence. Rather, smoking and lung cancer provides a useful criterion 9 for other associations.

Another extremely strong piece of evidence is that associating mesothelioma and exposure to blue asbestos, in which all the criteria are satisfied. In many other examples, for example the relationships between air pollution, asthma and lung cancer, exposure to mycobacteria and sarcoidosis, and occupational exposure to dusts and emphysema or pulmonary fibrosis, the evidence is less clear-cut and needs to be strengthened before a cause-and-effect relationship can be assumed.

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# LUNG DEFENCES AND IMMUNOLOGY

CHRISTOPHER HASLETT

Like the skin, the lung is continuously exposed to the external environment; unlike the skin it is a critically important gas-exchange organ, the membranes of which are delicate and need to be kept moist. Every day the lungs are exposed to more than 7000 L of air and its fine tissues require protection from the daily bombardment of particles, including dust, pollen and pollutants, and the viruses and bacteria that have the potential, respectively, to cause lung injury or to invade the lung and generate life-threatening infections. However, these problems rarely occur because the lung possesses very effective local 'primary' protective mechanisms, which are the focus of this chapter. If an infectious agent is able to penetrate these defences and set up a bridgehead, highly effective and complex 'secondary' responses including the inflammatory and classical immune responses can rapidly be recruited. In the event that an immune or inflammatory response is initiated, the lung also has mechanisms by which it can protect itself from their potentially detrimental local effects. The inflammatory and immune responses themselves are only briefly mentioned; detailed treatment of these processes can be found in Chapters 27 and 33, where their roles in the adult respiratory distress syndrome and asthma are discussed.

The respiratory tract is protected by different mechanisms at its various levels. In general terms, physical mechanisms including cough are particularly important in the upper airways. The lower airways are served by the mucociliary clearance mechanism, and the gas-exchange units (terminal bronchioles and alveoli) are protected by surfactant and cellular defenders, including the patrolling alveolar macrophages. The lung lining fluids (mucus in the upper airway and surfactant in the gas-exchange units) contain a variety of proteins with important properties in host defence against infection and also other proteins that can help protect local healthy tissues against bystander injury in the event that it is necessary for the lung to generate a protective secondary inflammatory or immune response. The lining cells of the lung, especially the epithelial cells, are able to generate many of these pro-

teins themselves. These cells have also evolved important cytoprotective antioxidant and antiproteinase mechanisms, and it is now recognized that, like the resident lung macrophages, they are able to synthesize a wide range of important cytokines and chemokines and thereby play a central role in the initiation of inflammatory and immune responses.

This chapter considers physical defences including cough and mucociliary clearance, surfactant and other protective agents in the lung lining fluids, epithelial and endothelial cytoprotective mechanisms, and the role of alveolar macrophages and other cells in lung defence.

## Physical defences

The nose is the first important contributor to the physical defences of the upper airway. It comprises a stack of fine aerodynamic filters of respiratory epithelium covering the turbinate bones that remove most large particles from the inspired air. The filtering effect is greatly enhanced by fine hairs in the anterior nares and by mucociliary action which, apart from a small area anterior to the inferior turbinates, is directed posteriorly such that trapped particles are swallowed or expectorated. During cough and expectoration the larynx acts as a sphincter, which is an essential protective mechanism for the lower airways during swallowing and vomiting. Larger particles that penetrate the nose and are deposited by impaction or sedimentation in the main airways are trapped by the lining fluids of the trachea and bronchi and cleared by the mucociliary clearance mechanism (also termed the mucociliary escalator); those smaller particles, down to a few nanometers in size, deposited in the acinar part of the lung are dealt with by alveolar macrophages.

## Cough

Cough is both an important reflex mechanism protecting the airways [1] and a common symptom of respiratory disease. The cough reflex can be stimulated by particulate

matter, extremes of air temperature and irritant fumes, as well as by excessive production of mucus itself. A range of inflammatory mediators is also known to provoke cough. The nature of the neuronal mechanisms involved in the afferent component of the reflex is uncertain in humans. It is likely to involve myelinated irritant fibres and intravascular non-myelinated J receptors, which are thought to transmit cough via C fibres as well as myelinated fibres. Agents in the fluids bathing sensory nerves in the airway are important in their state of activation and sensitivity to other stimuli. For example, prostaglandins have been shown to activate and also sensitize the afferent fibres. The central nervous component of the cough reflex may be located to the region of the medulla oblongata and it is now thought that 5-hydroxytryptamine receptors are involved. The efferent part of the reflex involves the nerve supply to the larynx, rib cage and diaphragm and is generated in four distinct phases: inspiration, compression of intrathoracic gas against a closed glottis, explosive expulsion as the glottis opens, and relaxation of the airways. This results in expectoration of foreign debris and mucus from the large airways as a result of the extremely high local turbulent airflows generated by the reflex. Cough contributes little to tracheobronchial clearance in healthy individuals but in chronic bronchitis may account for up to 50% of clearance, compensating for deficient mucociliary transport [2].

The cough reflex can be inhibited by a number of mechanisms. One such physiological inhibitory mechanism is mediated by swallowing, which causes a reduction in coughing. This can be stimulated by the presence of either a solid or liquid in the pharynx, which induces the inhibitory reflex via an unknown mechanism. Opiates have a direct, rather than a sedative, effect on the central nervous system component of the cough reflex since other sedative drugs are without effect. Local anaesthetic agents can effectively abolish the cough reflex via blockade of the afferent signals in the nasopharynx and upper airways. This effect can last a few hours and obviously needs to be borne in mind when advising patients who have undergone fiberoptic bronchoscopy or upper alimentary endoscopy.

### Mucociliary escalator

In healthy subjects cough is not effective in removing small inhaled particles and it is likely that mucociliary transport is entirely responsible for tracheobronchial cleanliness [3]. The mucociliary clearance mechanism works by a complex interaction between cilia, which are a series of projections on the bronchial epithelial cells, and mucus [4]. The mucus forms a 'raft' on top of the cilia, which sweep in a cephalic direction; the effectiveness of cilia in sweeping the mucus is greatly enhanced by small claws at their tips that penetrate the overlying mucus raft (Fig. 4.1). Each of the pseu-

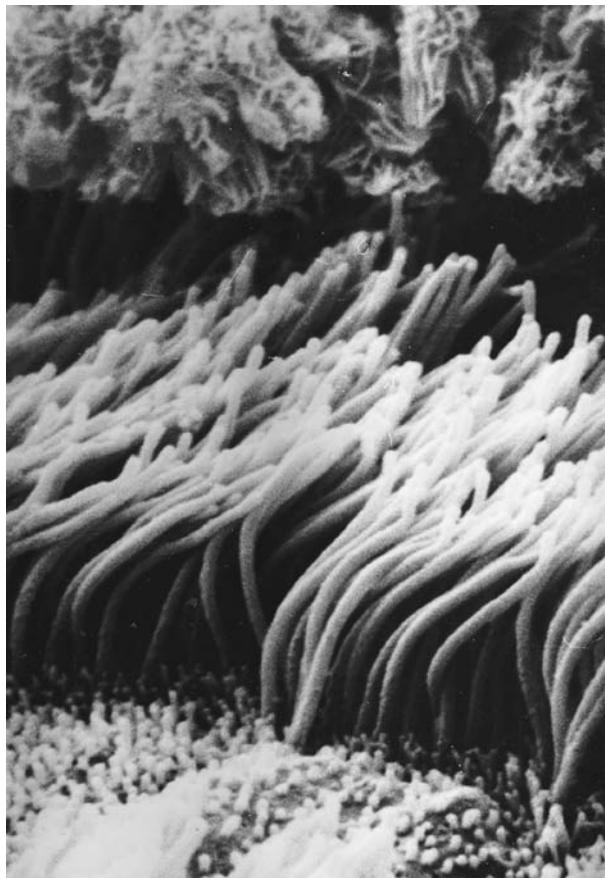


Fig. 4.1 Scanning electron micrograph of the mucociliary escalator showing the mucus 'raft' above and the projections of the cilia below. (Kindly provided by Dr. Peter Jeffery.)

dostratified columnar epithelial cells lining the bronchi possesses about 200 cilia on its surface; calculations have shown that the cilia can carry weights of up to 10 g without slowing. The cilia beat 12–14 times per second and their motor function is mediated by the contraction of fibrils that contain the contractile protein tubulin arranged as nine outer and two central microtubular pairs (see Fig. 1.13, p.12). The biochemical mechanisms serving the ciliary motor are not fully established but there is an important role for dynein, an ATPase protein that forms a major part of the cilium. Dynein appears to derive energy from ATP along the cilium that is then converted into the forces generated by the contractile proteins.

Cilia can survive freezing for up to a month and may beat for several hours after the death of the host. Thus it is possible to assess ciliary motility directly on cytological specimens from nasal and bronchial brushings and to enumerate ciliary beat frequency in epithelial specimens sampled by biopsy. The structure of the cilia can be assessed by electron microscopy. A simple and practical clinical test for ciliary function involves establishing the time taken for saccharin placed in the anterior nares to cause a sweet taste in the mouth (normally less than 30



min). Other more complex methods of assessing mucociliary clearance *in vivo* include direct cine-bronchographic measurement of the movement of small Teflon discs [5] and assessment of the rate of clearance of radio-aerosols by external imaging techniques [6].

Mucus is secreted by the goblet cells and submucosal glands of the first several bronchial generations. A variety of chemical mediators have been implicated in the control of mucous secretion. Neuropeptides, including substance P, vasoactive intestinal peptide and bombesin, vagal stimulation and acetylcholine cause increased mucous secretion. In health, mucus is composed of 95% water, mucous glycoproteins or mucins, and a variety of other proteins (see below), which although present in low concentration probably play an important part in the defence of the bronchial tree. The main physical functions of mucus are to trap and clear particles, dilute noxious influences, lubricate the airways and humidify inspired air. The viscoelastic or rheological properties of mucus are probably controlled by different concentrations of the various mucins and are important in determining adequate mucociliary transport. There is now a great deal of interest in abnormal constitution and rheological properties of mucus [4], and in the deranged mucociliary clearance in cystic fibrosis. In this condition the mucus appears to be abnormally viscous and has markedly altered rheological properties that contribute to dysfunction of the mucociliary clearance mechanism (see Chapter 30).

A number of external factors may also reduce mucociliary clearance, either by interfering with ciliary function or by causing direct ciliary damage. These include cigarette smoke, pollutants, local and general anaesthetic agents, bacterial products and viral infection. In severe asthma it is thought that some eosinophil products, such as major basic protein, may have detrimental effects on ciliary function. There is also an autosomal recessive condition (occurring with a frequency of about 1 in 30 000 of the population) called primary ciliary dyskinesia in which defects in ciliary dynein may be associated also with male infertility and situs inversus. Primary dyskinesia is associated with repeated sinusitis and respiratory infections that often progress to persistent lung suppuration and severe bronchiectasis, thereby underlining the importance of normal ciliary function in antibacterial lung defences.

## Surfactant

As discussed in Chapter 1, surfactant is a complex surface-active material lining the alveolar surface that reduces surface tension and prevents the lung from collapsing at resting transpulmonary pressures. It also provides a simple but elegant mechanism for alveolar clearance, since at end-expiration surface tension decreases and the surface film moves from the alveolus towards the bron-

chioles, thus carrying small particles towards the mucociliary transport system.

Surfactant is synthesized by the alveolar type II pneumocytes and comprises phospholipids, neutral lipids and at least four different specific proteins, known as Sp-A, Sp-B, Sp-C and Sp-D. It is now recognized that in addition to promoting the surface-active properties of surfactant these proteins have important roles in host defence. There are now many studies showing that surfactant from normal lungs exerts a variety of influences on alveolar macrophages, including chemotaxis and enhancement of phagocytosis and killing of microorganisms.

Normal surfactant also enhances local pulmonary non-specific immune defence mechanisms by suppressing the development of specific T lymphocyte-mediated immune responses to inhaled antigens and T-cell proliferation. It is also likely that surfactants exert influences on neutrophil functions including neutrophil adherence.

## Surfactant proteins

Sp-A is the most abundant protein in surfactant, accounting for 3 mg of protein per 100 mg of phospholipids. At an ultrastructural level it closely resembles the complement component C1q and interacts with a C1q receptor (or 'collectin' receptor). It has been shown to enhance alveolar macrophage phagocytosis of microorganisms including *Staphylococcus aureus*, and may also be important in *Pneumocystis carinii* recognition. Sp-A adheres to pollen grains and enhances FcR- and CR1-mediated phagocytosis of a variety of particles opsonized with IgG or C3b, respectively. Sp-D may also share many of the effects of Sp-A on inflammatory cells and macrophages. Surfactant proteins have also been shown to inhibit endotoxin-stimulated release of interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF).

The *in vivo* significance of these observations is uncertain. Nevertheless, surfactant can be damaged by a number of noxious stimuli, and alterations of surfactant both quantitatively and qualitatively are thought to be important mechanisms in the pathogenesis of adult respiratory distress syndrome (see Chapter 27). This may manifest not only as effects on lung function and gas exchange but also by contributing to the known susceptibility of the injured lung to bacterial colonization and infection. There are also implications for surfactant replacement therapy in both neonatal and adult respiratory distress syndrome, since the artificial surfactants do not contain these protective proteins.

## Other protective proteins of the lung lining fluid

Apart from the surfactant proteins, a number of other

**Table 4.1** Protective proteins in lung lining fluids.

<i>Antibacterial</i>
Surfactant proteins (especially SpA and SpD)
Immunoglobulins (especially IgA)
Defensins
Lactoferrin
Lysozyme
Complement (especially C3)
<i>Antiproteinases</i>
$\alpha_1$ -Proteinase inhibitor
$\alpha_1$ -Antichymotrypsin
$\alpha_2$ -Antimacroglobulin
Secretory leukoproteinase inhibitor
Elafin
Tissue inhibitors of metalloproteinases

proteins are present in lung fluids and are important in lung defences (Table 4.1). These may be derived from plasma (e.g. albumin, antiplasmin,  $\alpha_2$ -macroglobulin and transferrin), by secretion from local epithelial cells (a variety of antiproteinases), airway macrophages and lymphocytes or inflammatory cells (e.g. defensins, lysozyme, lactoferrin), or by selective epithelial transport (IgA). In the event of an inflammatory response the local availability of plasma-derived proteins increases greatly during the exudative phase of oedema, and this would obviously deliver more complement antiproteinases, immunoglobulins, cytokines, etc. to the inflamed site.

**Immunoglobulins**

Normal lung secretions contain all the immunoglobulins present in plasma but in different proportions [7]. By comparison with plasma, IgA is greatly in excess and there are only small contributions from IgG and IgM. In the absence of disease, immunoglobulins are produced by local lung tissues, probably from B lymphocytes and plasma cells scattered throughout the bronchial tree, often in association with bronchial epithelial cells. The role in health of collections of lymphocytes in the bronchial tree, the bronchial-associated lymphoid tissue, is uncertain. It may be that these lymphoid aggregates are more a feature in smokers and in patients with chronic respiratory disease. With regards to IgA production it is thought that B lymphocytes produce secretory IgA in the upper airways by a collaborative mechanism involving the epithelial cells. Dimeric IgA is assembled in the plasma cells from two monomeric IgA molecules and joined by another protein called the J chain. Dimeric IgA binds to the secretory component of epithelial cells, leading to formation of a dimeric IgA–secretory component complex that is pinocytosed, transported through the epithelial cell and released from its luminal surface into the airways [8]. The secretory com-

ponent appears to protect IgA from enzymatic attack during bacterial infection and inflammation. IgA is produced in very high concentrations in the upper airways and probably serves a number of important anti-infective roles, not all of which have been fully elucidated. However, IgA deficiency is associated with local defects in immunity to bacterial infections [9].

**Defensins and other proteins with antibacterial effects**

Defensins are a family of cytotoxic cationic peptides secreted mainly by leucocytes [10]. Their antibacterial effects correlate with their charge, which is determined by the arginine content of the molecule. Defensins are able *in vitro* to kill a variety of Gram-positive organisms, fungi and viruses. Lactoferrin is an iron-binding protein, the antibacterial action of which is in part related to competition with iron, an essential growth factor for certain bacteria. Lysozyme is a highly cationic protein able to disrupt a range of bacteria that contain susceptible cell wall peptidoglycans.

**Complement proteins**

Most of the proteins involved in the complement system have been identified in lung secretions. However, during inflammation their delivery to the lung is probably greatly increased by plasma exudation. Alveolar macrophages are able to secrete C3a, C3b and C5a. Patients with C3 deficiency have recurrent upper and lower respiratory tract infections, particularly with *Streptococcus pneumoniae* and *Haemophilus influenzae*. Therefore C3 is likely to play a key role in bacterial defences of the lung, perhaps because of its action as an opsonin (via C3bi), thereby enhancing the removal of bacteria by macrophages and other phagocytes.

**Antiproteinases**

Lung secretions contain a variety of antiproteinases, including those of high molecular mass ( $\alpha_1$ -proteinase inhibitor and  $\alpha_2$ -antimacroglobulin) and those of low molecular mass (secretory leukoproteinase inhibitor (SLPi) and elafin). Many of these agents may be derived from alveolar macrophages and airway epithelial cells, and during inflammatory and injurious processes the rate of secretion of these important protective agents is likely to be greatly enhanced. It is widely agreed that these enzyme inhibitors play an important part in the antiproteinase shield necessary to protect healthy local tissue against damage that would otherwise inevitably accompany the release of proteinases by inflammatory cells. During an acute inflammatory response it seems likely that the small molecular mass antiproteinases such as SLPi and elafin are

more effective in the restricted intercellular microenvironments created by neutrophils tightly adherent to endothelial/epithelial cells or basement membrane/matrix proteins [10].

#### **$\alpha_1$ -Proteinase inhibitor**

Together with antithrombin III, antiplasmin and  $\alpha_1$ -antichymotrypsin,  $\alpha_1$ -proteinase inhibitor is a member of the serpin family that inhibit enzymes of the metalloproteinase type. It is particularly effective against neutrophil elastase, which has been specifically implicated in a number of inflammatory diseases of the lung. Although  $\alpha_1$ -proteinase inhibitor is highly effective against elastase, it may well be too large a molecule to work efficiently in the restricted microenvironment between neutrophils adherent to target cells or tissue matrices. It is also quite vulnerable to damage by oxidizing agents, such as those contained in cigarette smoke.

#### **$\alpha_1$ -Antichymotrypsin**

$\alpha_1$ -Antichymotrypsin is also a member of the serpin family. Although its concentration in serum is low, its concentration in bronchial secretions is high, suggesting that either it is secreted locally or there is an active concentration mechanism in the bronchial mucosa. It does not inhibit neutrophil elastase but is extremely effective against cathepsin G. A genetic defect of this protein has recently been described and has been linked with chronic lung diseases, suggesting that it may well have an important role in lung defence against proteinase attack.

#### **$\alpha_2$ -Antimacroglobulin**

$\alpha_2$ -Antimacroglobulin, like  $\alpha_1$ -proteinase inhibitor, is a major serum inhibitor of proteolytic enzymes, and has a wide range of effects against those proteinases, including the metalloproteinases, not influenced by  $\alpha_1$ -proteinase inhibitor. Like  $\alpha_1$ -antichymotrypsin it is present in significant quantities in bronchial secretions.

#### **Secretory leukoproteinase inhibitor**

SLPi is produced by the submucosal glands in the bronchi and also by the epithelial cells of the small airways. It is found in significant concentrations in the sputum and bronchoalveolar lavage fluid but is barely detectable in the serum. Its low molecular size may allow it access to the restricted intercellular microenvironments that appear to be necessary for neutrophil-mediated injury (see Chapter 27). SLPi is an extremely potent and rapid inhibitor of neutrophil elastase but can also inhibit a number of other serum proteinases, including cathepsin G, trypsin and

chymotrypsin. SLPi forms more than 80% of the antielastolytic capacity of the bronchial secretions and is thought to be an important component of the antiproteinase shield protecting the lung.

#### **Elafin**

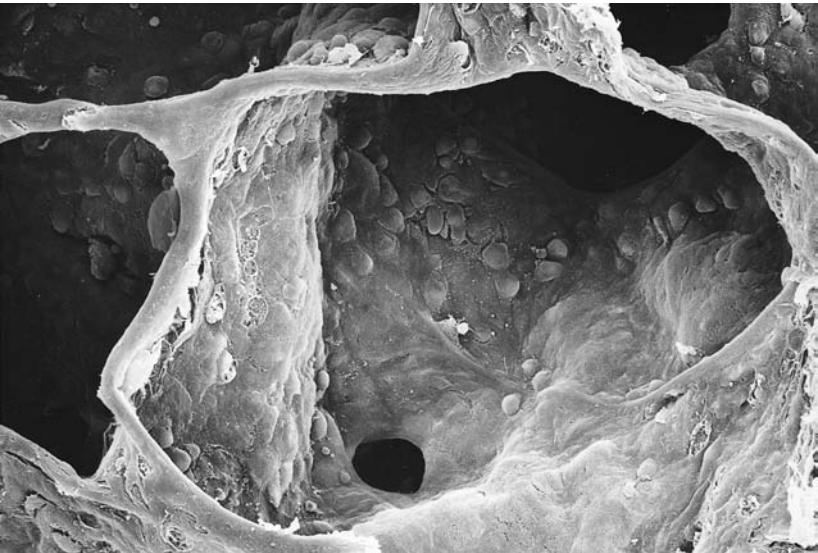
Elafin is another small molecular mass (6 kDa) antiproteinase that, like SLPi, is extremely effective against neutrophil elastase. It can be distinguished from SLPi biochemically in that it does not inhibit trypsin, chymotrypsin or cathepsin G.

#### **Tissue inhibitors of metalloproteinases**

A number of inhibitors of this type have been described. They are secreted by fibroblasts and alveolar macrophages and are able to inhibit all metalloproteinases. Again, because of their small molecular mass (around 25 kDa) they may have access to sites of metalloproteinase action that exclude the larger molecules such as  $\alpha_2$ -antimacroglobulin (molecular mass 780 kDa).

#### **Alveolar macrophage**

Alveolar macrophages are derived from blood-borne monocytes that originate in the bone marrow [11]. They are highly differentiated cells that normally patrol the alveolar lining, where they probably live for several weeks (Fig. 4.2; see also Fig. 1.16). Their accessibility to bronchoalveolar lavage has greatly facilitated the *ex vivo* study of the various functions of these highly versatile cells (Table 4.2). It has been known for some time that alveolar macrophages possess marked phagocytic ability, being able to ingest and destroy pathogenic bacteria and particles, although their capacity to generate mediators of central importance in the initiation of inflammation and to present antigen in the initiation of immune responses has been fully recognized only recently. The alveolar macrophage has a vast array of receptors on its surface (Table 4.3) and can respond to a wide range of external stimuli and subsequently generate a wide range of secretory products. In the control of the inflammatory response the alveolar macrophage can be considered analogous to a microcomputer, sampling and sensing the external environment and determining whether to initiate or amplify the inflammatory response. It is also likely to assist the inflammatory monocyte-derived macrophages in the scavenging roles required during the aftermath of infections and in the resolution of inflammation. The alveolar macrophage may play further important roles in the processes whereby inflammatory tissue injury is repaired, since it can produce a number of proteins involved in tissue repair processes and can generate a wide range of growth factor cytokines that influence fibroblast



**Fig. 4.2** Scanning electron micrograph of the alveolar surface showing ‘patrolling’ alveolar macrophages. (Kindly provided by Dr. Peter Jeffery.)

**Table 4.2** Some functions of macrophages.

<i>Primary host defence</i>
Phagocytosis and killing of microorganisms by oxygen radicals, nitric oxide-dependent mechanisms and enzymes
<i>Inflammatory response</i>
<i>Initiation</i>
Generation of neutrophil chemokines (e.g. IL-8)
Generation of monocyte chemokines (e.g. MIP-1 $\alpha$ )
Generation of agents (IL-1, TNF- $\alpha$ ) that activate endothelial cells
Generation of acute-phase response (IL-1, TNF- $\alpha$ , IL-6)
<i>Amplification</i>
Secretion of agents that stimulate bone marrow generation of leucocytes (IL-1, TNF- $\alpha$ )
<i>Resolution</i>
Scavenging of necrotic and apoptotic cells and debris
<i>Repair/fibrosis</i>
Remodelling: elastase, collagenase
Scar formation: IL-1, PDGF, FGF
<i>Immune response</i>
Antigen presentation: lymphocyte activation
<i>Antitumour effects</i>
Lysis of tumour cells by TNF- $\alpha$ and nitric oxide-dependent mechanisms

FGF, fibroblast growth factor; IL, interleukin; MIP-1 $\alpha$ , macrophage inhibitory protein-1 $\alpha$ ; PDGF, platelet-derived growth factor; TNF- $\alpha$ , tumour necrosis factor  $\alpha$ .

proliferation and secretion of collagen and other matrix proteins.

**Phagocytosis and bacterial killing**

Macrophages can recognize and ingest (via their surface CR3 or FcR receptors) opsonized or non-opsonized particles. Within the phagolysosome ingested particles are sub-

**Table 4.3** Some receptors on and molecules binding to macrophages.

<i>Complement components</i>
C1q, C3b, C3bi, C3d, C5a
<i>Immunoglobulins</i>
IgG, IgA, IgE
<i>Growth factors and cytokines</i>
IFN- $\alpha$ / $\beta$ , IFN- $\alpha$ , CSF-1, GM-CSF, TNF- $\alpha$
IL-1, IL-2, IL-3, IL-4, IL-6
<i>Adhesion molecules and phagocytic receptors</i>
LFA-1, MAC-1, p150/95, ICAM-1, $\alpha_v\beta_3$ (VnR), CR-1, CR-3, FcR
<i>Glycoproteins and carbohydrates</i>
Mannosyl fucosyl receptor, mannose-6-phosphate
Heparin, advanced glycosylation end-products
<i>Proteins and hormones</i>
Fibronectin, laminin, transferrin, fibrin, lactoferrin
Calcitonin, oestrogen, insulin, parathormone, progesterone
<i>Peptides and small molecules</i>
Adenosine, bombesin, bradykinin, epinephrine
Dexamethasone, glucagon, histamine
Tachykinins, platelet-activating factor, serotonin, substance P, vasoactive intestinal peptide
<i>Lipids and lipoproteins</i>
Leukotrienes, C, D <sub>4</sub> , B <sub>4</sub> , E <sub>2</sub>
LDL, $\beta$ VLDL, modified LDL

CSF, colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LDL, low-density lipoprotein; TNF, tumour necrosis factor; VLDL, very low density lipoprotein.

jected to the combined destructive forces of both reactive oxygen intermediates generated via the metabolic burst and a wide range of degradative enzymes that have the capacity to digest proteins, lipids and carbohydrates (Table 4.4). It appears that the local intracellular generation of nitric oxide (NO) is an important defence mechanism against a variety of microorganisms. Activated macrophages also form nitrite (NO<sub>2</sub>) and nitrate (NO<sub>3</sub>). *In vitro* experiments suggest that these products, particularly NO and the peroxynitrite anion, also contribute to the antifungal, antiparasitic and tumoricidal activities of macrophages. Macrophages may also call in reinforcements comprising other phagocytic cells, including neutrophils, monocytes (which then mature into

inflammatory macrophages) and eosinophils, by the generation of specific chemotaxins (see below). Despite the availability of such powerful mechanisms, it is clear that not all phagocytosed particles are effectively destroyed. Minerals such as asbestos and quartz and a number of microorganisms, including *Mycobacterium tuberculosis* and trypanosomes at various stages of their life cycle, are able to resist destruction within macrophages.

### Initiation and control of the inflammatory response

Macrophages can secrete a number of chemotactic proteins, including members of the 5-lipoxygenase and cyclooxygenase pathways (see Chapter 33), which exert important proinflammatory effects, and leukotriene B<sub>4</sub>, which is a specific neutrophil chemotaxin. Perhaps more importantly in terms of chemoattraction, lung macrophages are a potent source of neutrophil chemokines, including IL-8, NAP-1, NAP-2, etc., and also secrete chemokines for monocytes and eosinophils, including MCP-1, MIP-1 $\alpha$  and RANTES. Other macrophage-derived cytokines may have important secondary proinflammatory effects through their influences on other local cells. For example, both TNF- $\alpha$  and IL-1 generated by alveolar macrophages can act on the endothelium to stimulate the expression and activation of surface adhesion molecules necessary for neutrophil adhesion and emigration, but they can also act on local fibroblasts, epithelial cells and endothelial cells to produce IL-8 and other chemokines that attract more neutrophils and thereby amplify the inflammatory response. Thus macrophages are not only able to generate chemoattractants for inflammatory cells themselves but can also indirectly recruit other local cells to help in the initiation of inflammation, thereby exerting further levels of control on the initiation and amplification of the inflammatory response. The acute inflammatory and the allergic inflammatory responses are considered in detail in Chapters 27 and 33 respectively.

### Initiation and control of the immune response

Alveolar macrophages are effective antigen-presenting cells and can display partially degraded antigens on their surface that interact with recirculating T and B lymphocytes, thereby generating clonal expansion and initiating the immune response (see Chapter 33). However, the main cells responsible for this role, dendritic cells, are also present in the lung but are less accessible, more difficult to purify and therefore less easy to study *in vitro*. With regard to antigen presentation, resident alveolar macrophages are not likely to be as effective as recently matured monocyte-derived inflammatory macrophages, or 'professional' dendritic cells. The evolution of an allergic immune response is considered in more detail in Chapter 33.

**Table 4.4** Some secretory products of macrophages.

#### *Cytokines and growth factors*

IFN- $\alpha$ / $\beta$ / $\gamma$ , IL-1, IL-6, TNF- $\alpha$   
IL-8, gro  $\alpha$ , MCP-1  
TGF- $\beta$ , PDGF, FGF, IGF, GM-CSF, G-CSF  
Erythropoietin, lactoferrin

#### *Enzymes*

Elastase, collagenase, lysozyme  
Phospholipase A<sub>2</sub>, amylase  
Hyaluronidase, acid hydrolases  
 $\beta$ -Galactosidase,  $\beta$ -glucuronidase  
Nucleases, ribonucleases, acid phosphatases  
Sulphatases, cathepsins

#### *Enzyme inhibitors*

$\alpha_1$ -Antiproteinase,  $\alpha_2$ -antimacroglobulin  
Lipomodulin,  $\alpha_1$ -antichymotrypsin  
Inhibitors of plasminogen and plasminogen activator

#### *Reactive oxygen intermediates*

O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, OH $\cdot$ , hypohalous acid

#### *Reactive nitrogen intermediates*

NO $\cdot$ , NO<sub>2</sub>, NO<sub>3</sub>

#### *Complement components*

C1, C4, C2, C3, C5, factor B, factor D, properdin

#### *Lipids*

Leukotrienes B, C, D and E, PGE, PGF<sub>2 $\alpha$</sub>   
Platelet-activating factor, prostacyclin, thromboxane A<sub>2</sub>

#### *Matrix proteins*

Fibronectin, thrombospondin, proteoglycans

#### *Coagulation factors*

Factors X, IX, V, VII, tissue factor, prothrombin, thromboplastin

FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; PDGF, platelet-derived growth factor; PG, prostaglandin; TGF, transforming growth factor; TNF, tumour necrosis factor.

### Tissue modelling and repair

Alveolar macrophages can secrete proteins, including vitronectin, fibronectin and laminin, that are important in tissue repair. They also secrete a number of growth factor cytokines [12], including platelet-derived growth factor, transforming growth factor  $\beta$  and IL-1, all of which can influence the behaviour of fibroblasts in terms of both proliferation and secretion of collagen and other matrix proteins.

### Pulmonary marginated pool of neutrophils

The neutrophil is the archetypal acute inflammatory cell and is equipped with an armamentarium of granule contents (see Chapter 27) that have probably evolved to aid its rapid transit through tissues and the killing of bacteria such as streptococci. After release from the bone marrow, mature neutrophils remain in the vascular compartment with a half-life of about 6 h. Unlike red blood cells, up to half the neutrophils in the vascular compartment at any given time are not circulating but form the 'marginated pool', which is in dynamic equilibrium with the 'circulating pool' of vascular neutrophils. The marginated pool can be released into the circulating pool by exercise or epinephrine (adrenaline). The vascular bed of the lung and spleen make the most important contributions to the marginated pool and may therefore serve as a source of rapidly releasable neutrophils in time of stress or injury. However, the presence of large numbers of neutrophils loitering in the pulmonary microvascular bed may also be

of local advantage in host defence. Their mobilization and effectiveness is likely to be augmented in local lung responses to inhaled microorganisms or toxins and in the generation of a local inflammatory response to lung invasion by streptococci for example (the role of neutrophils in lung inflammation is considered in Chapter 27). However, there may be a downside to the presence of this marginated pool of neutrophils in pulmonary microvessels: they may put the lung particularly at risk of developing injury in multiple organ failure (see Chapter 27).

The mechanisms underlying the formation of the marginated pool in the lung are uncertain. It is possible that it occurs as a result of low-grade adhesive interactions between neutrophils and lung capillary endothelial cells. However, it is more likely that the rheological properties of neutrophils in pulmonary capillaries are relatively more important in their physiological margination in the lung compared with other microvascular beds. The mean diameter of the pulmonary capillary is 5.5  $\mu\text{m}$ , whereas that of the neutrophil is 7.5  $\mu\text{m}$ . Thus neutrophils are normally required to 'squeeze' through pulmonary capillaries, and minor changes in their deformability or alterations in the fluid pressure gradient across the lung capillary bed would be expected to exert a marked influence on the size of the pulmonary marginated pool. It is of interest that many inflammatory mediators known to be important in neutrophil attraction and sequestration in the lung not only cause increased expression of neutrophil surface adhesive molecules and activation of those already expressed but can also markedly reduce the deformability of neutrophils.

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# GENETICS OF LUNG DISEASE

JULIAN M. HOPKIN

Genetics, the study of inherited differences between individuals, is now linked strongly to the discipline of molecular biology, whose aim is to delineate the structure and function of genes, their protein products and other biologically important molecules. A recent explosion in molecular techniques, particularly in molecular genetics, has revolutionized the study of the genetic factors underlying disease. Disorders of the lung have featured prominently in this progress, especially cystic fibrosis (CF) and  $\alpha_1$ -antitrypsin (AAT) deficiency. The extensive range of genetic effects in lung disorder should not be surprising for an outbred species like the human, in whom it is estimated that there is some kind of genetic variation or polymorphism, functional or not, every 500 base pairs (bp) of DNA; even using fairly crude techniques such as protein electrophoresis, it was plain some 20 years ago that many human enzymes (>30%) showed significant genetic variation [1,2].

These genetic effects in lung disease range between (i) monogenic effects (mutations at a single genetic locus) such as CF [3], and (ii) multifactorial and genetically heterogeneous effects, for example those underlying the syndrome of atopy and its associated clinical disorders such as asthma, in which there are crucial interactions between genetic effects and environmental factors that cause disorder and disease [4]. In the future, we will see increasingly subtle genetic factors discovered that may in part explain human susceptibility to disease, for example those that modulate the risk of respiratory infections such as tuberculosis. We will recognize that the genetic heterogeneity underlying common disorders, such as asthma and atopy, may be an important pointer towards the need for different treatments for different individuals with apparently the same clinical syndromes.

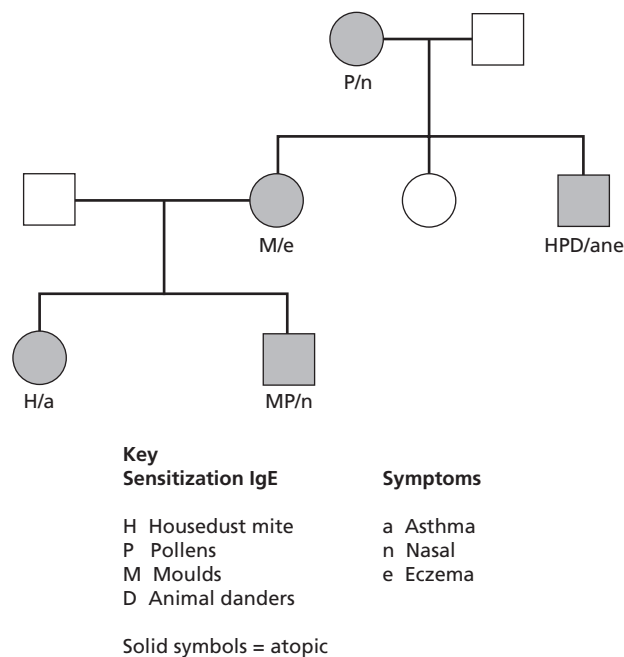
This bright age of molecular reductionism will need a cohort of visionary physiologists and clinicians to create an understandable synthesis of human lung function and disease in all its diversity.

## Genetic counselling

The occurrence of a genetic disorder in a family causes particular distress. Expert genetic counselling is invaluable in providing emotional support, answering questions about the origin of the disease and its likely progress, providing families with estimates of the risk of recurrence in other family members, and indicating what investigations and techniques are available to limit this risk — for example carrier detection, antenatal diagnosis and termination of pregnancy. The genetic counselling process aims to allow families to make their own, but well-informed, decisions on their reproductive future. The recent advances in molecular genetic techniques are having a major impact on this process: molecular DNA assays are now available for antenatal diagnosis and carrier detection in families for many genetic disorders, including CF and AAT deficiency.

## Evidence for genetic effect and the hunt for 'disease genes'

The main clue to a significant genetic effect in the aetiology of a disease lies in the observation that the disorder tends to cluster within families, although it must be recalled that shared familial environmental factors can also produce such aggregation (Fig. 5.1). The pattern of observed aggregation depends upon the genetic contribution to the disorder. When the genetic effect is predominant, i.e. both necessary and sufficient for causing the disease, monogenic or Mendelian patterns of inheritance are observed, for example autosomal recessive in CF. However, note that different patterns of inheritance may be observed in different families if there is genetic heterogeneity (different variants or mutations at one or more than one genetic locus can produce the same clinical syndrome) [5,6]. When a disorder is multifactorial in origin, i.e. when both genetic and environmental factors must interact to cause the disease, the incidence of disease in close relatives, for example siblings, is much lower than



**Fig. 5.1** Familial aggregation of atopy: solid symbols denote atopic individuals (elevated total serum IgE or specific IgE to any one or more common inhaled antigens) but note that the pattern of specific allergen sensitization and clinical disorder varies.

for the monogenic disorders but is of course higher than in the general population.

Twin studies have proved to be useful in clarifying whether genetic effects are important in causing disease. If they are, then monozygous twins (who share all their genes) will be significantly more concordant for the disorder than dizygotic twins (who on average share 50% of their genes). For example in atopy, twin studies suggest that 50% of the variability of total serum IgE levels can be attributed to genetic effects [7]; restated, the heritability (the portion of a disease due to genetic effect) for total serum IgE levels is 50%. Heritability ( $h^2$ ) can be estimated from twin studies using relatively simple formulae [8]; the estimate for  $h^2$  of decline in lung function (forced expiratory volume in 1 s) was found to be 67% in Swedish twins [9].

The discovery of ‘disease genes’ has now become a major enterprise and is an integral part of the Human Genome Project [10,11]. Such ‘disease genes’ happen to have mutant or variant forms that are present in some members of the population and which promote or cause disease in these individuals. Investigating the origin of a genetic effect, i.e. the discovery of the genetic locus at which variants confer risk of disease, has been pursued in two major ways in recent years: (i) the positional cloning (or reverse genetics or linkage) approach, and (ii) the candidate gene approach [12].

**Positional cloning**

In positional cloning [13,14], the emphasis of the initial investigation is to delineate some chromosomal region for which one can demonstrate co-inheritance of local DNA polymorphisms with the disorder/disease of interest in some families with the disorder, i.e. demonstrate *genetic linkage* [15]. Following this, the chromosomal region can be ‘mapped’ [16], using other local polymorphisms or markers, in order to identify the polymorphism that shows the most perfect co-inheritance with the disorder; this provides evidence for more precise localization of the disease locus. Structural genes, those that encode proteins, can then be identified and cloned from around such closely linked polymorphic markers and the search for mutations in appropriate cloned genes started. Ultimately, a gene with a mutation or variant that shows association with the disorder in unrelated individuals will be found [17,18]; then functional experiments on the variant protein product are conducted. This kind of positional cloning exercise represents a scientific *tour de force* and the discovery of the CF gene and its protein product is a prime example of its successful deployment [13]. First, genetic linkage of CF to the mid-portion of chromosome 7q was discovered, then the region was laboriously but accurately mapped [16], local candidate genes identified and cloned, and ultimately a trinucleotide deletion discovered signifying the loss of phenylalanine at position 508 ( $\Delta F508$ ) for a membrane-associated protein [17].  $\Delta F508$  was very strongly associated with CF, accounted for 70% of CF mutations and has been shown to critically alter the chloride-transporting properties of a membrane-associated protein, since denoted the cystic fibrosis transmembrane regulator (CFTR) [19,20].

Positional cloning can also be used for investigating the genetics of multifactorial disorders, although the necessary interaction between environmental factors and the actions of variants at often more than one locus make the investigative process more difficult [14]. Even when dealing with apparently the same clinical disorder, the genetic locus involved may be different in different families; this genetic heterogeneity makes gene hunting more difficult and may lead to confusion when replication of linkage is attempted. For example, an early report of linkage of atopy to chromosome 11q13 [21] had to wait some 7 years before independent, large-scale replication was achieved [22]; current data suggest that the  $\beta$  subunit of the high-affinity IgE receptor is the principal candidate gene at the location [23]. Also in multifactorial disorders there is usually no clear mode of inheritance, and the necessary interaction of independent causal factors can lead to diagnostic errors in categorizing individuals within families as diseased or not; for example some individuals may not have the disease but will have inherited the genetic propensity, whilst others may have the disease due

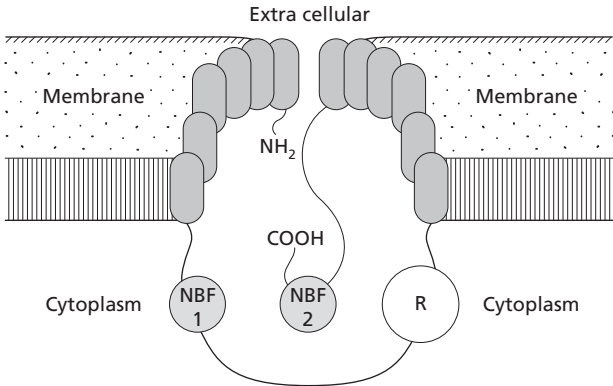
**Table 5.1** Genetic linkage by sibling-pair analysis. The shared phenotype for the sibs is shown under IgE serotype. Sharing of one (1) or neither (0) allele from either parent for a polymorphism within the T-cell receptor  $\alpha/\delta$  region on chromosome 14q is shown. This demonstrates linkage since the expected (null hypothesis) ratio of 1 to 0 is 50:50.

IgE serotype	Alleles shared		$\chi^2$	P
	1	0		
House-dust mite (HDM)	71	44	6.34	0.01
Grass pollen	74	48	5.54	0.02
IgE > 70%	79	46	8.71	0.003
Der p I (HDM)	57	25	12.5	0.0004
Der p II (HDM)	66	34	10.2	0.001
Fel d I (cat)	42	15	12.8	0.0004

to great environmental burden but have not inherited significant genetic risk factors. The method of *affected sibling-pairs analysis* has recently emerged as a useful technique for addressing these difficulties [24,25]; the method needs no prior decision on mode(s) of inheritance and it limits (because of its inclusion of affected individuals only) the effect of variable genetic penetrance (Table 5.1). The sib-pair method has been used very productively in investigating type I diabetes mellitus [26] and has shown that effects at some six genetic loci underlie the development of this disorder; the sib-pair method was allied to semi-automated, fluorescent methods of detecting microsatellite length polymorphisms at some 300 locations that effectively covered the ‘genome’ [27]. Similar searches conducted for atopy and asthma have also emphasized important genetic heterogeneity [28,29].

**Candidate gene**

The candidate gene approach offers a far more direct method but represents a form of inspired molecular-pathological guesswork that may or may not be successful for any particular exercise. The fruitful work on the globin genes involved in sickle-cell disease and the thalassaemias represented the first attempt at this kind of approach. In this procedure, variants at a particular genetic locus are suspected of causing a disease because of the known functions of the gene’s protein product and through knowledge of the pathology of the disorder. For example, interleukin (IL)-4 plays an important role in determining the switch from IgM to IgE synthesis in B lymphocytes [30] and enhanced IgE synthesis is a recognized part of the atopy syndrome and its associated clinical disorders asthma and rhinitis [31]. Based on this knowledge, Marsh and colleagues [32] considered the loci for IL-4 and closely related cytokines on chromosome 5 as candidate genes for atopy; they conducted linkage studies using microsatellite polymorphisms within the cytokine cluster on chromo-



**Fig. 5.2** A schematic model of the cystic fibrosis transmembrane regulator (CFTR) protein showing the transmembrane channel, ATP-binding domains (NBF 1 and 2), and R domain for binding protein kinases.

some 5 and sib-pair analysis for low total serum IgE levels. They found evidence for genetic linkage and this has been replicated; the locus involved awaits identification. The candidate gene approach need not use linkage or sib-pair analysis; intragenic polymorphisms can be used directly in a case-control genetic association study.

**Syndromes and genetic effects**

This account of respiratory syndromes/disorders with significant genetic input is loosely classified according to the respiratory structure or function mainly affected.

**Bronchial tree**

**Cystic fibrosis**

CF is the most common fatal autosomal recessive disease in Caucasians with an incidence of 1 in 1500 and carrier frequency of 1 in 22. Since CF is characterized by mucus of low water content [33] that is moved with great difficulty, the major impact is on mucus-secreting organs and results in the secondary clinical disorders of meconium ileus, pancreatic destruction (with malabsorption and diabetes mellitus), sinus disease, bronchiectasis, and infertility in males. Based on a successful positional cloning investigation [16–18], we now know that CF is due to mutations in a gene on chromosome 7q31.2 [13]. The gene is large, with 27 exons spanning 250 kb of DNA, and encodes an mRNA of 6.2 kb and a protein of 1480 amino acids, CFTR. CFTR is a cyclic AMP-regulated chloride channel with transmembrane domains forming its channel, an R domain and nucleotide-binding domains, which are involved in coupled ATP hydrolysis and opening and closing of the channel (Fig. 5.2) [3]. CFTR is expressed in specialized epithelial cells, including nasal and tracheal epithelium and submucosal glands. Disorder of CFTR leads to

**Table 5.2** Percentages of cystic fibrosis chromosomes with certain CFTR mutations in different population groups.

	ΔF508	G551D	G542X	621+16T	R117H	W1282X	N1303K	3849+10 kb CT
Canada	70.1	2.9	2.4	1.7	1.3	1.0	0.8	0.4
South-east USA*	61.9	1.7	0.9	1.1	1.4	1.8	1.4	1.8
UK	81.2	3.9	1.2	0.8	0.6	0.2	0.4	0
France	72.5	0.9	2.6	0	0.9	1.4	1.4	0.2
Spain	50.6	0	8	0.02	0	0.6	3.3	0
Italy	52.7	0	4.2	0	0	1.7	3.7	0
Israel (Ashkenazi)	26.9	0	8.8	0	0	48.7	3.8	6.3

\* In Black Americans the frequency of ΔF508 is about 38%.

defective electrolyte transport; defective chloride transport has been shown for the apical membrane of epithelial cells from the airways, pancreas and sweat glands [19,20].

The commonest mutation is a 3-bp deletion causing loss of phenylalanine at amino acid position 508 (ΔF508) and is the mutation on 81.2% of CF chromosomes in the UK [17]. Like many other inherited disorders, careful genetic analysis shows that a great number of mutations in the same gene can result in the disorder. So far, over 500 pathological mutations of CFTR have been recognized, although six to eight mutations account for some 90% of the mutations in any population; however, there are significant differences in the relative frequencies of mutations worldwide [3] (Table 5.2). One provisional classification categorizes CF mutations into class I mutations with defective protein production, class II mutations with defective protein processing (including ΔF508), class III mutations with defective regulation of CFTR, and class IV mutations showing defective conduction through the channel. Studies continue on the association between particular genotypes and phenotype (including the severity of lung disease, pancreatic involvement, age at *Pseudomonas* colonization) but these are not easy because different mutations often occur in combination in those with the disease; however, ΔF508 does correlate with severe pancreatic disease. One set of CFTR mutations is associated with isolated congenital bilateral absence of the vas deferens without systemic CF [34].

Genetic counselling strategies in CF have been greatly aided by the advances in molecular genetics. In any family with an affected child, the parents are obligate heterozygotes and the risk of CF in any further child is 1 in 4. Two-thirds of the normal siblings will be carriers but the risk of CF in their children is relatively low (i.e.  $2/3 \times 1/22 \times 1/4 = 1/132$ ). Molecular diagnosis for CF is well established, being based on direct mutation analysis. In the family with an affected child it is particularly valuable for prenatal diagnosis on chorionic villous samples and can also be used for carrier detection within families. Significant ethical and logistic issues are attached to the application of carrier and neonatal screening in the

general population, but a start has been made in some communities [35,36].

Approaches to local gene therapy have been piloted for nasal and bronchial epithelium, using viruses or liposomes as vectors (or carriers) for normal cDNA of CFTR; transient correction of electrophysiological abnormalities has been achieved. However, a number of major practical difficulties, not least the need for prolonged expression, remain to be overcome before gene therapy becomes a realistic clinical option [37,38].

### Immotile cilia syndrome

The immotile cilia syndrome or primary ciliary dyskinesia is a rare genetically heterogeneous disorder in which inheritance is usually autosomal recessive [39]. Its incidence is approximately 1 in 30 000. The ciliary abnormality can normally be observed on electron microscopy of a ciliated mucosal biopsy or spermatozoa from an ejaculate. Defects of the ciliary axoneme are visualized, the most common being lack of dynein arms (see Fig. 1.13). The impaired ciliary function results in impaired clearance of mucus and leads to chronic rhinitis and bronchiectasis, sinusitis (often with absence of the frontal sinuses) and ear disease. As in CF, males are normally infertile. Kartagener's syndrome is one clinical subgroup of the immotile cilia syndrome where there is also dextrocardia or situs inversus (the result of random organ rotation in development as a result of poor ciliary function). The genetic heterogeneity of the syndrome reflects the likelihood that many genes, and their proteins, participate in the construction of the normal cilium and that genetic mutation affecting any one of them may impair ciliary function. None of these genes has been formally identified.

### Atopy and associated asthma and rhinitis

Atopy, the state of allergic disorder to common antigens such as the house-dust mite and pollens, is a common and complex disorder in which heterogeneous genetic influences interact with the environment to result in the

immunological abnormality and its associated clinical disorders that include asthma and rhinitis [4]. Asthma and rhinitis have other causes besides atopy.

Twin studies show that both genetic and environmental factors are important and suggest that the greatest genetic contribution acts on the immunological phenotype rather than that of clinical disease *per se* [7]. The highest concordance (71%) in monozygotic twins is for allergic response to *any* one or more common inhaled allergens, the concordance for this characteristic in dizygotic twins being 36% [7].

Genetic linkage studies for both atopic IgE responses and asthma (or bronchial hyperreactivity) have identified a whole set of linkages on many chromosomes [21,28,29,31,40]. The first demonstration of genetic association and accompanying functional change was for the IL-4 receptor IL4R $\alpha$  [41]. Substitution of isoleucine for valine in the extracellular domain of the receptor (position 50) associates strongly with atopic asthma in Japanese children; in transfection experiments Ile50Val upregulates the cellular response to IL-4 challenge and leads to increased secretion of IgE. A second variant, Arg576Glu, has been associated with defective binding of the negative regulator SHP-1 and the hypereosinophilic syndrome [42].

On chromosome 14, the principal candidate locus is the  $\alpha\delta$  complex of the T-cell receptor and the linkage may be with allergen-specific IgE responses rather than general atopy; gene mutations associated with atopy are yet to be described [40]. Chromosome 5q has several candidate loci, including those encoding a number of relevant cytokines, (IL-4, IL-13, IL-5); genetic linkage of asthma and total serum IgE levels has been shown to this region; the locus and relevant mutations await identification [31,32]. On chromosome 11q, Fc $\epsilon$ RI- $\beta$  remains the clearest candidate but no functional action of any variant has been determined.

Although variants of human leucocyte antigens (HLA) are associated with allergic reaction (and production of IgE) to fractions of certain allergens [43], for example ragweed *Amb aV* [44], there is little evidence to suggest that these variants enhance the risk of clinical disorder; this may be due to the immunological complexity of whole allergens or the possibility of 'molecular promiscuity' at antigen presentation and T-cell recognition [45,46].

The relative importance of these different loci, and the question as to which of them impact on IgE responses or asthma *per se*, is likely to be ultimately clarified in large-scale population association surveys. In the long term, novel therapies may target some of the commonest of the protein variants and, furthermore, may be administered specifically to those with the matching inherited molecular pathology. However, it is noteworthy that the recent rise in atopy and asthma emphasizes the importance of interactive environmental effects [47].

## Pulmonary parenchyma

### $\alpha_1$ -Antitrypsin deficiency

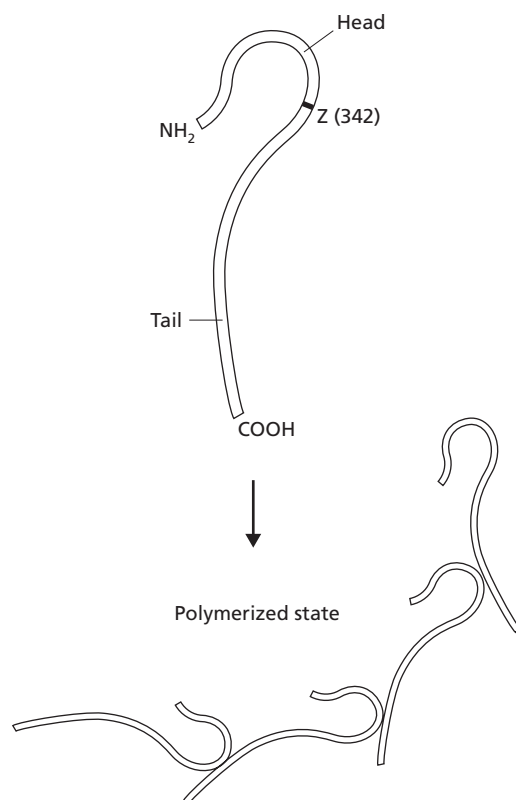
Emphysema, the pathological entity of destruction of alveolar walls with secondary alveolar dilatation and disruption of ventilation-perfusion matching, is mainly the consequence of cigarette smoking. The observation that significant AAT deficiency is a major risk factor for the development of accelerated emphysema in cigarette smokers was made originally by Laurell and Eriksson over 30 years ago and has led to the proteolysis hypothesis for emphysema in smokers [48]. This proposes that proteases, such as elastase, are released from pulmonary neutrophils and macrophages 'excited' by cigarette smoke. The actions of the elastase on supportive tissue in the lung is opposed by the serine protease inhibitor (serpin) AAT. When AAT is deficient or when smoking is very heavy, the balance falls in favour of tissue destruction and the development of emphysema. Additionally, there is evidence that free radicals in cigarette smoke oxidize a critical methionine residue at the active site of AAT causing a reduction in its inhibitory activity against elastase [49].

AAT is a glycoprotein (molecular mass 52 kDa) and is encoded at the Pi (protease inhibitor) locus on chromosome 14q32.1. The gene shows alternative splicing in that the mRNA for AAT is longer in the macrophage than in the hepatocyte. Many pathological mutations of the AAT gene have been described, the commonest of which is the PiZ allele that causes substitution of lysine for glutamic acid at position 342. ZZ homozygotes have some 20% of normal AAT levels in plasma and therefore correspondingly reduced levels in the lungs. Z variant molecules tend to polymerize (Fig. 5.3) and are not effectively transported from the hepatocyte where AAT is normally produced [50]; therefore many individuals with ZZ variants develop liver disorder; 10% develop hepatitis with jaundice in infancy and some 50% show disturbances of liver function tests [51]. Other variants include the S (valine for glutamic acid at position 264) and null forms. The S variant molecules do not fold correctly, have a short half-life and effectively reduce AAT levels to 60% of normal [52].

Clinically significant deficiency of AAT arises only in homozygotes (ZZ or null/null) or compound heterozygotes for two different deficiency alleles (e.g. SZ) and therefore AAT deficiency-induced emphysema is an autosomal recessive disorder. In deficient individuals, the most important practical point in management is absolute avoidance of cigarette smoking [53]. Replacement of AAT protein, now available as a molecular engineered product, can increase lung levels when administered by infusion or aerosol inhalation, although trials showing clinical impact are awaited [54,55].

In a family with an affected individual, the risk of AAT





**Fig. 5.3** A schematic figure of  $\alpha_1$ -antitrypsin molecules showing the site of the Z variant. This leads to interaction between the head of one molecule and the tail of the next and hence polymerization.

deficiency in a further sibling is 1 in 4 and molecular prenatal diagnosis is established. The risk to the children of normal but carrier siblings is very small since the incidence of severe AAT deficiency alleles in the population is low.

#### Miscellaneous rare disorders

Pulmonary alveolar proteinosis is a rare heterogeneous disorder characterized by the accumulation of PAS-positive proteinaceous material in the alveoli. It can be secondary to malignancy or infection, for example histoplasmosis. In its infant form it is usually fatal and in some families is probably a genetic disease. One study has reported absence of surfactant protein B and its mRNA but markedly increased amounts of surfactant protein C in the alveoli in one family with two affected siblings [56].

Rare but striking reports of familial aggregation of early-onset diffuse alveolitis and pulmonary fibrosis are recorded but their molecular genetic origins are obscure.

In pulmonary alveolar microlithiasis, there are multiple minute calcifications in the alveoli producing a typical

radiographic appearance. Affected sib-pairs are well described and the observation of consanguinity suggests a very rare autosomal recessive disorder, of currently obscure molecular genetic origin.

#### General genetic syndromes with parenchymal lung involvement

A number of well-described genetic syndromes may display a relatively minor pulmonary component, for example diffuse interstitial pulmonary infiltrates on chest radiography is recorded in a number of inborn errors of metabolism such as Farber's lipogranulomatosis, Niemann-Pick disease type A and Gaucher's disease types I and III. Lethal pulmonary involvement may occur in lysinuric protein intolerance.

The molecular genetic pathology of these disorders is being increasingly characterized. Niemann-Pick disease [57] is a consequence of mutations in the gene for acid sphingomyelinase and results in the development of abnormal 'Niemann-Pick cells', histiocytes whose cytoplasm is filled with lipid droplets or particles. Particularly severe pulmonary involvement in Niemann-Pick disease type B is accompanied by infiltration of these abnormal cells into the substance of the lung and also its lymphatics and vessels [58]. In Gaucher's disease [59], a lysosomal glycolipid storage disorder characterized by the accumulation of glucosylceramide (glucocerebroside), there are mutations in the gene on chromosome 1 encoding the enzyme  $\beta$ -glucosidase. Though pulmonary involvement is rare, it is severe and progressive when present; pathology shows infiltration with Gaucher monocytes/macrophage cells that exhibit characteristic tubular cytoplasmic inclusions.

In the phakomatoses, for example neurofibromatosis or tuberous sclerosis, pulmonary involvement may be observed in the form of pulmonary fibrosis, bulla formation or leiomyomatosis [60].

In Marfan's syndrome, there is not surprisingly an increased risk of spontaneous pneumothorax. There is a clear clinical impression that many young individuals presenting with spontaneous pneumothorax are, whilst not plainly marfanoid, rather asthenic and tall. They may ultimately prove to have genetically determined mild connective tissue disorder. In some subjects with Marfan's syndrome apical bullae are present; more rarely, congenital cystic lung disease may be found [61].

#### Immune system

The lung is constantly exposed to the risk of infectious disorder and there are well-recognized genetic syndromes that predispose to chest infection. Many other genetic variants, with more subtle effects on the risk of infections such as tuberculosis, are likely to be discovered.



### Immunoglobulin deficiency

Antibody deficiency may be primary or secondary (for example to protein loss in renal or bowel disorder). X-linked and autosomal recessive types of the primary form are described and make infection with encapsulated bacteria and mycoplasmas common and severe [62]. Variable combinations of IgA and IgG subclass and IgM deficiency are recognized. The clinical picture may be of repeated pneumonias, with typical systemic upset, or of bronchiectasis with chronic sepsis.

### Combined deficiency of T and B lymphocyte function

Severe combined immunodeficiency (SCID) is a genetically heterogeneous syndrome with profound functional deficiency of both cellular (T-cell) and humoral (B-cell) immunity. In the X-linked form of the disease, most of the mutations are in the  $\gamma$  chain of the cellular receptor for the cytokine IL-2 [63]. Recessive disease in most cases is due to mutations in the purine catabolic enzyme adenosine deaminase (ADA); notably, successful gene therapy has been achieved for ADA deficiency [64]. In SCID, symptoms start in infancy with failure to thrive, diarrhoea due to parasitic and viral infections and pneumonia due to *Pneumocystis carinii*, an organism that typically requires effective T-lymphocyte function for its control.

Ataxia telangiectasia is a more complex autosomal recessive disorder that includes variable immune deficiency, cerebellar ataxia and a propensity to develop leukaemias; one locus of the disorder has been mapped to chromosome 11q22 [65]. Wiskott-Aldrich syndrome, which includes combined immune deficiency, is X-linked. Haemorrhage due to thrombocytopenia, autoimmune disorder and a tendency to malignancy may occur. The locus is unidentified.

### Leucocyte abnormalities

Chronic granulomatous disease, associated with recurrent pyogenic infection of the respiratory tract, skin and lymphoid tissue by catalase-positive bacteria and fungi, is genetically heterogeneous. Oxygen-dependent microbial killing is crucial in phagocytes and the process is mediated by a multicomponent NADPH oxidase, the four major oxidase components being encoded at different chromosome locations: 1q, 7q, 16p and Xp. The most frequent form is X-linked and due to mutation in the gene for the major subunit of cytochrome *b* [66].

Another important property of the phagocyte is accumulation at the site of infection, which in turn is dependent upon adhesive properties of the cell and mobility. In leucocyte adhesion deficiency, an autosomal recessive condition, there are mutations in the gene for CD18, the  $\beta$  subunit of  $\beta_2$ -integrin [67].

### Complement

The complement system, a series of plasma proteins and membrane receptors, plays an essential role in the propagation of inflammation and host defence. Deficiencies have been described for many of its components. Deficiency of C3, an autosomal recessive disorder, increases susceptibility to encapsulated bacteria because of the deficiency of C3b-dependent opsonization [68,69].

### Vascular system

#### Pulmonary embolism

Pulmonary embolism, due to venous thrombosis, is a common and important pulmonary syndrome. There is increasing recognition of genetic deficiencies underlying the disorder in some individuals, particularly those with early onset of disease, unusual sites of venous thrombosis and recurrent disease [70].

Antithrombin is one of the serpins acting on thrombin and other factors in the clotting cascade to inhibit their function; 30 deficiency-causing mutations have been recognized in the gene for antithrombin on chromosome 11q23 [71]. Deficiency is inherited as an autosomal dominant but, because the clinical course is variable, the clinical history cannot reliably exclude the defect. Lower limb venous thrombosis and pulmonary embolism are the commonest clinical problems, although thrombosis may occur in mesenteric, cerebral and other veins.

Activated protein C is a serine protease that has an anticoagulant effect by the inhibition of activated factors V and VIII; this effect requires protein S as a cofactor (see below). Some 30 or so deficiency-causing mutations have been recognized in the protein C gene on chromosome 2 and cause an autosomal dominant pattern of familial deep vein thrombosis and pulmonary embolism [72]. As in antithrombin III deficiency, thrombosis may occur at unusual sites, such as in cerebral and splenic veins.

Protein S deficiency occurs as an autosomal dominant thrombotic disorder that is not clinically distinguishable from protein C deficiency.

Resistance to activated protein C is a relatively common variant due to a point mutation in the factor V gene, the so-called Leiden mutation [73]. In numerical terms, this abnormality is an important cause of venous thrombotic disease in the population [74].

#### Miscellaneous rare syndromes

Pulmonary arteriovenous fistulas may occur as single or multiple lesions and may be sporadic or genetic disorders. The clearest form of the latter is as part of the Osler-Rendu-Weber (hereditary haemorrhagic telangiectasia)

syndrome, a genetically heterogeneous autosomal dominant disorder [75,76]. In this disease, the pulmonary lesions usually are multiple and asymptomatic. However, on bleeding, they can cause haemoptysis, breathlessness and chest pain.

There are a number of reports of primary pulmonary hypertension clustering in families, although this is rare and its mechanism, if distinct from a thrombotic tendency, is unknown.

### **Pulmonary function/neuromuscular disorders**

There are many genetic syndromes of the neuromuscular system that can cause secondary respiratory insufficiency or failure with a tendency to recurrent chest infection because of impaired coughing. The most notable are the muscular dystrophies (e.g. the X-linked recessive Duchenne muscular dystrophy), dominantly inherited myotonic dystrophy and autosomal recessive acid maltase deficiency (type II glycogenosis) [77]. In acid maltase deficiency, diaphragmatic involvement is common and patients may therefore present with respiratory failure [78].

### **Pharmacogenetics**

Idiosyncratic reactions to various therapeutic drugs, which result in a great range of pulmonary disorders, are well recognized. The response of patients to therapeutic agents administered for lung disease also varies both in terms of therapeutic response and toxicity. A number of factors underlie such responses, including age, state of nutrition and hepatorenal function, but in a significant proportion there may be discrete underlying genetic causes though relatively few have been well characterized [79].

The cytochrome P450 enzymes are a large family of haemoproteins that metabolize foreign chemicals, including therapeutic drugs and some carcinogens as well as some endogenous compounds such as steroids. Genetic polymorphisms are well described for some of the P450 series and influence the metabolism and hence response to drugs, those due to debrisoquine and phenytoin being well described [80,81]. Genetic polymorphism is also recognized at one of the two genetic loci (pNAT) encoding *N*-acetyltransferase [82]. These polymorphisms or variants of pNAT influence the rate of acetylation and therefore detoxification of isoniazid; slow acetylators are at risk of drug-related neuropathy (due to accumulated isoniazid) or hepatitis (thought to be due to production of a toxic isoniazid metabolite via an alternative biochemical pathway) [83]. Therefore these slow acetylators need lower doses of medication to achieve a therapeutic effect and to avoid toxicity. The genetic variants of pNAT can now be recog-

nized by direct and simple polymerase chain reaction (PCR)-based assays and are most commonly found in Asian populations [84].

Generally, however, the response of infections to antibiotics depends more on microbial than on human genetics.

### **Tumour genetics**

The observation that many potent carcinogens are also potent mutagens (DNA-damaging agents) has strongly suggested that malignant transformation of a cell is based on DNA change, or mutation, in the somatic cells (somatic mutation) and that the change is inherited by the population of daughter cancer cells [85]. Cigarette smoke is a particularly powerful mutagen for human cells, containing a great range of chemical mutagens including aromatic hydrocarbons, nitrosamines and pyrrolized amino acids [86].

There is now increasing information on the sites and types of somatic mutation underlying malignancy, ranging from visible chromosomal rearrangements to discrete mutations at well-defined loci [87,88]. Among the latter are oncogenes, genes for cellular growth factors and their receptors, and tumour suppressor genes that encode growth-regulating and growth-retarding factors [89]. The interplay of these different molecular factors, which act in the cell nucleus and cytoplasm, in promoting and controlling cell growth is very complex; however, associations are being defined between certain mutations and disturbance of cell growth and type of tumour. For example, in both small-cell and non-small-cell carcinomas of the bronchus somatic mutations in the gene for P53, an important growth regulator, are well described. Mutations in the cellular oncogene *K-ras* are found in adenocarcinomas of the lung [90].

Germline mutations are also important in influencing risk of developing tumour in a number of ways, for example via pre-existent mutations in an oncogene or variant metabolism of carcinogens. Thus polymorphisms of P4501A1 (which metabolizes polycyclic aromatic hydrocarbons) and P4502E1 (which metabolizes nitrosamines) are associated with increased risk of lung cancer in smokers [91].

### **Microbial genetics**

Respiratory infection causes morbidity and mortality on a worldwide scale: the pneumococcus and *Haemophilus influenzae* are estimated to kill some 5 million children under the age of 5 years in the world annually; the influenza and measles viruses cause numerous epidemics; *Mycobacterium tuberculosis* is the single organism that causes most deaths annually every year; and *Pneumocystis carinii* has been a leading cause of fatal pneumonia in the

severely immunosuppressed, e.g. those with AIDS, and in patients on transplant and oncology treatment programmes. The molecular characteristics of these organisms and others are now being successfully defined and the essential genetic foundations for pathogenicity and response to antimicrobial drugs are being clarified.

In the case of antibiotic resistance, a number of genetic mechanisms have been identified [92].

1 Antibiotic-inactivating enzymes are an important mechanism and involve  $\beta$ -lactams, macrolides and chloramphenicol, e.g.  $\beta$ -lactamase production by *Haemophilus influenzae*; this kind of resistance can be transferred between bacteria by gene transfer on plasmids [93].

2 Change of target is another mechanism, e.g. mutation in bacterial cell-wall peptidoglycans inhibits penicillin binding in *Streptococcus pneumoniae* [94]. Antibiotic resistance in *M. tuberculosis* has been of special interest; in one form of isoniazid resistance, mutations in the *InhA* gene, whose protein mediates mycolic acid metabolism and hence cell-wall structure, result in impaired binding of isoniazid to the target enzyme [95].

3 Another mechanism involves bacterial mutations that limit antibiotic penetration through the cell wall; this is thought to occur in the lipoproteins of the cell wall of *Pseudomonas* species and causes reduced permeability and hence resistance to  $\beta$ -lactams and aminoglycosides [96].

Characterization and cloning of gene sequences from these organisms has important practical aims, and molecular genetic techniques help further in realizing these goals. For example, organism-specific DNA sequences can be used as powerful diagnostic tools whose specificity and sensitivity are impressive when linked to *in vitro* DNA amplification by PCR [97]. Successful PCR diagnostic assays have been developed for a number of pulmonary pathogens, including *Pneumocystis carinii* (Fig. 5.4), and there are indications that a successful method is emerging for tuberculosis [98]. Rapid DNA diagnostics can be also used to identify specified mutations that predict antibiotic resistance [99]. Finally, DNA vaccines may become very effective immunizers for intracellular pathogens such as the influenza virus or *M. tuberculosis*; this is because the chosen microbial DNA is taken up by cells and, following incorporation and expression, is presented 'more naturally' to the immune system on the cell surface by HLA molecules [100].

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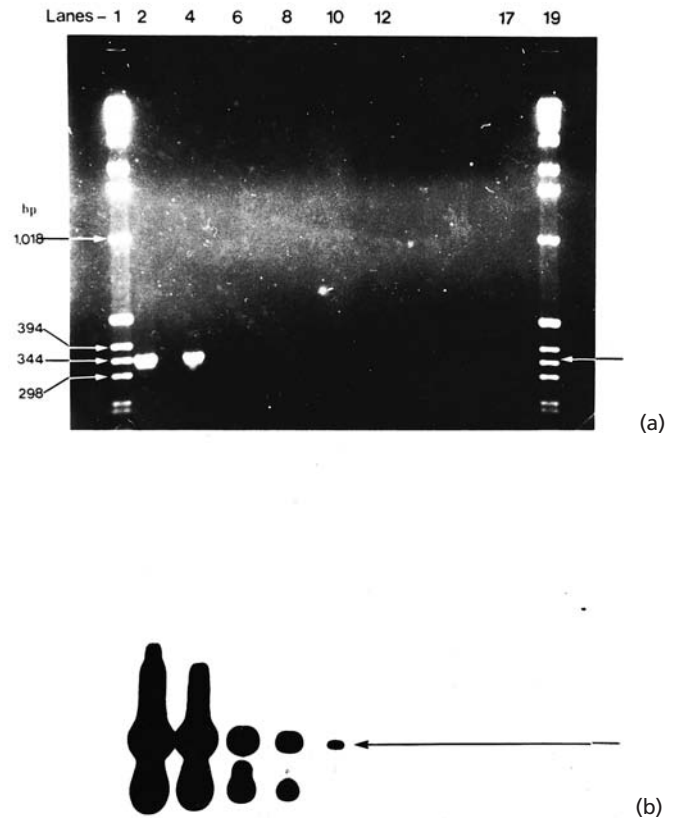


Fig. 5.4 A diagnostic band of amplified DNA from the sputum of a patient with *Pneumocystis pneumonia*, visualized after electrophoresis and ethidium staining, with confirmatory signal of specific hybridization beneath. (a) Control sample; (b) patient test.

## Conclusions

Genetic mechanisms play a central role in determining the risk and patterns of lung disease. They act in a great variety of ways, including the inheritance of variants or mutations, the development of mutations in somatic cells and through mutation or transfer of genes in pathogenic microorganisms. The current revolution in molecular biology and genetics is steadily discovering and clarifying these mechanisms and will present great opportunities in the future for improved recognition, prevention and treatment of disease. Finally, the outbred genetics of humans reminds us that patients are truly individual and that clinical medicine, with its scientific content, will continue to be an art.

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# CLINICAL ASPECTS

ANTHONY SEATON

The clinical history and examination are fundamental to the assessment of respiratory health even in the epoch of computer-assisted tomography and bronchoalveolar lavage. Indeed, too great an emphasis on the technology of medicine may lead to atrophy of clinical skills and thus loss of judgement in the assessment of an individual's health. No apology is made therefore for including a chapter on basic clinical manifestations.

The patient with respiratory disease is understandably nervous on first consulting a specialist. The main symptoms of respiratory disease are common to a large number of conditions but are likely to be associated in the patient's mind with bronchial carcinoma or tuberculosis. This is especially so if, as is often the case, the patient has been referred on account of a radiological abnormality. Simple matters, like a courteous approach, a friendly smile and sitting patients beside rather than across the desk, help put them at ease and make the history less liable to be coloured by fear or anger. Similarly, the efficiency of the consultation is much enhanced by having basic tests, such as chest radiography and spirometry, carried out before the clinical interview.

Contrary to what the undergraduate may perceive as the proper order, examination of the patient begins as soon as the consultation starts. Especially important is the physician's perception of the patient's non-verbal response to questions; hesitancy or lack of eye contact may indicate that there is more, or less, in an answer than meets the ear. Further questioning following such clues often reveals, for example, that the patient did in fact cough some blood a few weeks ago, or that he has only been a non-smoker for 24 h. Observation of the patient during the questioning usually allows assessment of the patient's mood, which inevitably affects the reaction to whatever symptoms he or she may have, and is particularly important in interpreting subjective symptoms such as dyspnoea.

In taking the history, it is important to remember that most respiratory diseases are acquired or made worse by the inhalation of toxic material. While this is often

obvious, for example in the case of cigarette smoke, common allergens or pathogenic bacteria, sometimes the source of the disease is far from clear. The history should always include questions directed towards environmental factors that may be responsible, such as exposure to dust or fumes and allergens or infective particles, at home or at work. In the case of suspected allergic disease of undetermined cause, examination may include a visit to the home and workplace. A history of drug-taking, generally for medical reasons but increasingly nowadays in drug and alcohol abuse, may be relevant to pulmonary disease.

The course of the history should lead to a narrowing down of the diagnostic possibilities. In addition it should allow the physician to understand how the patient's life differs from that of the fit individual. Since many patients with chronic disease tend to adapt to their condition and regard as normal what others would perceive as disability, it is useful to ask patients to compare themselves functionally with healthy people whom they know. It is also important to build up a picture of how the functional impairment has developed. The simplest way to do this is to take the patient back through landmarks in his or her life, enquiring as to symptoms and illnesses at these times; for example, recurrent illnesses as a child, playing games at school, fitness for military service, chest trouble during pregnancy, and so on. A sequential history of the current illness, with emphasis on its commencement and progression, usually allows differentiation of different diseases, for example asthma from smoking-induced chronic airflow obstruction, because of the typical variability of the former, and breathlessness due to acute pulmonary embolism, laryngeal carcinoma and emphysema, because of the different time-courses of their onset. While these points may seem obvious, the author has seen many cases in which these different conditions have been misdiagnosed, sometimes with unhappy results, because a careful history had not been taken.

At the end of the clinical consultation, and with the help of chest radiographs and lung function tests, the physician should usually know the most likely causes of the



patient's ill-health and be in a position to plan treatment or further investigation. At this stage, the doctor should spend time explaining the position to the patient or, in the case of children or the confused, a relative. A simple statement of the suspected diagnosis, its implications and the planned course of action, with a moment for answering questions, is ideal and the timing of the consultation should be planned with this in view. Each doctor develops a personal method of imparting information about potentially fatal disease; suffice to say that there is no one way of doing this but that attempts to deceive a patient are rarely successful or to the benefit of the patient and the family. An optimistic approach by the doctor towards either the response to curative treatment, if feasible, or palliation of symptoms should be maintained. Equally, in the case of non-fatal disease, it is often important for the doctor to state explicitly that the patient does not have cancer. It should be remembered also that for many older patients the diagnosis of tuberculosis implies at best some years in sanatoria and at worst death, so appropriate reassurance should be given.

## Principal symptoms of respiratory disease

### Cough

Cough is one of the most common reasons for a patient to consult a doctor at all ages [1,2]. Nevertheless, patients with chronic cough, especially when related to cigarette smoking, may become so accustomed to it that they deny they have it, even when they admit to the regular production of sputum. The act of coughing is under voluntary control, although it commonly occurs as a result of an involuntary reflex, and is designed to remove secretions or inhaled particles from the bronchial tree or pharynx. Cough consists of contraction of the respiratory muscles against a closed glottis, with resultant rise in intrathoracic pressure, followed by opening of the glottis and forced expiration with very high flow rates in the upper airways. These rates are increased by the narrowing of the airways that occurs due to invagination of the non-cartilaginous part by the high intrathoracic pressure prior to glottal opening, and can only be sustained momentarily since after glottal opening the airways collapse as in any forced expiration. In patients with severe airflow obstruction, high rates of flow cannot be generated because of the fixed airway narrowing; such patients may have prolonged wheezy coughs that sometimes cause the involuntary effects of a Valsalva manoeuvre and resultant cough syncope. Such episodes may occasionally be accompanied by convulsions that mimic epilepsy [3].

The involuntary initiation of cough takes place through a reflex arc that has its receptors in the respiratory tract [4]. In the mucosa of the larger airways (larynx, trachea and

bronchi) lie rapidly adapting stretch or irritant receptors sensitive to mechanical stimuli. Their principal effect is to initiate a forced expiration without an initial inspiration that would suck inhaled particles further into the lung. Further down the airways, probably as far as the acinus (since cough is a feature of allergic alveolitis and pneumonia), lie receptors sensitive to chemical stimuli, such as the inhalation of irritant gases, which initiate a reflex inspiration and forced expiration. The precise roles of several different receptors identified in the lung, such as C receptors and slowly adapting stretch receptors, in the initiation or suppression of cough have not yet been clearly defined. The efferent messages of the cough reflex travel down the vagus to the larynx and by the spinal nerves to diaphragmatic, thoracic, abdominal and pelvic muscles, all of which contract during a cough [5,6].

Although the receptors may accommodate to repeated stimuli, as in smokers who only cough after their first cigarette of the day, paroxysms of cough may occur when the inspiration prior to cough in turn stimulates the receptors and initiates a vicious circle. The cough reflex becomes less sensitive in the elderly and is lost in anaesthesia and unconsciousness, contributing to the increased danger of aspiration of stomach contents in such circumstances.

Some features of cough are of diagnostic significance. The non-explosive or bovine cough associated with recurrent laryngeal nerve paralysis is easily recognizable, as is the prolonged wheezy cough of the patient with emphysema. Paroxysms of cough without sputum production occur in people with increased airway reactivity and are commonly provoked by attempts at spirometry. They often follow upper respiratory viral infections and persist for some months as the 'reactive airways dysfunction syndrome' (see Chapter 36). A bubbly cough indicates sputum in the larger airways and the likelihood of expectoration. The paroxysms of coughing followed by a prolonged stridulous inspiration characteristic of pertussis is not easily forgotten by those who have heard them, still less by those who have suffered them.

Most acute episodes of cough are caused by respiratory infections, usually viral. However, the common causes of persistent cough differ at different ages. In neonates, cardiac disease and aspiration through congenital fistulae should be excluded. Later in childhood, chronic maxillary sinusitis, asthma, cystic fibrosis and inhaled foreign body are important causes, although viral infections may cause cough lasting for several months associated with increased bronchial reactivity. Psychogenic cough, sometimes related to maternal anxiety, may occur in children and it should not be forgotten that some children may start to smoke at a very young age. In adult life, persistent cough is most commonly related to cigarette smoking. This usually occurs with the first cigarette and does not trouble the patient unless it is exacerbated by infection. A change in the pattern of cough is an important symptom of

bronchial carcinoma. In adult non-smokers, persistent cough is usually due to asthma, though again viral infections may provoke a cough that lasts for some months. Other less common causes are extrinsic allergic alveolitis and humidifier fever. Exposure to dusts and fumes at work is now well recognized as a cause of persistent cough, even in non-smokers. Tuberculosis, bronchiectasis, cystic fibrosis, sinus and laryngeal disease, sarcoidosis, lymphoma, pulmonary fibrosis and pulmonary oedema are other causes of persistent cough. In adults, especially older people, oesophageal reflux is a not uncommon cause, probably based on a reflex, that is often overlooked [7]; all patients with chronic cough of undetermined cause should be investigated with this in mind, especially as it may occur in the absence of symptoms of reflux [8]. Cough may also be caused by recurrent aspiration related to reflux, oesophageal stricture or neurological disease affecting swallowing. Asthma and cardiac failure also commonly cause cough in the elderly; these three latter causes frequently provoke a predominantly nocturnal cough. The use of angiotensin-converting enzyme (ACE) inhibitors in cardiovascular therapy is another cause of cough in older patients [9], perhaps caused by a failure of the normal breakdown of bradykinin by ACE [10]. Fortunately, this occurs much less frequently with the newer angiotensin II inhibitors, which can usually be substituted for the ACE inhibitor if cough is a problem [11,12]. In some cases, no physical cause for cough may be found; in a few of these patients psychogenic factors may be important, although this is a diagnosis that should not be made lightly and without some positive evidence of an appropriate psychological cause.

The management of cough depends on the cause [2]. Since most coughs are transient and related to upper respiratory tract infections it is normally appropriate to treat such a suspected infection and/or to wait for 2–3 weeks before investigating further. The history of course provides clues about the aetiology, helping to exclude such causes as bronchiectasis, aspiration, dust inhalation and allergic factors. Chest radiography and spirometry should be carried out on patients with persistent cough and this may be followed in appropriate cases by bronchoscopy, otorhinological examination, barium swallow, bacteriological investigation and so on. Treatment is then normally that of the cause, although sometimes it may be necessary to suppress the cough. This is most commonly the case with cough due to viral infections, when a paroxysmal non-productive cough becomes a social nuisance, and with bronchial carcinoma, when cough may be an important contributor to the misery of a terminally ill patient (see Chapter 60).

It is not uncommon in respiratory practice to see patients in whom an irritant, unproductive cough persists for months or even years. Such patients, who in the author's experience are more frequently female than male

(and there is evidence that sensitivity of the cough reflex is greater in females [13]), complain of paroxysms of cough, often unprovoked or after laughing, talking or exposure to smells, and commonly give a history of what sounds to have been an initial upper respiratory tract infection. Lung function and chest radiography are normal. The first step in managing these patients is to exclude treatable disease. This includes investigation for sinus disease and oesophageal reflux. If there is any evidence of reflux, it should be treated medically, and this often improves the cough. A test for bronchial hyperreactivity is useful and, if present, a trial of antiasthma medication is worth giving with a fair prospect of success. Indeed, it is reasonable to give such a course without prior methacholine testing and anticipate a 50% success rate. If neither of these measures help, the patient is likely to have increased cough sensitivity, demonstrable by a capsaicin challenge test [14,15]. Such patients are difficult to manage. They should first be reassured that there is no serious disease and told that they have irritable airways. It is the author's practice then to explain that treatment may be unsatisfactory but that there are a number of options, any one of which might help. The aim is to break the vicious circle of cough, airway irritation and more cough. These options include the use of proprietary cough mixtures (paradoxically, those containing small doses of capsaicin such as Fisherman's Friend are often helpful), more powerful cough suppressants and anticholinergic inhalers. The use of small regular doses of codeine linctus, supplemented by steam inhalation and cups of tea, is adequate in many cases. For more severe cough, a course of the potentially addictive methadone linctus may be justified. In some cases, psychogenic factors may seem important (though generally anxiety is secondary to the tiresome cough) and anxiolytic therapy may be tried.

### Sputum

The production of bronchial secretion has been described in Chapter 1. Expecterated secretions are known as sputum or phlegm and examination of this material is an important component of the clinical examination of a patient with chest disease. In enquiring about sputum production, the important points are its volume, timing and colour. In addition, a patient may be able to comment on its consistency and occasionally its smell. Most patients with chronic airways disease produce less than an eggcupful daily, but the volume increases during infective exacerbations. Large volumes are sometimes expectorated in bronchiectasis, when cough may be provoked by postural changes. Volumes in excess of 100 mL daily are arbitrarily defined as bronchorrhoea [16–19]; this condition may occur in many chest diseases for unknown reasons. The author has seen it in asthma and chronic bronchitis as well as in patients with alveolar cell carcinoma. It is also a

feature of acute organophosphate poisoning and may follow ingestion of neurotoxins from eating exotic fish [20,21].

The history of sputum production is important in differential diagnosis. Chronic morning expectoration over years suggests smoking-induced bronchitis; variable morning or nocturnal expectoration suggests asthma; recent onset suggests infection. This information, together with information on the colour and consistency of the sputum, often leads to a working diagnosis. In particular, green or thick yellow sputum usually means infection. The yellow colour and the changed consistency come from the presence of leucocytes. Stagnation of sputum containing leucocytes results in a green colour because of the liberation of the green enzyme verdoperoxidase (or myeloperoxidase) from the cells as they are broken down [22]. While infection is the usual cause of persistently green sputum, it should be noted that the first sputum produced in the morning by many bronchitic subjects may be green because of nocturnal accumulation of leucocytes, while that produced later in the day reverts to a clear colour. Moreover, asthmatic sputum is often heavily laden with eosinophils [23] and these may also give a yellow or green colour to the sputum. Rusty coloured sputum is characteristic of pneumococcal pneumonia. Blood-stained sputum is discussed in the next section. Sputum like anchovy sauce is diagnostic of a ruptured amoebic liver abscess, while treacly black sputum (melanoptysis) results from expectoration of the contents of necrotic massive fibrosis of coal-miners.

Patients often notice the consistency of sputum, though they may find it difficult to describe. In general, sticky sputum that is difficult to expectorate occurs in infection and bronchial asthma. As the condition responds to treatment, the sputum becomes looser and more easily produced. An important indication of recovery from an acute attack of asthma is the ability to expectorate [24]. Often in these circumstances, the patient coughs up worm-like structures that are casts of bronchi and that histologically consist of eosinophils, desquamated epithelium, Curschmann's spirals (curious spiral arrangements of eosinophils) and Charcot-Leyden crystals [25]. Such bronchial casts are also a feature of the sputum of some patients with allergic bronchopulmonary aspergillosis [26]. Rarely, expectoration of intrabronchial tumour may occur; this is particularly characteristic of metastatic renal carcinoma [27]. Important clinical information may occasionally be obtained from the smell of sputum. Anaerobic infection may produce a very offensive smell, characteristically occurring in some patients with bronchiectasis and lung abscess. Gram-negative organisms also may impart a distinctive odour to sputum, similar to that of *Escherichia coli* on a culture medium. These odours may be used as a guide to initial antibiotic treatment while awaiting bacteriological results.

In spite of much study of the biochemistry and rheology of sputum, little has been learned that is of practical value to the clinician. The worthwhile investigations of sputum, apart from the observations described above, are microscopy for bacteria, malignant cells and occasionally other microorganisms, culture for bacteria, and tests for pneumococcal antigen. Culture for fungi may be misleading, as these organisms are commonly inhaled from the aerospora and are of no pathogenic importance. However, microscopy for fungal hyphae is important when fungal infection is suspected [28]. Differentiation of sputum from saliva can be made by microscopic observation of alveolar macrophages, while differentiation from gastric contents can be made by testing for pH. Specimens of sputum for bacteriology or cytology are best obtained first thing in the morning by a deep cough, if necessary stimulated by steam inhalation or ultrasonically nebulized saline.

Management of sputum production depends on treatment of the primary condition. In patients with asthma the cough may be useful (productive of sputum) or a nuisance [29] and, if the latter, usually responds to bronchodilators. Except in terminally ill patients it is unwise to suppress a productive cough, although this may occasionally be necessary to allow a distressed patient some rest. Green sputum is usually an indication for antibiotics, or occasionally antiasthmatic drugs, whereas clear mucoid sputum in the presence of pulmonary infection suggests that antibiotics should, in the first instance, be those active against *Mycoplasma pneumoniae* and similar organisms. Bronchorrhoea is often difficult to control. If a primary cause cannot be found and treated, prednisolone 40 mg daily for a week may produce improvement. Erythromycin has also been used with success in some cases associated with alveolar cell carcinoma and would seem to be worth a trial [30]. Fluid restriction and anticholinergic drugs may be tried though they are often unsuccessful and the unfortunate patient may have to put up with the symptom. In idiopathic cases, spontaneous remission may occur.

### Haemoptysis

Blood-stained sputum should be differentiated from bleeding in the mouth or pharynx and from haematemesis. Usually, but not always, this can be ascertained from the history. Haemoptysis is rarely a solitary event, almost always being followed by the production of further blood-stained sputum. Although it is a symptom that should always be taken seriously, in approximately one-third of cases no obvious cause can be found.

The most common causes of haemoptysis in respiratory practice are bronchial carcinoma, pulmonary infarction, tracheitis, tuberculosis, bronchiectasis, pneumonia (especially pneumococcal) and trauma. Less common, but important, causes are cystic fibrosis, mitral valve disease,

haemosiderosis and Goodpasture's syndrome, aspergilloma, inhaled foreign body, arteriovenous malformations and primary haemorrhagic diseases. Blood-tinged sputum also occurs in acute left ventricular failure. Often, when none of the above causes is found haemoptysis may be ascribed to chronic bronchitis, usually associated with an acute infective exacerbation, or systemic hypertension. It is always important to exclude a source of bleeding in the upper respiratory tract, especially from tumours of the pharynx or larynx.

A chest radiograph is mandatory in anyone with haemoptysis and often shows a lesion. In adults over 40 and in smokers, bronchoscopy is usually advisable unless a non-malignant cause is obvious [31]. It should also be carried out in other individuals in whom the haemoptysis recurs after an interval of observation. Sputum cytology may be worth carrying out in patients with recurrent haemoptysis and normal bronchoscopy, as this symptom may be the first evidence of a very early bronchial tumour. Finding malignant cells in the sputum of such patients does of course raise considerable problems in further investigation. Examination of the sputum may also reveal iron-containing macrophages in patients with haemosiderosis and Goodpasture's syndrome. Other special investigations may include bronchography, pulmonary or bronchial arteriography [32] or ventilation-perfusion scanning (see Chapters 7 & 8).

The management of haemoptysis depends on the primary condition. Even massive haemoptysis is rarely fatal though it certainly can be, particularly when coming from bronchial arteries in aspergillomata and tuberculous cavities, or following iatrogenic trauma to vascular tumours with biopsy forceps or to fibrotic lung with drill or needle. Dramatic, fatal haemoptysis may also result from rupture of aortic or even pulmonary artery aneurysms. In general, haemoptysis settles if the patient is rested and sedated. Radiotherapy is often successful in stopping bleeding from bronchial tumours, while other local causes of persistent haemorrhage may sometimes be controlled by bronchial artery embolization [33,34]. Bleeding from aspergilloma may be controlled by radiotherapy or intracavitary instillation of antifungal drugs [35]. The fatal consequences of severe, massive haemorrhage may be postponed by assisted ventilation and transfusion while awaiting the assistance of the thoracic surgeon.

### Chest pain

Pain in the chest may derive from the chest wall, the pleura, the trachea and main airways or the mediastinal and abdominal structures. Cardiac pain and oesophageal pain are common and need to be considered in the differential diagnosis of a patient presenting to the respiratory physician with chest pain. Some of the important causes of chest pain are given in Table 6.1. The diagnosis of chest

**Table 6.1** Some causes of chest pain.

<i>Chest wall pain</i>
Persistent cough or breathlessness
Muscular strains
Intercostal myositis
Thoracic herpes zoster
Coxsackie B infection
Thoracic disc lesion or nerve compression
Intercostal nerve compression or infiltration
Rib fracture
Rib tumour: primary or metastatic
Tietze's syndrome
Slipping rib syndrome
<i>Pleural pain</i>
Infective pleurisy
Pneumothorax
Autoimmune disease
Asbestos pleural fibrosis
Mesothelioma
Metastatic tumour
<i>Airway pain</i>
Tracheitis
Inhalation of irritant gas
Intubation
Central bronchial carcinoma
<i>Mediastinal pain</i>
Cardiac ischaemia/infarction
Massive pulmonary embolism
Oesophagitis
Pericarditis
Sarcoid adenopathy
Lymphoma
Mediastinitis
Aortic dissection
Aortic aneurysm

pain is largely dependent on an ability to take a careful history. The mode of onset, length of time, site and radiation, relationship to movements and breathing, and severity are all important points to enquire about. Specific causes of pain are dealt with in appropriate chapters of this book, but a few general points are made here.

Many patients with chronic breathlessness, caused for example by asthma or emphysema, admit to rather generalized chest pains when asked directly, and in some it is a presenting symptom. This is usually over the lower lateral parts of the chest and related to breathing and coughing. It is rarely severe enough to be the main complaint. More severe generalized chest wall pain occurs in Bornholm disease (Coxsackie B virus infection) and in some collagen diseases such as polymyalgia rheumatica and dermatomyositis. Localized chest pain is frequently due to muscle strain related to persistent cough or unusual exertion and associated with local tenderness and pain on movement, although a similar symptom is often expressed by people with diffuse pleural fibrosis caused by asbestos. Pain in

the distribution of a spinal nerve should always raise the suspicion of prevesicular herpes zoster; the spine should be examined carefully and a spinal radiograph taken. Tumours of the spinal canal are sometimes referred initially to chest clinics, though osteoporotic and malignant vertebral collapse are more common causes of this syndrome. Localized rib pain associated with tenderness usually denotes a fracture, which may be due to coughing bouts in the elderly or to osteoporosis. If so, the rib involved is usually around the seventh. Pain that keeps a patient awake is always to be regarded as organic and is often of sinister import. Rib tumours, infiltration of intercostal nerves by carcinoma (as in the Pancoast syndrome) and mesothelioma, and compression of spinal nerves are important causes of such pain.

Central anterior chest pain is usually related to either cardiac ischaemia or oesophagitis. However, occasionally disease of other mediastinal structures may be responsible. The most frequent is tracheitis, which causes a burning pain related to inspiration. A central carcinoma sometimes causes a dull ache, occasionally referred to the lateral chest wall over the involved lobe. Enlarged mediastinal nodes due to sarcoidosis or lymphoma sometimes cause anterior chest pain that may be severe, although more usually they are symptomless. Pain associated with retrosternal goitre or thymoma suggests that the lesion has become malignant.

Pleuritic chest pain is discussed further in Chapter 43. It occurs on inspiration and disappears when an effusion appears. If the central diaphragmatic pleura is involved, it is referred to the shoulder-tip as the sensory fibres run up the phrenic nerve (C3,4). Pleurisy can be mimicked exactly by Bornholm disease.

### Breathlessness

Shortness of breath is one of the commonest reasons for referral of a patient to a chest clinic. The clinical approach to this symptom has been little influenced by the considerable amount of physiological research that has gone into explaining the sensation of dyspnoea, nor does it pay much attention to the nice distinctions between dyspnoea, tachypnoea, hyperpnoea and hyperventilation. A simple but useful clinical approach considers breathlessness as due to cardiac, respiratory or other causes (Table 6.2). The history, with special emphasis on the mode of onset, timing, progression and severity of the symptom, normally allows its tentative ascription to one of these causes. Cardiac dyspnoea is usually progressive, first noticed on exertion, often associated with orthopnoea and sometimes with paroxysmal nocturnal dyspnoea. Examination of the patient's cardiovascular system and ECG usually reveals diagnostic abnormalities. Non-cardiorespiratory causes of breathlessness are relatively uncommon. The most frequent one seen in chest clinics is related to psychogenic

**Table 6.2** Some causes of breathlessness.

<i>Cardiac</i>
Left ventricular failure
Mitral valve disease
Cardiomyopathy
Pericardial effusion or constriction
<i>Non-cardiorespiratory</i>
Psychogenic
Anaemia
Haemorrhage
Acidosis
Hypothalamic lesions
<i>Respiratory</i>
Airways disease
Chronic bronchiolitis and emphysema
Asthma
Bronchiectasis and cystic fibrosis
Laryngeal or pharyngeal tumour
Bilateral cord palsy
Cricoarytenoid rheumatoid
Tracheal obstruction
Tracheomalacia
Amyloid of airways
Parenchymal disease
Allergic alveolitis
Sarcoidosis
Fibroses and diffuse alveolitis
Obliterative bronchiolitis
Pneumonias and toxic pneumonitis
Diffuse infections
Respiratory distress syndrome
Infiltrative and metastatic tumour
Pneumothorax
Pulmonary circulation
Pulmonary embolism and hypertension
Pulmonary arteritis and thrombosis
Chest wall and pleura
Effusion or pleural fibrosis
Fractured ribs
Ankylosing spondylitis
Kyphoscoliosis
Neuromuscular, bilateral diaphragm paralysis

factors. The patient often complains of shortness of breath while resting more than on exertion, and of the need to take a deep breath or the sensation of being unable to take a full breath. Exercise tolerance is often unimpaired. In extreme cases the patient overcompensates by hyperventilating, causing dizziness, lightheadedness, tingling in the fingers and even tetany or syncope. There are often associated features of anxiety or depression and the patient is usually a rather introspective or obsessive individual. The syndrome tends to occur in younger people and is not uncommon in unsophisticated and over-coached athletes. Other non-cardiorespiratory causes of breathlessness are

rare. They include anaemia, haemorrhage and intracranial lesions.

Respiratory causes of breathlessness may be divided into those due to disease of the airways, the lung parenchyma, the pulmonary circulation and the pleura and chest wall. Airway diseases usually cause a pattern of airflow obstruction; asthma, chronic bronchiolitis and emphysema are the usual causes of this. The former typically causes a history of intermittent and variable breathlessness, with nocturnal episodes. As the disease progresses untreated it may become less variable, but a good history will reveal variability over the initial years. Chronic airflow obstruction due to smoking is typically of insidious onset with little variability and remorseless progression. It only rarely starts after the individual has stopped smoking, an important point in differentiation from asthma which not infrequently presents for the first time in an ex-smoker. Less common than the above two causes of airflow obstruction is that due to obstruction at the larynx or pharynx, usually by tumour. Here the patient may complain of noisy or wheezy breathing, as in asthma, but the history is short and progressive over a few weeks or months. It may be worse on lying down. Obstruction of the trachea by tumour causes a similar type of breathlessness, while obstruction of a main bronchus leading to collapse of a lung or lobe usually causes rather rapid onset of dyspnoea to which the patient may partially adapt quite quickly. This is the one airway disease not associated with an obstructive pattern on lung function testing. Less common causes of breathlessness due to airflow obstruction include bronchiectasis, cystic fibrosis and diffuse airway diseases such as amyloidosis and tracheomalacia. Inhalation of toxic liquids or fumes may also lead to permanent airflow obstruction.

Diseases that affect the lung parenchyma usually cause a steadily progressive type of breathlessness with a restrictive pattern of lung function. Moreover, they are often associated with clinical signs and radiological appearances that make their diagnosis relatively straightforward. Diffuse infiltrative diseases include sarcoidosis, various forms of alveolitis and fibrosis, alveolar cell and metastatic carcinoma (carcinomatous lymphangitis causes particularly marked and intractable breathlessness) and diffuse infections with organisms such as *Pneumocystis carinii* and *Cryptococcus neoformans*, as seen increasingly since the arrival of AIDS. Allergic alveolitis may cause a slowly progressive dyspnoea, although commonly there is variability in symptoms and improvement with avoidance of the antigen. Simple pneumothorax, of course, causes chest pain and breathlessness of sudden onset with subsequent amelioration, while tension pneumothorax causes steadily progressive and ultimately severe breathlessness leading to a medical emergency.

Diseases of the pulmonary circulation, such as arteritis or primary pulmonary hypertension, cause a progressive

dyspnoea often with very severe exercise limitation in the later stages. Pulmonary embolism usually causes acute dyspnoea of very sudden onset, while multiple small emboli can mimic primary pulmonary hypertension. Pulmonary arterial thrombosis is sometimes responsible for acute worsening of dyspnoea in an already disabled patient with chronic airflow obstruction and polycythaemia.

A variety of chest wall diseases may cause breathlessness. Kyphoscoliosis, if severe and situated in upper or mid-dorsal spine, may lead to cor pulmonale in the 30–40-year age group. Ankylosing spondylitis may also cause severe restriction and breathlessness even in the absence of the accompanying pulmonary fibrosis. Motoneurone disease, poliomyelitis and some muscular dystrophies may cause breathlessness and respiratory failure. Bilateral diaphragmatic paralysis is an uncommon but easily missed cause of breathlessness. When the patient lies down, paradoxical movement of the abdomen with respiration may be observed.

There has been much debate about the mechanisms of dyspnoea [36,37]. It is reasonable to suppose that different mechanisms are responsible in different situations, for example the sensations in asthma of difficult inspiration and uncomfortably overfilled lungs are probably quite different to those in left ventricular failure or psychogenic breathlessness. All have in common the impingement on the consciousness of a normally subconscious process. This is even true of the normal breathlessness at extremes (for an individual) of exertion. The sensory limb of the neural control of respiration is from receptors in lung and respiratory muscles via the vagus and spinal nerves to the respiratory centres in the brainstem and sensory cortex. The motor limb is also under both cortical and brainstem control. Some of the reflexes involved in respiratory control have been described in Chapter 2. One concept of dyspnoea suggests that it results when there is disturbance in the relationship between the force applied to the lung and the movement to which it gives rise, so that the resulting ventilation does not equate with the demand of the respiratory centres [38,39]. This theory of length-tension inappropriateness holds that subconscious comparison is constantly being made between ventilation and activity, between ventilation demanded and ventilation achieved, and between muscle tension exerted and change in muscle length achieved. When the inappropriateness of these relationships exceeds a certain threshold, the sensation of the need to breathe more deeply or rapidly reaches consciousness. This sensation may arise in the respiratory muscle spindle, although the diaphragm appears to be somewhat deficient in these structures [40].

It is useful clinically to record the severity of breathlessness in terms of restriction of a patient's activity. This is usually best done for milder degrees by comparison with healthy members of family or friends. In more severe



breathlessness, the length of time taken to do certain tasks, like shaving, dressing or getting down to breakfast, is a useful indicator. The length of time to walk known distances has found application in a simple test of lung function [41] (see Chapter 2). Grading of breathlessness on a scale, such as those designed by the Medical Research Council [42] and Davis *et al.* [43], is of value in research and particularly in epidemiology but tends to be confusing clinically as different doctors use different scales. Table 6.3 shows these two best-known scales, the one designed for use in the epidemiological study of chronic chest disease and the other for research in patients hospitalized with acute severe asthma. The different applications of these two are implicit in the questions; the Jones scale is of severe dyspnoea from grade 2a upwards while grade 1 is roughly equivalent to the most severe grade of the MRC scale, which of course was designed for use on ambulant populations. Others studying the mechanisms of dyspnoea on exercise use the 10-point Borg scale, 1 and 2 being slight and 9 and 10 severe [44].

The management of dyspnoea, as of other respiratory symptoms, depends on determining and treating the cause. It is unfortunately true that if the cause cannot be removed there is often little that can be done to relieve the symptom. This situation occurs distressingly frequently in respiratory practice, particularly in emphysema, pulmonary fibroses and neoplastic bronchial obstruction and pulmonary infiltration. In terminal disease, opiates and antidepressants are helpful. In other conditions, aids in the house, walking aids and wheelchairs may be of assistance and oxygen may be used for temporary relief of acute breathlessness. The use of long-term oxygen is discussed in Chapter 24. The patient with chronic airways obstruction can show benefit from a fitness-training programme [45] and this may also be a considerable morale-booster. The breathless patient often suffers more from loneliness

due to immobility and isolation than from the dyspnoea and any measures to help in this direction are of great value. The sensation of dyspnoea may be affected by centrally acting drugs such as diazepam as well as opiates, and it is possible that in the future drugs acting on the peripheral receptor mediators may be found useful. Indomethacin, the prostaglandin inhibitor, has been shown to alter dyspnoea on exercise in normal subjects [46]. Any of these drugs might justifiably be tried in the emphysematous patient distressed by dyspnoea.

## Signs of respiratory disease

### General observations

#### Pattern of breathing

The most important general observations made by the chest physician relate to the patient's breathing and psychological state. Clearly, one affects the other and skilful management of the patient depends on a proper assessment of both. The physician should observe the patient's breathing during the interview and while undressing for the examination. Moreover, if a patient complains of breathlessness on exertion, it is as sensible to observe the breathing pattern during mild exercise on stairs or along a corridor as it is to examine the nose of someone complaining of rhinitis. This is especially important if the patient is being considered for thoracic surgery.

In the clinic a number of different types of breathing may be observed. Noisy inspiration denotes narrowing in large airways, usually due to asthma or chronic bronchitis though occasionally a tracheal, pharyngeal or laryngeal tumour may be responsible. The noise of breathing is generated by turbulent flow in the large airways, where rates of flow are sufficient to generate it. The noise consists of the whole range of audible frequencies and is sometimes called white noise by analogy with white light [47]. Rapid flow rates through normal large airways, as on exercise, generate greater turbulence and therefore more noise. However, noise during quiet breathing is always a sign of disease of the larger air passages. With severe obstruction of these passages, the noise takes on the characteristics of stridor, a high-pitched musical note on inspiration (and in very severe obstruction also on expiration). This sound is familiar to most parents of young children as croup. In adults it usually denotes carcinomatous narrowing, although intrinsic laryngeal disease (e.g. caused by rheumatoid disease and vocal cord palsies) and tracheal narrowing due to lymph nodes, granulomata, aortic aneurysm or cylindroma may be responsible. Occasionally stridor is a feature of severe attacks of asthma with anaphylactic features; it can also occur sometimes during hysterical hyperventilation. Some causes are shown in Table 6.4. The musical note of stridor is generated by

**Table 6.3** Classifications of breathlessness.

#### *After Medical Research Council*

- Grade 1: troubled by shortness of breath when hurrying on level ground or walking up a slight hill
- Grade 2: short of breath when walking with people of own age on level ground
- Grade 3: have to stop for breath when walking at own pace on level ground

#### *After Sherwood Jones [43]*

- Grade 1a: able to do housework or job with moderate difficulty
- Grade 1b: carrying out job or housework with great difficulty
- Grade 2a: confined to chair or bed but able to get up with moderate difficulty
- Grade 2b: confined to chair or bed and only able to get up with great difficulty
- Grade 3: totally confined to chair or bed
- Grade 4: moribund

**Table 6.4** Some causes of stridor.

<i>Children</i>
Croup
Laryngotracheobronchitis
Inhaled foreign body
Diphtheria
<i>Adults</i>
<i>Gradual onset</i>
Laryngeal and pharyngeal tumours
Cricothyroid rheumatoid
Bilateral cord palsy
Tracheal carcinoma or cylindroma
Paratracheal node compression
Post-tracheostomy or intubation granulomas
<i>Sudden onset</i>
Anaphylaxis
Toxic gas inhalation
Inhaled foreign body

vibration of the airway walls when those airways are close to closure, while the pitch is related to the rate of airflow. Stridor occurs predominantly on inspiration because extrathoracic air passages are reduced in diameter when air is drawn into them, owing to the relatively negative pressure engendered (the Bernoulli effect). With abnormal narrowing of these airways acceleration of airflow occurs, which causes a further drop in pressure due to this effect [48].

Wheezy breathing is often audible to the unaided ear and is evidence of intrathoracic airways narrowing; this is discussed further in the section on auscultation (see p. 114). Relatively quiet breathing accompanied by pursing of the lips on expiration is characteristic of pure emphysema, where the airways narrow only on expiration because of loss of elastic recoil. It seems likely that pursing of the lips increases the pressure during expiration, thus reducing the extreme degree of airways collapse that occurs in these patients [49]. It has also been shown to have important mechanical effects on the respiratory muscles that results in protection of the diaphragm from fatigue and improvements in arterial oxygen saturation [50]. Irregular breathing interspersed with sighs is characteristic of psychogenic dyspnoea.

In the hospital setting, other forms of breathing may be observed; the characteristics of breathing during sleep are the subject of Chapter 47. The respiratory rate at rest while awake, faithfully if unnecessarily recorded by nurses from the days of the pneumonic crisis, is normally about 15/min. Slow breathing may be seen in myxoedema, raised intracranial pressure and with hypothalamic lesions. Rapid breathing occurs with lobar pneumonia, pulmonary oedema, pulmonary embolism and pulmonary fibroses, as well as in anxiety. Cheyne-Stokes breathing, or periodic respiration, is a condition of increas-

ing rate and volume of respiration followed by a period of apnoea or hypopnoea. It is seen most frequently in patients with raised intracranial pressure and after sedative drug overdoses, but in a less dramatic form occurs in sleep and in cardiac failure. It seems to be related to a delay in circulation time between the lung and the chemoreceptors [51,52], together with probable altered sensitivity of the respiratory centres to chemical control. It is noteworthy that the  $P_{CO_2}$  is low even during the phase of hypopnoea and that the respiratory response to carbon dioxide is increased [52,53]. Finally, hyperventilation with deep, sighing respirations (Kussmaul breathing) is a well-known physiological response to metabolic acidosis, as in renal failure, salicylate or methyl alcohol poisoning or as a side-effect of treatment with phenformin. This is the one manifestation of increased ventilation in which the patient may deny breathlessness.

### Cyanosis

Cyanosis is an abnormal blue coloration of skin and mucous membranes, generally due to arterial hypoxaemia though occasionally caused by methaemoglobinaemia or sulphhaemoglobinaemia. It is often difficult to appreciate in artificial light unless quite gross, and is best seen on the lips and under the tongue [54]. In good conditions it is detectable when oxygen saturation of arterial blood drops to about 87% but is a sign subject to considerable observer variability. It can easily be missed in a careless examination of a vasoconstricted patient and is less prominent in severe anaemia, since it is dependent on the amount of reduced haemoglobin. Conversely, it is frequently present but not necessarily of clinical significance in polycythaemia.

### Appearance of the chest wall

The chest wall may look abnormal or may move abnormally. Overinflation, where there is an increased antero-posterior diameter, is often accompanied by reduction in the length of trachea above the suprasternal notch and increased prominence and activity of sternomastoid muscles. In such circumstances, the normal lateral and outwards (bucket handle) movement of the ribs is lost, the thoracic cage being pulled up solely by the anterior and upwards (pump handle) movement of the ribs. Sometimes indrawing of the lower ribs and intercostal spaces on inspiration may be seen due to contraction of a flattened diaphragm. Fibrosis or collapse of upper lobes, or severe pleural thickening, may cause flattening of the chest wall anteriorly and diminished respiratory excursion. Long-standing disease on one side may be the cause of a mild scoliosis.

Two common deformities, pectus excavatum (funnel chest) and pectus carinatum (pigeon chest), do not cause

respiratory problems though both may cause social embarrassment sufficient to justify corrective surgery. Pectus carinatum was often the sequel to poorly controlled childhood asthma. In contrast, kyphoscoliosis, if severe and situated primarily in the mid or upper dorsal spine, does lead to respiratory failure in early and middle adult life (see Chapter 45).

Occasionally, other important clinical clues may be apparent on inspection of the chest. A prominent sternomastoid muscle on one side indicates a deviated trachea. Scars of previous thoracotomy, phrenic nerve crush or scalene biopsy should be noted. Rarely, a rib tumour, direct spread of pleural tumour, diffuse metastases or even aortic aneurysm present as swellings on the chest wall. Neurofibromata and spider naevi are other lesions that may indicate general disease with effects on the respiratory system.

### Clubbing and hypertrophic osteoarthropathy

Finger (and toe) clubbing is clearly present when the normal angle between the proximal part of the nail and the distal skin over the nail bed is lost [55–60] (Fig. 6.1). At the same time it may be possible to convince oneself that the nail bed is more fluctuant than usual. As the condition progresses, the whole terminal phalanx becomes swollen and appears like a drumstick. Equally clearly, clubbing is not present when the terminal phalanx looks normal. Difficulty arises when the finger looks somewhere in between; this may be a normal variation or an early stage of clubbing. Not surprisingly there is considerable observer variability when indefinite clubbing is present, and the clinical significance of this sign is correspondingly small. Acknowledgement of this fact is made in Dr Gerald Anderson's half-jocular definition that clubbing is present when three physicians say it is. A simple classification is to divide clubbing into definite, doubtful and absent. In doubtful cases, a tracing round the end of a finger can be put in the notes for future comparison. In any scientific study of the condition, it is necessary to define it more

carefully, and various measurements have been used [61,62]. A relatively simple one sums the ratios of the circumferences of the 10 fingers at the nail bed and at the terminal interphalangeal joint, a 'digital index' that is normally below 10. Confusion sometimes occurs when the ends of the fingers have been subjected to trauma or partial amputations. Hyperparathyroidism and psoriatic arthritis with absorption of terminal phalanges and acroosteolysis due to vinyl chloride exposure may also be confused with clubbing. Clubbing due to any cause may progress to hypertrophic pulmonary osteoarthropathy (HPOA), although this condition is almost always associated with bronchial carcinoma, usually of squamous differentiation. The patient often complains of pain and stiffness about the wrists and ankles and oedema or boggy swelling is sometimes present. Clubbing is usually well marked, although occasionally it may be absent when all other features are present. The diagnosis is confirmed by radiographs, not so much of the wrists and ankles as of the distal forearm and lower leg (Fig. 6.2). The films show subperiosteal calcification separate from the cortex of the long bones.

The patient with HPOA may also have gynaecomastia and rarely thickening and swelling of the end of the nose. While there are very many diseases in which clubbing has been described, the condition occurs most commonly in respiratory conditions associated with hypoxaemia, supuration or neoplasia. Some of the associated diseases are listed in Table 6.5. In the absence of clinical evidence of other disease, it is always wise to assume that the cause may be a bronchial carcinoma and to carry out a chest radiograph. Questioning the patient about the length of time the sign has been present is a curiously unrewarding exercise; even when quite marked changes must have developed relatively recently, patients rarely seem to have noticed them. Congenital and familial clubbing do occur and may lead to HPOA. In one such patient, further investigation was forestalled when his wife (a nurse) confirmed his story that she had insisted that he had a chest radiograph before she agreed to marry him 30 years



**Fig. 6.1** Clubbing of the fingers showing swelling of the nail beds and increased curvature of the nails.



**Fig. 6.2** Severe degree of hypertrophic pulmonary osteoarthropathy showing subperiosteal new bone formation on tibia and fibula.

previously because she had noticed his marked clubbing at that time. The causes of clubbing and HPOA are not known but the following theories have been put forward.

**1 Neurogenic theory.** In this theory it is suggested that afferent impulses from a focus of pulmonary or pleural disease travel via intercostal nerves or vagi to the brainstem and initiate reflex vasodilatation in nail bed and peripheral limb tissues. While no effector mechanism, whether hormonal or neural, has been described, vagotomy or intercostal nerve section does occasionally relieve the symptoms and signs of HPOA [56,57]. On the other hand, most thoracic surgeons are aware that such an operation may be unsuccessful.

**2 Hormonal theory.** This theory suggests that the tumour or diseased pulmonary tissue secretes a hormone that acts on the distal limb tissues. This receives support from the frequently made observation that resection of tumour results in relief of symptoms when the patient wakes from anaesthesia and regression of clinical signs often within a matter of days. Raised oestrogen levels have been found in men

**Table 6.5** Some causes of clubbing and hypertrophic osteoarthropathy.

<i>Non-cardiothoracic</i>
Idiopathic/familial
Coeliac disease
Cirrhosis: portal and biliary
Ulcerative colitis
Pregnancy
<i>Pulmonary</i>
Bronchial carcinoma (rarely oat cell) and carcinoid
Pleural fibroma
Mesothelioma
Metastatic tumour: carcinoma and sarcoma
Empyema
Lung abscess
Bronchiectasis
Cystic fibrosis
Chronic fibrotic tuberculosis
Idiopathic pulmonary fibrosis
Asbestosis
Arteriovenous malformations
<i>Mediastinal</i>
Oesophageal carcinoma and leiomyoma
Peptic oesophagitis
Achalasia
Thymoma
Thyroid carcinoma and thyrotoxicosis
Lymphoma
Myeloid leukaemia
<i>Cardiac</i>
Congenital cyanotic heart disease
Bacterial endocarditis
Atrial myxoma

Note: Clubbing is not a usual feature of sarcoidosis, extrinsic allergic alveolitis, coal-workers' pneumoconiosis or silicosis, nor of uncomplicated chronic bronchitis and emphysema.

with HPOA prior to lung surgery, but it is rather unlikely that these are responsible [58].

**3 Shunt theory.** This theory proposes that substances normally degraded on passage through the lungs pass through them via arteriovenous shunts and then act on the tissues of the limb.

The evidence for each of these theories is insubstantial and it is unlikely that there is any one cause for the association of clubbing and HPOA with a wide variety of conditions. Certainly shunts are a feature of a number of them, such as congenital septal defects, arteriovenous malformations and possibly, via increased bronchial circulation, chronic pulmonary suppuration, idiopathic pulmonary fibrosis and bronchiectasis. On the other hand, there is unlikely to be an important increase in shunt with bronchial and pleural tumours, especially as HPOA seems to be associated with the rather less vascular tumours. Here, the secretion by tumour cells of a hormone seems a realistic possibility. All theories require an agent that acts

on the vascular system of the peripheries, causing vasodilatation possibly of arteriovenous anastomoses. There is evidence that the vascularity of the nail bed is not increased as a result of formation of new blood vessels, suggesting that vasodilatation is the common factor [63]. Many possible vasodilators have been proposed, reflecting the medical fashions of the time. Earlier suggestions included oestrogens [58] and ferritin [64], while more recently growth hormone [65], levels of which appear to be higher in patients with clubbing than in those without, and platelet-derived growth factors [66] have become popular. It is of interest that a high proportion of patients being treated for liver disease with prostaglandin E develop finger clubbing and changes of early HPOA [67].

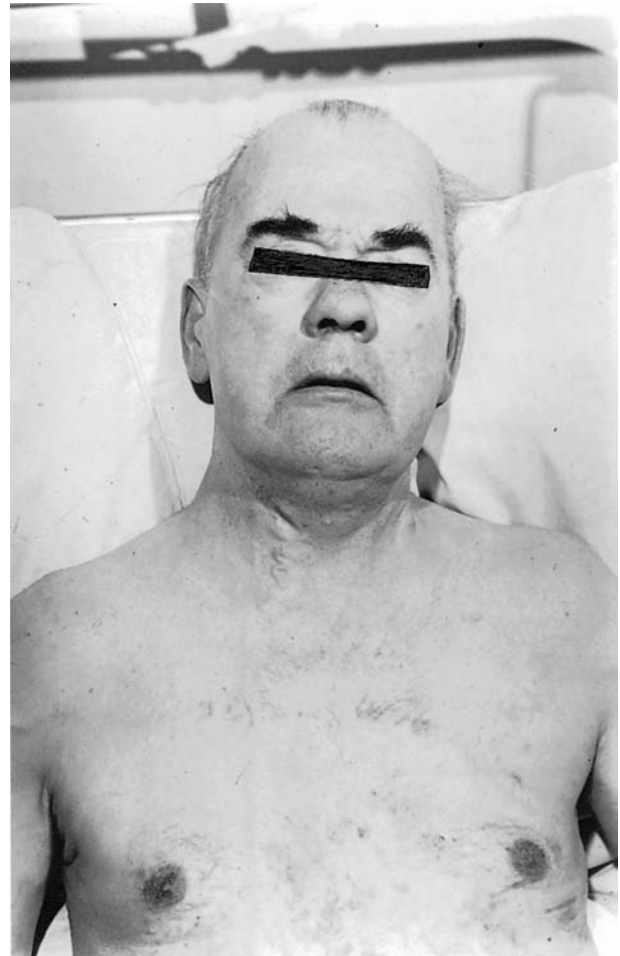
The relief of the symptoms of HPOA is best achieved by removal of the primary tumour. If this is not possible, radiotherapy or chemotherapy may be effective. Anti-inflammatory drugs such as indomethacin and other inhibitors of prostaglandin synthetase are well worth trying if other measures are impossible, and often provide good symptomatic relief. Occasional case reports suggest other drugs may have been of value in difficult cases, for example painful gynaecomastia may respond to tamoxifen and severely painful HPOA has responded to the hormone inhibitor octreotide [68].

### Tremors

The commonest tremor seen in respiratory patients is a fine finger tremor similar to that of hyperthyroidism. It is caused by excessive sympathetic activity due to bronchodilator drugs. Flapping tremor, known to all medical students as a diagnostic feature of hepatic encephalopathy, is seen much more often by the practising doctor in hypercapnic respiratory failure, where it accompanies confusion and electroencephalographic changes as a response to raised intracranial pressure; this in turn is due to cerebral vasodilatation resulting from an acute rise in  $\text{PaCO}_2$  [69].

### Jugular pulse and the superior vena cava syndrome

Apart from its well-known use in the interpretation of an irregular or rapid pulse, inspection of the jugular pulse has several important applications in thoracic medicine. In order to inspect it properly, the physician should move the patient into an appropriate position and light. Absence of pulsation and a persistently raised pressure indicates superior vena caval obstruction (Fig. 6.3). Many dilated venules are usually seen above the rib cage and the face and arms may be swollen and oedematous. The patient often complains of a full feeling in the face and there may be conjunctival reddening and oedema and proptosis. Care should be taken not to misinterpret a kinked external



**Fig. 6.3** The swollen face and neck of superior vena caval obstruction. The jugular veins are engorged and there are dilated chest wall vessels.

jugular vein as superior caval obstruction. The usual cause in the middle-aged and elderly is bronchial carcinoma, often of right upper lobe, with infiltration of the mediastinum, but in younger people lymphoma is more common. Thymoma and thyroid tumours are uncommon causes. Non-malignant causes include fibrosing mediastinitis, thrombosis secondary to a pacemaker wire and, very rarely nowadays, aortic aneurysm.

The diagnosis of the pathological cause of superior vena caval obstruction may pose a problem, as mediastinoscopy and bronchial biopsy may be hazardous because of the risk of bleeding. CT scanning and digital subtraction superior cavagrams are helpful in defining the extent of the lesion and indicate whether intraluminal or extraluminal obstruction is present. In occasional cases, scalene node biopsy may give the diagnosis, and ultrasound-guided transthoracic needle biopsy has been used by some investigators with good diagnostic yield [70]. In most cases it is reasonable to treat the obstruction with

radiotherapy, unless there is some indication that the cause is not a bronchial carcinoma. If biopsy proves possible and the cause is lymphoma or oat cell carcinoma, chemotherapy may give the best chance of inducing remission [71,72]. If recent thrombosis is thought to be the cause, intraluminal injection of thrombolytic agents has been used [73]; if the obstruction does not respond or is due to an untreatable cause, percutaneous insertion of a stent may give good relief of symptoms [74,75].

Pericardial effusions (which occur most frequently as a complication of bronchial carcinoma and tuberculosis) and constrictive pericarditis (which may occur with tuberculosis, rheumatoid disease and mesothelioma) cause the classical signs of elevated jugular pressure, steep 'y' descent and inspiratory rise (Kussmaul's sign). A paradoxical fall in systolic pressure, *pulsus paradoxus*, occurs during inspiration. It is worth noting that this also occurs in acute severe asthma (see Chapter 34), while all the signs of cardiac tamponade may occur in severe congestive heart failure and constrictive cardiomyopathies. Fortunately, ultrasonic investigation makes the insertion of a needle for pericardial aspiration less nerve-racking than it used to be.

### Palpation

Two important pieces of information may be obtained by palpation of the chest. The first is the position of the mediastinum. Upper mediastinal deviation is often accompanied by deviation of the trachea; this should be ascertained by placing the index finger directly into the suprasternal notch and noting which side of the trachea it touches first. As with most physical signs, minor deviations from normal are associated with wide interobserver variability and should only be interpreted in conjunction with other consistent signs. Deviation of the apex beat, along with consistent shift of cardiac dullness, may be an indication of shift of the lower mediastinum. These signs usually accompany other clear evidence of, for example, pulmonary collapse, effusion or tension pneumothorax.

The second piece of evidence concerns movements of the chest wall. These are often more easily felt than seen. It is important when palpating movements to feel them first during quiet breathing. Subtle reduction or delay in expansion, say of an upper lobe whose bronchus is partly blocked by tumour, may be detected quite easily on normal respiration but deep breathing may overcome the obstruction by increasing intrathoracic negative pressure and allowing the lobe to expand normally. While diminished movements may frequently accompany gross and easily detectable collapse, effusion and pneumothorax, the sign is more important as an indication of this incomplete bronchial obstruction where other signs are subtle and also easily missed (the other important one being diminished breath sounds over the involved lobe). An

extreme degree of this syndrome is seen in obstructive emphysema, although it should be stressed that partial degrees, usually with some loss of lobar volume, are much more common. In these cases, the chest radiograph is often apparently normal, the tumour being quite proximal, and if the signs are missed so also may be the opportunity for cure.

Detection of diminished movement largely depends on comparison of one side with the other, and apart from the above may be caused by unilateral fibrosis or bullous emphysema. Symmetrical loss of movement, as with bilateral upper lobe fibrosis, may be inferred if there are other consistent signs, such as flattening of the anterior chest wall and diminished breath sounds.

### Percussion

The technique of percussion was introduced by Leopold Auenbrugger in the eighteenth century [76] but was not widely adopted until rediscovered by Corvisart in the early nineteenth century. Done correctly, with the plexor finger tapping sharply and briefly at right angles to the middle phalanx of the pleximeter finger, it gives both audible and palpable information on the resonance of tissues beneath. Its value in assessing effusion, pleural thickening, collapse and consolidation by dullness is well known, as is its use in detecting (by increased resonance) pneumothorax and both generalized and local emphysema. As with all chest signs, comparison needs to be made with the other side and also with other parts of the same lung. Percussion is also of value in detecting overinflation, with loss of cardiac dullness and depression of liver dullness, and mediastinal shift. Less well known is its use in detecting reduced or paradoxical movements of the diaphragm, when percussion posteriorly at the end and beginning of a deep inspiration can give a reasonably accurate indication of extent and direction of movement.

### Auscultation

#### Breath sounds

The physical signs on auscultation of the chest were described by Laënnec in 1819 in the book in which he introduced the stethoscope to the world [77]; apart from some work on the physics involved in generating these sounds, little has been added to his description since [78,79]. The normal sound of breathing is largely generated as noise of all audible frequencies by turbulent flow in the large airways [47,80] (white noise), and is conducted from there to all parts of the chest. The normal larynx probably makes no significant contribution to this sound in quiet breathing [81]. The loudness and quality of the breath sounds as heard through the stethoscope at the chest wall depend on the distance from the point of origin



and the conducting properties of the intervening tissues. Thus, over the trachea and close to the trachea over the anterior upper lobes in thin people the sounds are loud and of all frequencies. Further from the trachea the sounds become less loud and the higher frequencies are filtered out by the lung. Therefore in auscultation of the lungs in the traditional manner, comparing sides and going from apex to base, there is a clear attenuation of the intensity of breath sounds from top to bottom. Any alteration to this, so that breath sounds are relatively louder at the bases, is as abnormal as a difference in intensity between the two sides.

The intensity of breath sounds may be reduced by obesity, in which case the changes are generalized. Local attenuation may be caused by reflection of sound at the interface between lung and pleural effusion/thickening or pneumothorax. In addition, emphysema is a well-known cause of reduction in breath sound intensity [82]. This is most marked when bullae are present, although gross emphysema of any type can cause it. Indeed, several studies have indicated a relationship between breath sound intensity and regional ventilation as measured by radioactive xenon [83,84], and it has been suggested that some of the inspiratory component of the breath sounds may even be generated in peripheral lung airways [85]. Collapse or partial collapse of a lobe or lung usually causes diminished breath sounds, though there may also be better conduction of the higher frequencies. This change in the frequency spectrum of the breath sounds, with more of the higher frequencies transmitted from the central airways, is called bronchial breathing. Such sounds are often no louder than normal breath sounds. They are characteristic of pneumonic consolidation but may also be heard over a collapsed lung, particularly if the obstruction causing the collapse (such as retained sputum) has been removed. Bronchial breathing may be associated with the sign of whispering pectoriloquy, in which the sounds of the whispering voice are clearly audible through the stethoscope over the area of consolidation.

The general availability of chest radiographs removes one of the major disadvantages of clinical examination of the chest, the inability to detect even large peripheral tumours that are neither obstructing major bronchi nor close to the chest wall. An ingenious physical sign that overcomes this disadvantage has been described, in which auscultation is used to assess the transmission of the sound of percussion on the other side of the chest [86]. This technique clearly requires much practice, but may be of value to the doctor without ready access to radiography.

### Added sounds

In addition to the sounds of breathing, added noises may be heard in an abnormal chest. The nomenclature of these in the English language literature has been confused,

largely because of overinterpretation or oversimplification of Lænnec's original descriptions [87]. The French word *râle* and the Latin word *rhonchus* were used by Lænnec synonymously to include all added sounds. It is therefore preferable to avoid either of these words when referring to a particular type of added sound. Modern French usage classifies the sounds as fine and bubbling crackles and high- and low-pitched wheezes [88] (*râles crépitants, sous-crépitanants, sibilants et ronflants*) together with pleural friction. This is very similar to Lænnec's original usage and to the classification suggested by Robertson [87] (Table 6.6).

The continuous musical note of a wheeze is generated by vibration of an airway at the point of closure. Acceleration of airflow through a narrowing airway, from the Bernoulli effect, causes a reduction in pressure in that airway and therefore tends to close it. This in turn reduces the flow and the airway opens again. This rapid vibration generates the wheeze, the pitch of which depends on the speed of vibration and not on the size of the airway [89]. Thus classification of a wheeze by its pitch is not particularly helpful. Wheezes of many different notes (polyphonic wheezes) are heard characteristically in asthma and chronic airflow obstruction. Each note represents an airway at the point of closure. These wheezes occur during both inspiration and expiration. Disappearance of the wheeze in a patient with an acute attack of asthma may indicate clinical deterioration, when the flow rates are no longer sufficient to generate vibration in the walls of the airways. Similarly, patients with severe airflow obstruction due to emphysema may have no wheeze at all because of low rates of airflow. Thus the presence or absence of wheeze alone is not a reliable indicator of the presence or severity of airflow obstruction. Wheeze comprising a single note (monophonic wheeze) necessarily comes from a single airway; while this is frequently heard in asthma and bronchitis, probably due to one airway being partially blocked by mucus or thickened walls, it may also be a sign of partial obstruction by neoplasm. If mucus is the cause, the wheeze can be removed by coughing. If a tumour or other organic narrowing is present, the wheeze may be modified by asking the patient to lie on his or her side. When the narrowed bronchus is in the uppermost lung it is expanded by the greater distending forces acting upon it and the wheeze may disappear. In the lower lung, the airway is narrowed further, resulting in either accentuation of the wheeze or, if bronchial narrowing is critical, loss of both wheeze and breath sounds. A similar technique can be applied to investigating possible obstructive emphysema, listening to the relative intensity of breath sounds with the patient lying first in one and then in the other lateral position.

The interrupted sound of a crackle may be generated by air bubbling through mucus in large airways. This sound has a coarse explosive quality and is modified by taking

**Table 6.6** Some classifications of lung sounds. (Adapted from Murphy [79]).

Acoustic characteristics	American Thoracic Society nomenclature	Some textbook terms	Our usage	Läennec's terms	Läennec's model
Discontinuous, interrupted explosive sounds, low pitch, loud	Coarse crackle	Coarse râle	Coarse crackle	Râle muqueux ou gargouillement	Escape of water from a bottle with mouth held directly downwards
Discontinuous, interrupted explosive sounds, less loud and shorter duration, higher pitch, repetitive	Fine crackle	Fine râle or crepitation	Fine crackle or crepitation	Râle humide ou crêpitant	Crackle of salt in a heated dish
Continuous sounds, longer than 250 ms, high pitch, dominant frequency of 400 Hz or more	Wheeze	Sibilant rhonchus	High-pitched wheeze	Râle sibilant sec ou sifflement	Prolonged whisper, chirping of birds
Continuous sounds, longer than 250 ms, low pitch, dominant frequency about 200 Hz or less	Rhonchus	Sonorous rhonchus	Low-pitched wheeze	Râle sec sonore ou ronflement	Snoring, cooing of a wood pigeon

deep breaths or by coughing. Indeed, very coarse crackles may be cleared by a good cough, which often reveals the cause as a piece of sputum. Finer crackles, often called crepitations, are of two sorts. The most widely recognized are explosive high-pitched sounds that occur in the later parts of the inspiratory cycle [89]. Several occur in each cycle and are repeated in subsequent cycles, even after coughing or deep breathing. They resemble the sound of hair rolled between the fingers close to the ear. Each crackle occurs at a particular transpulmonary pressure and represents the opening of a small airway that was previously closed [90]. Such crackles are heard in pulmonary fibrosis and oedema, allergic alveolitis, bronchiectasis and cystic fibrosis, and pneumonic consolidation, particularly as resolution begins. They are also commonly heard over a resolving collapsed lobe or segment and over infarcted lung. Auscultation at the lung bases of elderly patients first thing in the morning often reveals repetitive late inspiratory crackles; however, these disappear after a few deep breaths. In general, these crackles are gravity dependent, i.e. they occur in the dependent part of the lung. However, in allergic alveolitis (which characteristically affects bronchioles as well as alveoli) they may be quite widespread, while in pneumonia they are heard over the consolidated area of lung.

Lower-pitched explosive crackles may be heard in expiration and early in inspiration [91]. These are common in severe airflow obstruction, being associated with a forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity ratio

of less than 45%, and are often audible through a stethoscope held at the patient's mouth. They may be followed by an end-inspiratory wheeze. They are thought to represent intermittent obstruction in a larger airway, either related to abnormal collapse of the wall or to partial obstruction by secretions. They are not affected by posture and tend to be less profuse than the late inspiratory crackles discussed above. In patients with bronchiectasis, a variety of crackles may be heard, including all three types mentioned [92]. However, they typically occur in the early and mid phase of inspiration and tend to fade by the end of inspiration. They are not necessarily associated with severe airflow obstruction but may be heard at the mouth. Like the crackles associated with severe airflow obstruction, they are probably related to a combination of secretions in, and increased compliance of, larger airways.

### Pleural rub

The noise generated by inflamed pleural membranes may be quite characteristic and has been compared to the creaking leather of a new pair of shoes. Perhaps this simile is less useful to a younger generation in this era of synthetic materials. It may usually be heard on both inspiration and expiration, although the expiratory component may not be present. It is also sometimes possible to detect a superficial quality to the sound. However, when it is soft and confined to inspiration, it may be impossible to distinguish from repetitive inspiratory crackles.

## Conclusions

The clinical examination of a patient's respiratory system, as of any other, is intended to provide the physician with a picture of how that person's life and function varies from what the physician regards as normal. In the case of the pulmonary system much more information may be gained by these simple techniques than in examination of most other body systems. Thus it is possible to obtain information about the anatomy of the lungs, in terms of size and shape, displacement of mediastinal structures, state of inflation and position of the diaphragm. Sufficient physiological information can be obtained from the history and from observation of breathing and colour and chest and diaphragmatic movements to allow the experienced physician to make a reasonable estimate of vital capacity

and residual volume. With the addition of the simple test of timing a forced expiration, an estimate of FEV<sub>1</sub> can be added [93,94].

Finally, much information of a pathological nature may be inferred from the finding of abnormalities of structure and function and from knowledge of the most likely causes of these abnormalities. Indeed, it should be an infrequent event for the chest physician not to have a very good idea of the cause of a patient's symptoms at the end of a clinical consultation, supplemented by radiographic examination of the chest. This, together with the ready availability of simple tests of lung function such as peak expiratory flow rate and FEV<sub>1</sub>, should allow quick decisions to be made and appropriate management to be planned without delay, a most important factor in the handling of worried patients.

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# DIAGNOSTIC IMAGING

ARTHUR J.A. WIGHTMAN

## Chest radiography

The chest radiograph is the most frequently performed radiological investigation. Broad guidelines for its use have been drawn up by the Royal College of Radiologists [1] that recognize the requirement to avoid unnecessary patient irradiation when the diagnostic yield would be negligible. Until considerable experience in reading chest films has been gained, it is useful to have a methodical system for analysing each one.

### Indications

Chest radiographs are indicated when new lower respiratory, cardiac or other intrathoracic disease is suspected. Common examples include pneumonia, tuberculosis, malignancy, pleural effusion, myocardial infarction, or other undiagnosed causes of chest pain, dyspnoea or haemoptysis. Chest radiographs are generally not justified in the following circumstances:

- 1 pre-employment or screening medicals, except in a few high-risk groups (e.g. at-risk immigrants with no recent film) or for certain specific occupations (e.g. professional divers);
- 2 preoperatively in the absence of any suspected respiratory or cardiac disease;
- 3 in the routine follow-up of patients with chronic bronchitis and emphysema, asthma, heart disease or hypertension, unless the symptoms and signs have changed.

There are certain other instances when patients are sometimes referred inappropriately. For example, it is never necessary to obtain both right and left lateral views, it is seldom necessary to obtain an expiration as well as inspiration film in suspected pneumothorax, and follow-up films in pneumonia should not be obtained more frequently than every 7–10 days unless the clinical condition is deteriorating or a complication such as empyema is suspected. Pneumonia has a mean resolution time of 6 weeks, and is often much slower to clear in the elderly.

## Anterior views

The standard radiograph is the posteroanterior (PA) view; this may be supplemented with a lateral view. A reasonably accurate record of true cardiac size is obtained from the PA film, and fluid levels in lung cavities can be detected since the patient is examined in the erect position. Voltages in the range of either 60–75 kV<sub>p</sub> or in excess of 135 kV<sub>p</sub> are customarily used. With the former, the greater part of the lungs and bony detail of the ribs are seen well and ectopic calcification is readily recognized. The major disadvantage is that the mediastinum and those parts of the lungs behind the heart and behind the domes of the diaphragm are imperfectly shown. These blind areas of the lungs, as well as the trachea and main bronchi, the thoracic spine and certain of the mediastinal pleural reflections, are shown to advantage with a high kilovoltage technique and recognition of small lung nodules (as in pneumoconiosis) is improved. However, calcification in thoracic lesions is less readily appreciated and detail of bone structures is impaired because the absorption coefficients of soft tissue and calcium approximate to each other with increased kilovoltage.

An anteroposterior (AP) view is taken when the patient is insufficiently fit for a PA chest film. It may also be useful in providing a supplementary view, offering a slightly different projection to the PA view. For example, it may resolve whether a shadow seen on the PA view represents a true pulmonary lesion or an overlap of normal structures, or alternatively whether a small opacity lies in rib or lung. Variable magnification of the cardiac image occurs so true assessment of cardiac size cannot be obtained from the AP view.

The scheme outlined in the sections below is suggested for comprehensive analysis of the anterior chest film (Fig. 7.1). After completing the analysis, it may be extremely useful to compare current findings with those shown on previous films. For instance, confirmation that an abnormality is long-standing may eliminate the need for further investigation, and previous films are essential for



**Fig. 7.1** PA chest film of female showing central position of trachea (black arrow); mid-point of V-shaped right hilum (large white arrow); and shadow of aortic arch and lateral border of descending thoracic aorta (small white arrows).

monitoring the progression of disease or its response to treatment.

### *Preliminary observations*

#### *Is the patient straight?*

Compare the positions of the medial ends of the clavicles (anterior structures) relative to the sides of the thoracic vertebral bodies at the same level (posterior structures). The relationships should be symmetrical on the two sides. It is important to check this since rotation of the patient to one side brings more soft tissue of the chest wall and breast across the opposite lung, which may give a false impression of loss of normal lung transradiancy on that side.

#### *Is the film adequately penetrated?*

On a film of adequate penetration it should be possible to see the disc spaces between the thoracic vertebral bodies. If this is not so, the film is underpenetrated and important information in the lung behind the heart and domes of the diaphragm may be lost.

#### *Is the examination PA or AP?*

It is usually impossible to tell from the configuration of the chest whether the patient has been examined in the PA or

AP view. This information may be provided by the inscription on the film: labelling with 'portable' or 'P' or 'supine' indicates an AP examination. Knowledge of the projection is needed to determine if a true or magnified image of the heart has been obtained.

#### *Are accompanying chest films of the same patient?*

Occasionally one of a patient's chest films appears strikingly different from others, and the question arises of possible mislabelling or mixing of radiographs of patients with the same name. The most individualistic feature on a chest film is the pattern of calcification of the costochondral junction and costal cartilages of the first ribs, and comparison of these will quickly determine if the films are of the same or different patients.

### *Diaphragm*

On inspiration the hemidiaphragms normally lie between the anterior ends of the fifth and seventh ribs. A check of diaphragm position is important since apparently increased lung density or basal atelectasis may be due purely to poor inspiration in an unconscious or uncooperative patient. Usually the right hemidiaphragm is up to 1.5cm higher than the left. The situation is reversed with dextrocardia. When the left hemidiaphragm is higher than the right, a cause such as collapse of the left lower lobe or a subphrenic abscess should be considered. However, the left hemidiaphragm may on occasion be higher than the right as a normal finding.

### *Heart*

A check should be made of cardiac position. Normally between two-thirds and three-quarters of the diameter of the heart lies to the left of the midline, with one-quarter to one-third to the right. Displacement may be due to lobar collapse, tension pneumothorax, etc. Heart size should also be noted. It is rare in health to find a maximum cardiac transverse diameter exceeding 15.5cm; this is therefore a useful working upper normal diameter, although 1–2% of healthy people, usually of large physique, have a cardiac diameter in excess of this figure. Alternatively the cardiothoracic ratio (maximum cardiac transverse diameter/maximum transverse diameter of the thorax, measured to the inner aspect of the rib cage on each side) may be assessed and is usually less than 50%, although it may sometimes be greater than this in healthy people, for example trained athletes.

### *Trachea*

Assessment of the position of the trachea can next be made. It is normally central at the thoracic inlet but lies a



little to the right of the midline within the chest where it is crossed by the aortic arch.

### *Hila*

The normal hilar shadow is in the shape of a letter V lying on its side, the lower limb of the V being formed by the lower lobe branch of the pulmonary artery and the upper limb by the upper lobe veins crossing the hilum to reach the left atrium. The walls of the bronchi are too thin to contribute to the hilar shadows, and hilar lymph nodes are only visible when pathologically enlarged. The apex of each V-shaped hilum can usually be clearly identified. The apex of the right hilum normally lies at the level of the sixth rib in the mid-axillary line, while the apex of the left hilum is some 1–1.5 cm higher. It is important to take note of the hilar positions since displacement may provide a clue to lobar collapse. The hila may also be displaced by localized lung fibrosis, secondary for example to old tuberculosis or radiotherapy. Hilar enlargement may be due to enlargement of the pulmonary vessels (e.g. in cor pulmonale), lymph node enlargement or the presence of a primary hilar neoplasm. This is discussed later in the chapter.

### *Horizontal fissure*

In some 80% of chest radiographs part of the horizontal fissure separating the upper from the middle lobe can be identified. This normally runs almost horizontally, although an angulation of 10° upwards or downwards may not be significant, and lies in the line between the apex of the right hilum and the sixth rib in the mid-axillary line. Displacement occurs in lobar collapse, lobar shrinkage from previous destructive lung disease, or with large bullae.

### *Lungs*

It is convenient next to compare the two lungs zone by zone for any increased or decreased shadowing that may be present. The lungs may be divided for descriptive purposes into zones: the upper zone represents the region from the lung apex to the lower border of the second rib anteriorly; the mid zone is from the lower border of the second rib to the lower border of the fourth rib anteriorly; and the lower zone is the region below this. This division allows description of the site of the lesion on an anterior view but avoids the need for anatomical localization to a specific lobe, for which a supplementary lateral view or more complex imaging may be required. Note should be made of the characteristics and density as well as location of any lung abnormality, and particular care should be taken to inspect the regions behind the heart, behind the domes of the diaphragm and in the planes of the hila and

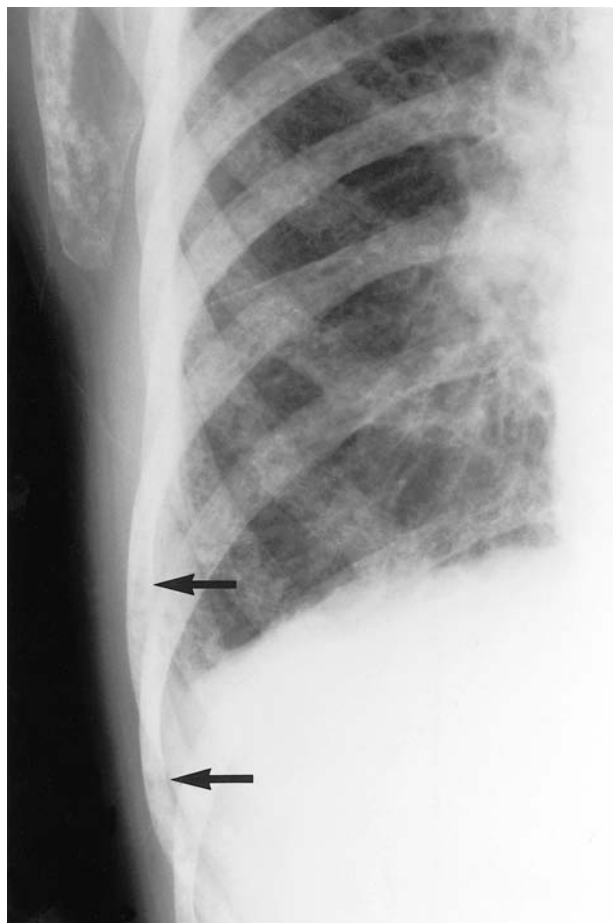
clavicles, these representing less readily seen areas in which abnormalities may be overlooked.

### *Soft tissues*

Unless attention is paid to the soft tissues of the chest wall, a previous mastectomy as a cause for unilateral hypertransradiancy may be overlooked. Nodules on the chest wall are silhouetted by air and may simulate lung nodules. Thus the cutaneous nodules of neurofibromatosis may be mistaken for pulmonary nodules when they are seen superimposed on the lungs, but their true nature will be recognized when similar nodules are identified on the skin surface outwith the planes of the lungs. Other causes of soft-tissue loss or increase, with or without displacement of the subcutaneous fat lines, and the recognition of air or calcification in the soft tissues may provide clues to the origin and nature of a chest radiographic abnormality.

### *Skeleton*

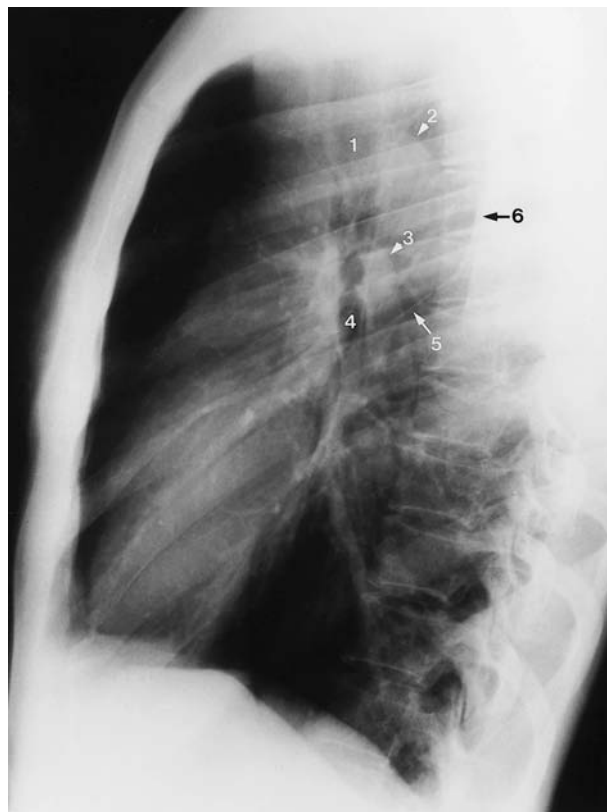
A search should be made for bony abnormalities contiguous with, or remote from, lesions of the lung. Thus ribs may be destroyed by carcinoma from direct extension of tumour to the chest wall or from haematogenous metastases; rib fractures may explain the presence of a pleural effusion; and pressure erosion (as distinct from destruction) may be seen on the undersurface of ribs at the site of an intercostal neuroma or in aortic coarctation. Very florid 'pseudocallus' occurs round healing fractures in patients with Cushing's syndrome and those on steroid therapy, and may be mistaken for lung nodules unless their relationship to bone is appreciated. Recurrent chest infection can be a presenting symptom of multiple myeloma, the diagnosis of which is suggested by multiple small clearly defined lytic lesions in the ribs, shoulder girdles or proximal humerus. Lytic metastases, for example from breast, can simulate myeloma deposits, although metastases are usually less clearly circumscribed. Bone density may be increased, the causes of several or numerous areas of sclerotic or mixed sclerotic and lytic lesions being most commonly breast carcinoma in female and prostatic carcinoma in male patients (Fig. 7.2). Carcinomas of other origin, including bronchial carcinoma, lymphoma, myelofibrosis, mastocytosis, and fluorosis in patients from endemic areas, are rarer causes of widespread sclerosis. Increased bone density is also seen in conjunction with modelling deformities, locally in Paget's disease and fibrous dysplasia and generalized in osteopetrosis. The shoulders should be inspected routinely, since these may show skeletal changes of a disease process affecting the chest (e.g. rheumatoid arthritis) or the effects of treatment of chest disease (e.g. avascular necrosis of the humeral head from steroid therapy).



**Fig. 7.2** Sclerotic and lytic (arrows) metastases in ribs and scapula in patient with prostatic carcinoma.

### Lateral view

The lateral view localizes an abnormality shown on an anterior view, may provide improved detail and characterization of such an abnormality, and occasionally may reveal a lung lesion that is invisible on the anterior view. For this last reason, it is important to obtain a lateral view in a patient with suspected bronchial carcinoma or other serious condition in whom the anterior view is negative. The lateral film can be analysed in a similar way to that described for the anterior view. Although lung detail is lost to some extent due to superimposition of the two sides, the retrosternal and retrocardiac areas of lung are seen with reasonable clarity (Fig. 7.3). The thoracic vertebrae should appear increasingly transradiant from top to bottom; sometimes the only evidence of lower lobe collapse or of other disease of the lower lobe is that the lower thoracic vertebrae appear as opaque as, or more opaque than, the upper. A lateral view is also sometimes helpful in showing unequivocal interstitial disease of the lung bases



**Fig. 7.3** Left lateral film showing trachea (1), aortic arch (2), pulmonary artery (3), left lower lobe bronchus (4) and oblique fissure (5), and edges of scapulae (6).

when this is uncertain on the anterior view because of superimposition of dense breast shadows.

### Computed tomography

Computed tomography (CT) has an established place in the investigation of pulmonary, mediastinal, hilar and pleural disease. Multiple cross-sectional images provide far more information than is available from the chest radiograph. For example, subpleural metastases may only be visible on CT, and mediastinal masses such as enlarged lymph nodes can be readily identified and located, particularly if a contrast-enhanced scan, entailing the intravenous injection of an iodine-containing contrast medium, is performed to distinguish vascular from low-vascularity or cystic structures.

Images of slices 5–10 mm thick are acquired while the X-ray tube and detectors rotate round the transverse axis of the patient. On early scanners rotation was limited on each exposure to 360° by the physical restraints of connecting cables and the patient was scanned in a repetitive scan–table movement–scan–table movement sequence, the tube and detectors rewinding back to their original positions before each scan. This slow stop–start procedure

required the patient to rebreathe and suspend respiration before every one or two scans; consequently lung lesions of up to 1.5cm diameter could be missed if the patient failed to do this at the same depth of inspiration before each scan, leading to gaps between neighbouring images [2].

Spiral (helical or volumetric) scanners have now superseded the earlier scanners. These use electro-optical slip rings instead of cables, such slip rings allowing for indefinite unidirectional rotation of the X-ray tube and detectors. During exposure the X-ray table slides longitudinally in a continuous movement and the entire chest can be scanned in a spiral action during one or two breath-holds. The problem of volumetric gaps due to different degrees of suspended respiration is therefore eliminated. Further advantages are that image reconstructions can be made embracing any thickness of a single or two contiguous cuts, and these can give much more positive detail of lesions such as small lung nodules. Coronal, sagittal and three-dimensional reconstructions can be made from such volumetric axial scans.

High-resolution CT (HRCT) of the chest is used when there is a need to examine subtle lung changes in maximum detail. The technique entails scanning the chest with thin-section cuts of 1–2mm thickness and employing data reconstruction using a high spatial frequency algorithm to maximize spatial resolution. Scanning very thin sections avoids including detail of overlapping structures on the cross-sectional image, and thus the clarity of the image is akin to looking at a cross-section of inflated lung with the naked eye. The effect of a high spatial frequency algorithm is to produce much sharper tissue interfaces with improved resolution. In contrast to volumetric scanning as described above, in which full coverage of the lungs may be sought, HRCT involves sampling tiny volumes of the lung, usually at intervals of 1–2cm, or more closely through a predetermined region of interest. The chief applications of HRCT can be summarized as follows.

- 1 Most instances of diffuse lung disease; however, for obvious reasons, a search for lung metastases requires a comprehensive examination of the lungs with thick cuts.
- 2 In bronchiectasis HRCT has replaced bronchography although correlation is not perfect.
- 3 Sometimes in focal lung disease, e.g. for detection of contained fat or calcium.

Radiation dose to the patient from chest CT is relatively large and highly variable. While the dose in planned limited HRCT may be similar to that from two pairs of PA and lateral chest radiographs, in full-volume scanning it is much higher and can be in excess of the dose from 150 chest films, two intravenous urograms or one barium enema [3]. For this reason the requirement for CT, and particularly for repeat scanning, should be carefully weighed in each case.

## Ultrasound

Ultrasound is an important aid in the investigation of pleural disease and in the search for subphrenic conditions (e.g. subphrenic abscess) that may be causing abnormalities of the lung or pleura. The wave frequencies used in diagnostic practice do not penetrate air and therefore ultrasound is not useful in the investigation of intrathoracic lesions where these are separated from the chest wall by aerated lung. Ultrasound is used to demonstrate an effusion concomitant with extensive consolidation when this cannot be confirmed from radiographs. Demonstration of such fluid is important before thoracocentesis is attempted. Pleural tumour, concealed on radiographs by a large accompanying pleural effusion, may also be shown by ultrasound.

Sonography can facilitate drainage of small effusions by providing precise localization of the pleural fluid. It may similarly be used as an alternative to fluoroscopy to assist percutaneous needle biopsy of pleural or pleural-based tumour. This is particularly useful when the pleural opacity is shallow and not easily seen in more than one plane on the radiograph. It is often simpler to confirm and localize small pleural effusions by ultrasound than by radiography in critically ill, immobile patients. If required, pleural aspiration can then be carried out with sonographic assistance at the bedside.

## Lung scintigraphy

Ventilation–perfusion ( $V/Q$ ) or perfusion ( $Q$ ) scanning alone is the primary investigation for pulmonary thromboembolism. The principle is that pulmonary emboli produce areas of defective perfusion of lung without corresponding abnormality in ventilation. Since the aim is to determine if perfusion is abnormal, it follows that a ventilation scan is superfluous in the investigation of pulmonary thromboembolism when the perfusion scan is normal. However, there is a technical advantage in performing the ventilation scan first, since the images from xenon ventilation scans are degraded in quality by scattered photons produced by technetium from a recent prior perfusion scan, and moderate-sized foci of airways obstruction may be overlooked. In practice, therefore, both ventilation and perfusion scans are usually performed, although perfusion scanning alone is sometimes carried out when there is little possibility of airways obstruction.

During ventilation scanning, sequential posterior images of the lungs are obtained while the patient breathes air containing approximately 75–80 mega Bq of  $^{133}\text{Xe}$ . At the end of the wash-in phase, equilibrium images are obtained on rebreathing through a closed system, followed by wash-out images until the xenon has cleared from the lungs or 10 min have elapsed. For perfusion

imaging, 75–80 mega Bq of  $^{99m}\text{Tc}$ -macroaggregated albumin are injected intravenously, this effectively producing iatrogenic pulmonary microemboli, and images including posterior, anterior, and anterior and posterior oblique views of both lungs are obtained.

### Diagnosis of pulmonary thromboembolism

The chest radiograph is of very limited value in the diagnosis of pulmonary thromboembolism. The majority of emboli produce no radiographic change; when abnormality is present it is usually non-specific, consisting of an area of consolidation, linear band shadows from atelectasis, pleural effusion or hemidiaphragmatic elevation. Therefore the main differential diagnosis is pneumonia. Occasionally more specific chest radiographic changes are seen, such as development of hilar vessel enlargement (from mechanical plugging of the pulmonary arteries by clot) or unilateral or lobar hypertransradiancy. These infrequent changes are more readily recognized when recent previous films are available for comparison. A further limitation of the chest radiograph is that non-specific changes such as consolidation take a minimum of 12–24 h to develop, so that signs are not found immediately after the clinical event.

V/Q scanning is the investigation of choice in suspected pulmonary embolism; in contrast to the chest radiograph, the Q scan is abnormal immediately after the event. While V/Q scanning is highly sensitive, it is relatively non-specific and pulmonary embolism is overdiagnosed unless careful criteria for interpretation are used. Based on studies comparing V/Q scanning with pulmonary angiography [4–6], the following protocol is used in the author's institution, classifying scans as normal, of high probability for pulmonary embolism, and non-diagnostic. For interpretation of the scan a recent chest film is required, since perfusion abnormalities that correspond exactly with radiographic changes are not diagnostic.

**1 Normal:** no perfusion abnormality and a normal chest radiograph, or perfusion abnormality that exactly outlines a non-pulmonary chest radiographic finding (e.g. hilum, unfolded aorta).

**2 High probability:**

- (a) two or more large segmental perfusion defects (each  $\geq 75\%$  of the volume of a segment) either without corresponding ventilation or chest radiographic abnormality, or substantially larger than either matching ventilation or chest film abnormality; or
- (b) two or more moderate segmental perfusion defects ( $\geq 25\%$  and  $\leq 75\%$  of a segment) without matching ventilation or chest radiographic abnormality, plus one large unmatched segmental defect; or
- (c) four or more moderate segmental perfusion defects without ventilation or chest radiographic abnormality.

**3 Non-diagnostic:** any scan that is not high probability or

normal, or a scan that has no perfusion defect but where the chest film shows a radiographic abnormality consistent with a pulmonary infarct (e.g. atelectasis, pleural-based infiltrate).

A normal scan effectively excludes pulmonary embolism demonstrable by any other means and no further investigation is required. A high-probability scan using the above criteria has a specificity exceeding 90% and treatment can be instituted. Further investigation is required in those patients with non-diagnostic scans. While pulmonary angiography would seem the logical next step, the large number of patients falling into this category, and the invasiveness, morbidity and specialist time required for angiography, render this an unrealistic option in many centres. For these reasons lower limb venography or Doppler offer an alternative next step by determining if there is evidence of a source in the legs for emboli to the lungs. The combination of positive venography or Doppler and an indeterminate scan provide a good argument for instituting treatment with anticoagulants, while the combination of negative venography or Doppler and an indeterminate scan require further consideration. In these circumstances investigation may be stopped when there is a low clinical suspicion and there are no risk factors for pulmonary embolism, while angiography is required when the clinical suspicion is high or risk factors are present.

Angiography is the final arbiter in the investigation of pulmonary embolism, positive signs being the outlining of intraluminal thrombus (Fig. 7.4) or abrupt obstruction of flow by thrombus. However, spiral CT angiography, where available, is becoming established as a less invasive alternative.

### Spiral CT pulmonary angiography

The shortcoming of V/Q scanning for pulmonary embolism is that the majority of scans ( $>60\%$ ) are equivocal (of intermediate or low probability) [7]. Where spiral CT is available, CT pulmonary angiography provides an alternative means of investigation. The lungs are scanned from the top of the aortic arch to the inferior pulmonary veins in thin, usually 3-mm, contiguous sections during intravenous infusion of contrast. The data can be manipulated to construct thinner sections for analysis if required.

Thrombus is seen as a filling defect within a main or segmental pulmonary artery (Fig. 7.5). Commonly a thin layer of blood lies between the thrombus and the vessel wall, creating a 'railway track' or 'polo mint' appearance (Fig. 7.6). Thrombus in vessels below segmental level is not reliably detected by CT pulmonary angiography. CT may also show supportive signs of pulmonary embolism, such as a small effusion or pleural-based segmental or subsegmental consolidation. Alternatively it may reveal



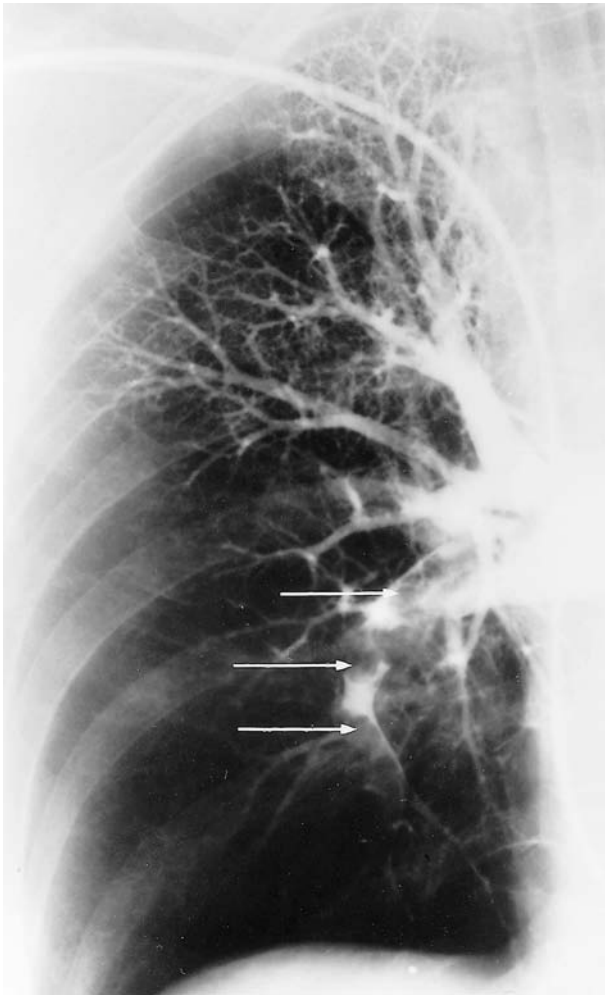


Fig. 7.4 Pulmonary arteriogram showing normal right upper lobe vessels but thrombus (arrows) present in lower lobe artery.

an unsuspected cause for the patient's symptoms, such as aortic dissection or unrelated chest disease.

Reports of the use of CT pulmonary angiography for the investigation of pulmonary thromboembolic disease are favourable, with sensitivities and specificities of 90% or better [8]. Large multicentre studies are currently in progress. The disadvantages of CT angiography compared with  $\dot{V}/\dot{Q}$  scanning are the increased burden on available CT time, increased radiation dose and the small risk of severe adverse reactions to contrast medium. CT angiography may be seen as a useful first investigation of patients in whom massive pulmonary embolism is suspected, or in situations in which a  $\dot{V}/\dot{Q}$  scan is likely to be indeterminate (e.g. history of pre-existing cardiorespiratory disease, abnormal chest radiograph).  $\dot{V}/\dot{Q}$  scanning remains a useful first investigation for pulmonary embolism in young to middle-aged patients without pre-existing cardiopulmonary disease where massive embolism is not suspected. Spiral CT is replacing conventional pulmonary angiography since it is non-invasive and less dependent on the skills of the operator.

### Magnetic resonance imaging

Both CT and magnetic resonance imaging (MRI) define lung nodules, lymph nodes and other masses in the hila and mediastinum, and vascular structures of the thorax. CT is preferred to MRI for the investigation of most chest disorders: data acquisition is quicker, cardiac gating is not required, spatial resolution is greater and recognition of calcification is much better. However, there are instances in which the superiority of MRI is recognized. Thus MRI is the better investigation for lesions of the spine and paraspinal region. Lateral thoracic meningoceles and

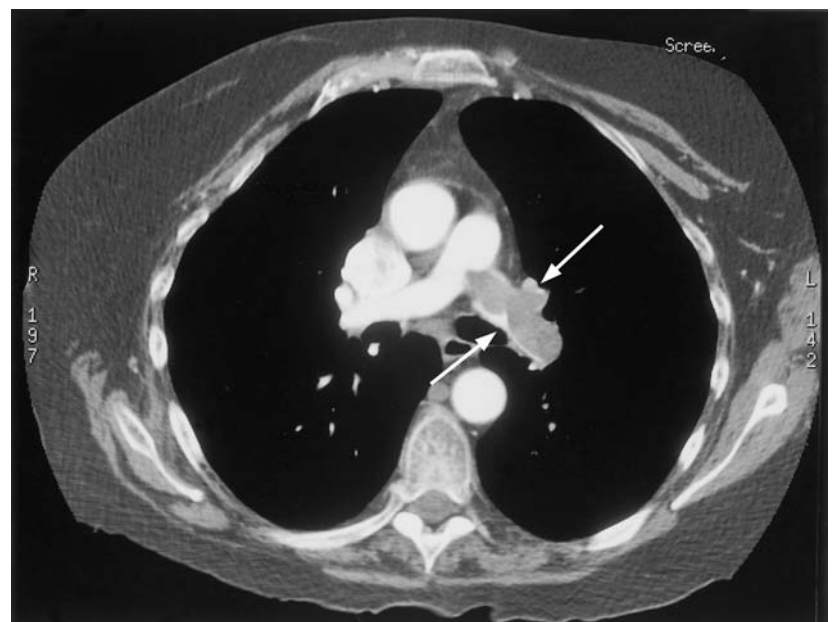
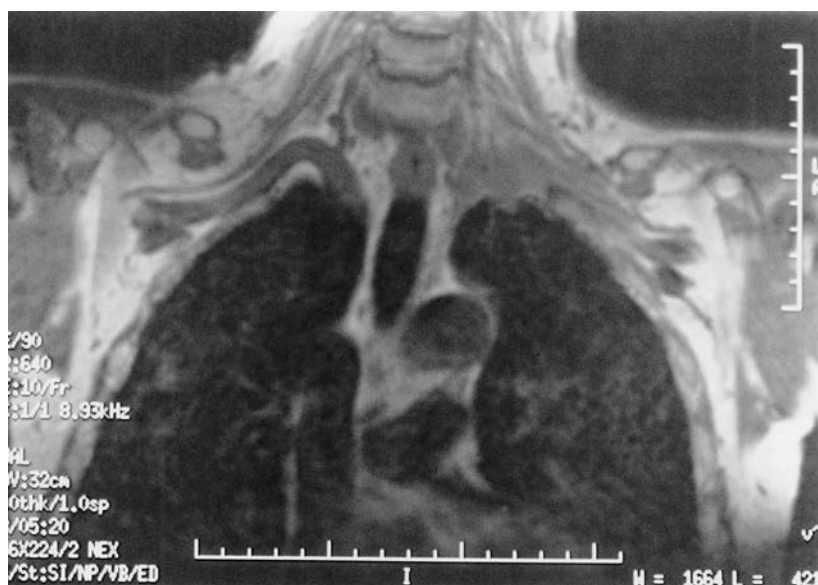


Fig. 7.5 Spiral CT arteriogram: the left pulmonary artery is filled with thrombus (arrows) and the right is clear.



**Fig. 7.6** Spiral CT arteriogram: 'polo mint' sign produced by a thin rim of contrast between thrombus and arterial wall (arrows).



**Fig. 7.7** MRI showing left superior sulcus tumour. The subclavian artery, spinal nerves and brachial plexus are clearly seen on the normal right side, contrasted by high fat signal. The carcinoma at the left apex in contrast is seen infiltrating the fat planes and invading the brachial plexus.

paraspinal neurofibromas are demonstrated well, and their exact relation to the intervertebral foramen and vertebral canal can be characterized further if necessary with coronal, parasagittal and other reconstructions. Furthermore, MRI may be superior to CT in showing early tumour invasion into the chest wall or mediastinal structures and is particularly helpful, for example, in mapping tumours extending into the brachial plexus [9] (Fig. 7.7). It therefore has a place in the preoperative investigation of lung cancer where the possibility of such invasion is raised by CT or other investigations.

In the cardiovascular system, MRI is valuable in elucidating complex congenital abnormalities of the heart and shows aneurysms and other abnormalities of the great vessels. While MRI angiography has shown potential in the diagnosis of pulmonary embolism, this application is largely being superseded by the advent of spiral CT angiography.

MRI has the advantage over CT of not involving ionizing radiation. It may therefore be used safely in patients requiring follow-up scans to gauge response to treatment, for example the response of lymphoma to chemotherapy,



or in the reappraisal of aortic dissections and in the investigation of children.

## Other methods of investigation

### Fluoroscopy

By viewing the chest during fluoroscopy during different phases of respiration or patient rotation, it can be readily determined if a chest radiographic opacity is located in lung, rib or chest wall and, if intrathoracic, its site and relationship to normal anatomical structures can be assessed. Fluoroscopy and ultrasound are equally accurate in confirming paralysis of a raised hemidiaphragm.

### Tomography

Linear tomography has been largely replaced by CT, which determines with much greater accuracy the existence and site of hilar lymphadenopathy, the characteristics of a thoracic lesion (e.g. whether it contains calcification or fat) and the presence of pulmonary metastases and interstitial lung disease. Conventional tomography suffers from the limitation that the borders of normal and abnormal mediastinal tissues are only defined where they are silhouetted by air in adjacent lung or trachea. In contrast, on CT the borders of mediastinal structures are outlined by surrounding fat, while artificial contrast between vascular and low-vascularity structures can be created with intravenous contrast medium.

### Barium swallow

Barium swallow examination may be useful in detecting upper gastrointestinal abnormality that accounts for chronic cough or recurrent aspiration pneumonia (e.g. pharyngeal pouch, achalasia).

### Pulmonary and bronchial angiography

Pulmonary angiography is the most sensitive examination for the detection of pulmonary thromboembolism. CT has largely replaced angiography in the assessment of aortic dissection; longitudinal reconstructions showing the extent of an aortic dissection can be made from the CT axial imaging data if required (Fig. 7.8). Transoesophageal echocardiography may also be employed, while MRI is probably the most accurate examination for dissection but suffers from the constraint that it may affect some life-support systems. Angiography is largely reserved for situations where the above examinations are equivocal.

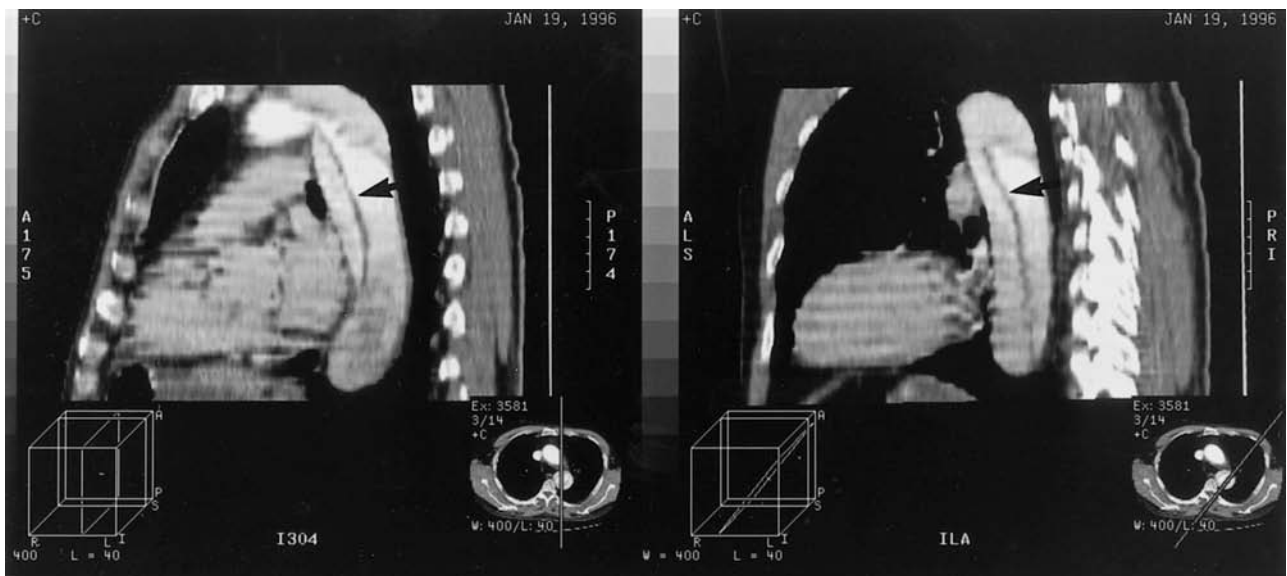
Bronchial arteriography and embolization provide an alternative to surgery in situations of severe haemoptysis due to benign conditions such as bronchiectasis and bleeding from old tuberculous cavities. Such intervention can be life-saving, although there is a tendency for haemoptysis to recur as other feeding vessels bleed in turn. Arterial embolization has also increasingly replaced surgery in the management of shunts and haemoptysis from pulmonary arteriovenous fistulae.

## Consolidation and collapse

### Lobar consolidation

The term 'consolidation' embraces those conditions that cause replacement of air-containing lung by fluid-filled or

Fig. 7.8 Longitudinal reconstruction of CT scan showing aortic dissection (arrow).



cellular tissue without change of volume. The causes are therefore numerous and are discussed in other chapters. This section describes the radiological features.

In lobar consolidation the affected lobe is opaque, the region of opacity corresponding with the normal anatomical position of the lobe and clear linear demarcation from normal lung being produced by curtailment of the consolidation at the respective fissure or fissures. The patterns of consolidation of the different lobes are illustrated in Figs 7.9–7.16. Accumulation of fluid in a lobe is to some extent influenced by gravity, so there is a tendency for the consolidation to be maximal in the dependent part of the lobe, or posteriorly if the patient has been lying supine. The most specific sign of consolidation is the air bronchogram, seen as black branching tubes and representing air-filled bronchi silhouetted by surrounding fluid-filled lung (Fig. 7.17).

The diaphragm and lateral borders of the mediastinum are visible on a normal chest radiograph because they are silhouetted by adjacent low-density lung. Consolidated lung has the same radiographic density as soft tissue, so the normal silhouette of the heart border or diaphragm is lost when consolidation develops in adjacent lung. Application of this principle, the silhouette sign, is useful in determining from an anterior radiograph the lobe involved in consolidation. For example, the heart border is obscured in middle-lobe or lingular consolidation (Figs 7.11 & 7.13) but is preserved in lower-lobe consolidation when the diaphragm may be obscured.

Consolidation is often patchy and non-lobar in distribu-

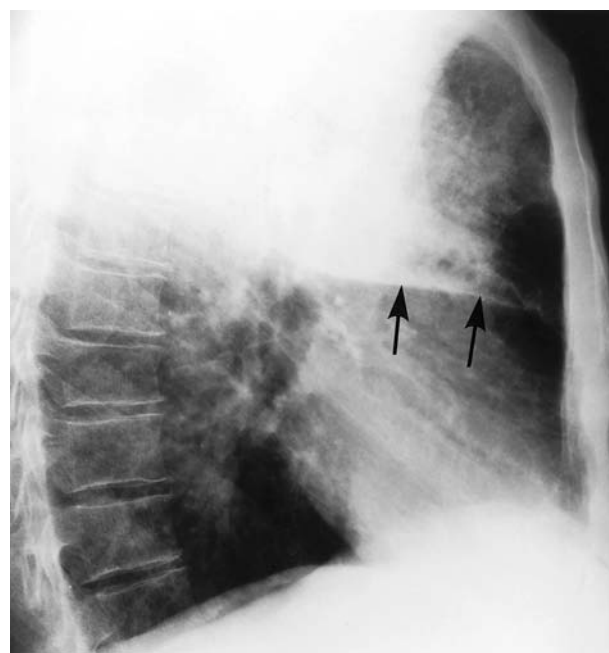
tion and can be due to a great variety of causes, e.g. pneumonia, oedema, haemorrhage or pulmonary infarction. Frequently the cause is not evident and it is important to consider the radiographic findings in conjunction with the clinical and laboratory parameters in each case. Sometimes the location and characteristics of the consolidation suggest the cause, e.g. patchy consolidation associated with areas of cavitation in the upper thirds of the lungs is likely to be due to pulmonary tuberculosis.

The consolidation of pulmonary oedema can be patchy and non-specific. The diagnosis is suggested if it is perihilar and bilateral, particularly if associated with cardiomegaly, Kerley lines (see below) and pleural effusions. If the patient has been nursed on one side for several hours, the oedema may be largely confined to the dependent side. Left ventricular failure leading to pulmonary oedema often occurs in conjunction with pneumonia and it can be impossible to distinguish the relative contributions of each on the radiograph. Pulmonary oedema may clear very rapidly in response to treatment, with striking radiographic improvement in 12–24 h; this rapidity of clearing is one sign that differentiates oedema from pneumonia.

Air bronchograms may be seen in certain conditions that produce cellular infiltrates in the lung, notably lymphoma, alveolar cell carcinoma and sarcoidosis. These conditions should therefore be considered in a patient with radiographic consolidation but without clinical pneumonia, or in persisting radiographic change of pneumonia unresponsive to treatment.



**Fig. 7.9** PA film showing consolidated right upper lobe.



**Fig. 7.10** Lateral film of same patient as in Fig. 7.9 showing consolidation limited inferiorly by horizontal fissure (arrows).



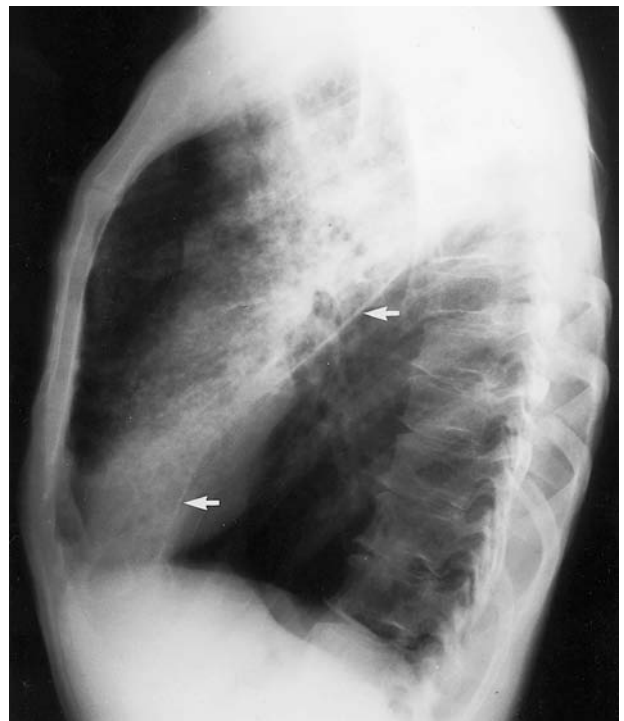
**Fig. 7.11** PA film showing right middle-lobe pneumonia: note obscured cardiac border adjacent to the consolidation.



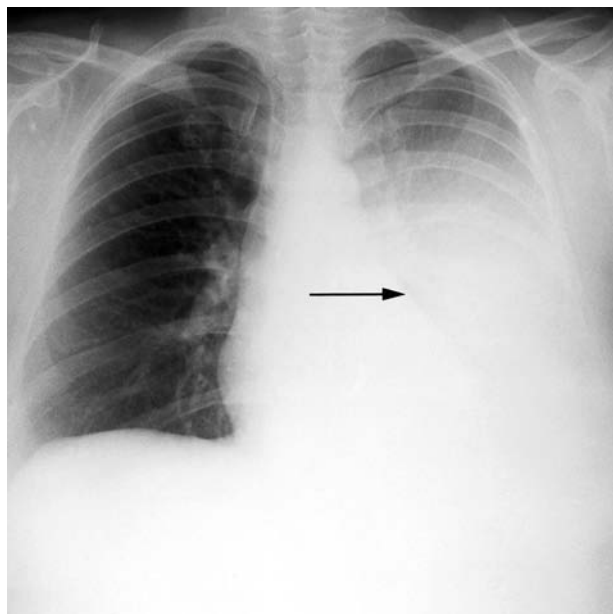
**Fig. 7.13** PA film showing consolidation of left upper lobe including lingula.



**Fig. 7.12** Lateral view of same patient as in Fig. 7.11 showing consolidation demarcated by horizontal and oblique fissures.



**Fig. 7.14** Lateral view of same patient as in Fig. 7.13 showing consolidation demarcated posteroinferiorly by oblique fissure (arrows).



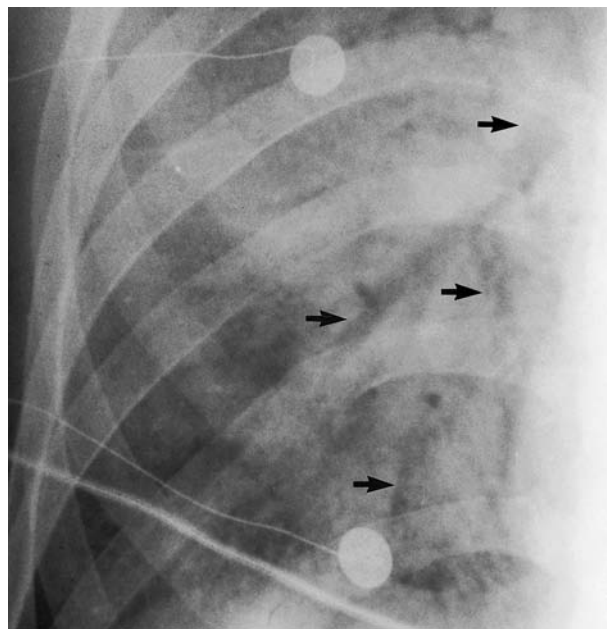
**Fig. 7.15** PA film of left lower lobe consolidation: note left heart border is visible through consolidation (arrow).



**Fig. 7.16** Lateral view of same patient as in Fig. 7.15 showing consolidation demarcated anterosuperiorly by oblique fissure.

### Lobar collapse

In lobar collapse the affected lobe is opaque but, unlike pure lobar consolidation, is accompanied by the following changes to a variable extent: displacement of the heart and



**Fig. 7.17** Air bronchograms in right lower lobe consolidation: the black branching bronchi (arrows) are clearly outlined against the opacified lung.

trachea to the affected side, elevation of the corresponding hemidiaphragm, displacement of the fissures bounding the lobe and splaying out of the vessels in the remaining part of the lung to produce hypertransradiancy. The appearances of lobar collapse are shown in Figs 7.18–7.25. Observation of the silhouette sign may provide the only clue to middle-lobe collapse on an anterior radiograph (Fig. 7.20), since this lobe is too small to produce any significant displacement of neighbouring structures.

Differentiation on the radiograph between pure lobar consolidation and collapse is important, since lobar consolidation usually indicates a simple pneumonia that is likely to clear while lobar collapse implies the presence of an underlying bronchial obstruction that usually requires further investigation by bronchoscopy. In a middle-aged or elderly adult, lobar collapse is most commonly due to an underlying bronchial carcinoma, while in a child it may be due to an inhaled foreign body.

### Pleural effusion

Pleural fluid first collects under the lung in an erect patient. The effect is to produce apparent slight diaphragmatic elevation but, since the level of fluid is shallow and the normal position of the diaphragm is variable from individual to individual, it can rarely be detected at this stage. As the effusion increases, fluid starts to collect in the costophrenic angles, first posteriorly where the sulcus is lowest, then laterally and finally anteriorly. An effusion is therefore first visible radiographically on a lateral view, and later an anterior view, as a homogeneous opacity



**Fig. 7.18** Collapsed right upper lobe showing elevation of horizontal fissure and deviation to right of trachea.



**Fig. 7.19** Right lateral view of same patient as in Fig. 7.18 showing horizontal fissure elevated and bowed upwards and oblique fissure forwards (arrows).



**Fig. 7.20** PA view of middle-lobe collapse showing obscuration of right heart border.



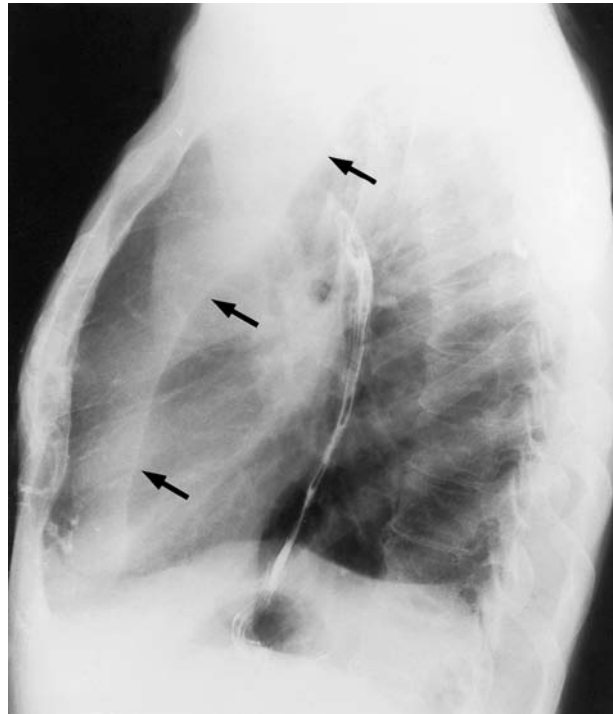
**Fig. 7.21** Lateral view of same patient as in Fig. 7.20 showing retraction forwards of oblique fissure (arrows).

filling in the costophrenic angle with a concave border facing the lung. The minimum volume of fluid required for detection on a PA chest film in an erect subject ranges from 250 to 600 mL [10,11].

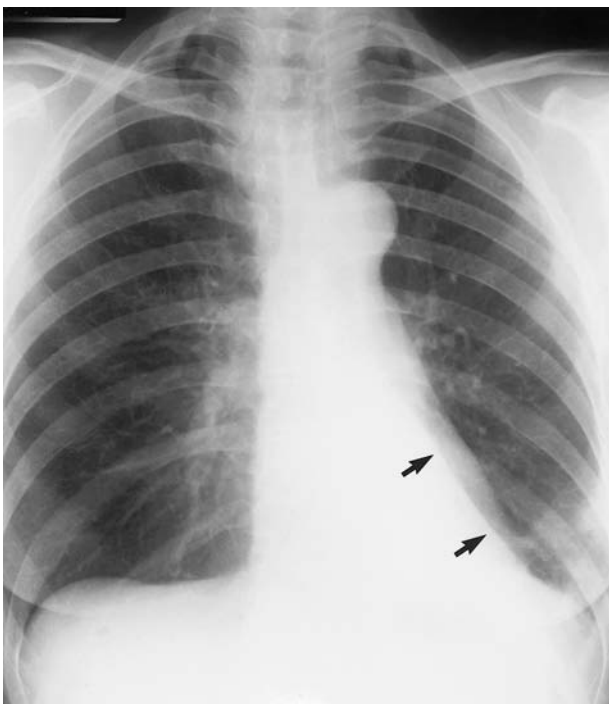
As the effusion increases it spreads over the lung like a mantle, forming a meniscus-shaped homogeneous opacity that is highest at the chest wall. The elastic recoil of the lung is least on its medial aspect, where it is partially



**Fig. 7.22** Left upper lobe collapse showing homogeneous density over upper and middle zones.



**Fig. 7.23** Same patient as in Fig. 7.22 showing oblique fissure pulled forwards by collapsed left upper lobe (arrows).



**Fig. 7.24** Collapsed left lower lobe showing double shadow at left heart border. The edge of the collapsed lobe is arrowed.



**Fig. 7.25** Lateral view of same patient as in Fig. 7.24 showing increase in tissue density over lower thoracic vertebrae.



tethered by the hilum and pulmonary ligament, allowing less fluid to accumulate on this surface. On an anterior radiograph the meniscus-shaped upper edge of the opacity of a moderate-sized effusion therefore slopes downwards from the lateral to the medial aspect of the hemithorax. On a lateral radiograph the anterior and posterior borders of the meniscus are at the same level, since fluid collects to an equal extent in front of and behind the lung, and this is at the same height as the top of the effusion in the axillary line seen on the anterior radiograph.

A very large effusion produces total opacification of the hemithorax. In the absence of disease of the underlying lung, this causes displacement of the mediastinum away from the affected side, and also produces marked depression and even inversion of the underlying hemidiaphragm. On the left side this is seen as downward displacement, flattening and sometimes convexity of the air-filled gastric fundus.

A very large effusion with collapse of one or more lobes of the underlying lung from endobronchial obstruction gives rise to an opaque hemithorax with little or no mediastinal or diaphragmatic displacement, the opposing effects of volume change counteracting each other. An opaque hemithorax without volume change may be seen also in extensive mesothelioma, the volume loss of the lung secondary to encasement and constriction of the hilum countering the opposing effect of an associated effusion. Total lung opacification occurs also in complete consolidation of a lung. This is rare, and an air bronchogram or evidence of patches of aerated lung within the consolidation is usually visible. A hemithorax may at first sight appear totally opaque in a patient with a moderate pleural effusion who has been examined in a supine position, but on closer inspection normal vessel markings are visible that indicate aerated lung lying in front of the pleural fluid in the posterior pleural space.

An opaque hemithorax with mediastinal displacement and elevation of the diaphragm on the affected side is produced by collapse of the lung due to central bronchial obstruction, and there may be a small accompanying effusion. A similar appearance occurs following pneumonectomy, the radiographic clue to which may be deformity of the fifth or sixth ribs posteriorly from surgical transection and partial regeneration.

While a moderate volume of pleural fluid needs to be present to be visible on chest radiography, very small quantities (as little as 10–15 mL) can be detected by ultrasound; this is the examination of choice to confirm the presence of a small effusion, to distinguish between an effusion (which changes position on change of posture) and pleural thickening (fixed), and to determine the optimum site for thoracocentesis. Where ultrasound is unavailable, the presence of an effusion can be confirmed with a lateral decubitus view or a supine view, which is

not as good but sometimes more practicable in a seriously ill patient.

### **Subpulmonary (intrapulmonary) effusion**

As mentioned above, a pleural effusion usually first collects under the lung and soon spills into the costophrenic sulci, rising over the lung like a mantle as it enlarges. On occasion, and in the absence of underlying pleural disease, the effusion continues to collect under the lung where it may accumulate to a depth of several centimetres. On the anterior radiograph this presents as an apparent high diaphragm, which therefore has to be differentiated from true diaphragmatic elevation. Several signs may enable such a distinction to be made.

1 When a subpulmonary effusion is present there is often a little fluid producing blunting in the costophrenic angle, which provides a clue to the presence of pleural fluid; on a lateral view there is similarly often a little fluid visible in the lower end of the oblique fissure.

2 The separation between the left hemidiaphragm and air-filled gastric fundus is usually no more than 1 cm, and greater separation suggests a subpulmonary collection.

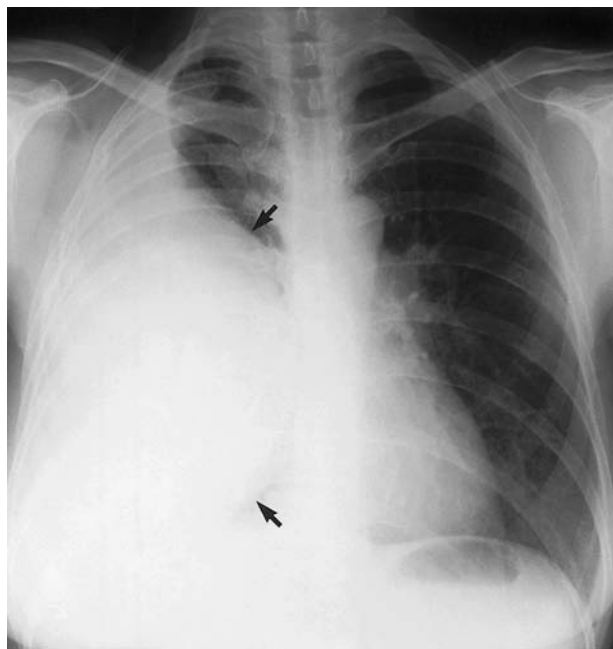
3 The peak of the hemidiaphragm is normally approximately midway from side to side, while the peak of a pseudodiaphragm is often more lateral, at approximately the junction of the middle and outer thirds, with a steep slope downwards from the peak to the costophrenic angle.

If doubt persists, ultrasound or a lateral decubitus view of the chest will establish if an effusion is present, the fluid shifting to the side of the chest when the patient lies on the affected side because a subpulmonary effusion is not associated with pleural adhesions.

### **Loculated effusions and empyema**

Pleural fluid may collect in an atypical distribution when there are adhesions between the pleural layers that prevent free communication within the pleural space. An empyema, for instance, may appear as a D-shaped shadow when viewed in profile, most commonly lying posteriorly or laterally (Fig. 7.26), but when viewed *en face* presents as a much less characteristic opacity of homogeneous density. The D-shaped shadow of an empyema may simulate the appearance of a tumour of pleural or extrapleural origin, as described below. A useful point in differentiation is that an empyema is usually accompanied by a small effusion lying in a normal position at the costophrenic angle. If necessary, an empyema may be differentiated readily from a tumour mass by ultrasound. An empyema may also on occasion simulate a peripheral lung abscess, and CT with intravenous contrast injection can be helpful in differentiation [12].

Fluid may also collect within the fissures to produce an interlobar effusion. When viewed *en face* this may appear



**Fig. 7.26** Large empyema: arrows indicate upper and lower edges of the D-shaped shadow.

as a rounded mass with smooth outline simulating a lung neoplasm. However, when viewed along its length an interlobar effusion has a characteristic spindle or elliptical shape, lying in the position of one of the fissures, and with an entirely smooth margin that reflects its intrapleural location (Fig. 7.27). Such collections are most often seen in heart failure, their rapid disappearance with treatment earning them the name of ‘vanishing tumours’.

Difficulty may sometimes arise in distinguishing between an interlobar effusion in the lower end of the right oblique fissure and middle-lobe collapse. On the lateral view, an interlobar effusion bulges the fissures on each side while in lobar collapse the fissural edges are straight or slightly concave. On the anterior view also, middle-lobe collapse almost always obscures the right heart border while encysted fluid virtually never does so.

### Pleural calcification

The commonest causes of pleural calcification are following pleural tuberculosis, empyema and haemothorax and, in workers who have been exposed to asbestos, pleural plaques or diffuse pleural fibrosis. The pleural calcification following tuberculosis, empyema and trauma is more commonly unilateral than bilateral and may be extensive, encasing the lung (*lung en curasse*). Pleural plaques, which may be calcified or uncalcified, are more commonly bilateral and frequently involve the diaphragmatic pleura: when viewed end-on these may be seen as bands of calcification on the pleural surface; when seen *en*



**Fig. 7.27** Loculated effusion in horizontal fissure showing characteristic spindle shape.

*face* they simulate dripping candle grease or holly leaves beneath the rib cage. In diffuse pleural fibrosis associated with asbestos exposure, calcification is often bilateral and extensive (see Chapter 43).

## Solitary chest lesion

### Extrapulmonary lesions

The chest radiograph may reveal the presence and, with variable clarity, the characteristics of a solitary mass lesion. The first requirement in interpretation is to decide if the lesion is intrapulmonary or arises from pleura, chest wall, mediastinum or diaphragm, since the diagnostic possibilities are largely different for each. A lateral film usually localizes the lesion, although sometimes CT or other investigation is required if detailed characterization of the lesion is sought.

A lesion is intrapulmonary if it is projected in the plane of the lungs on each of two radiographs at right angles to each other and the entire margin is silhouetted by lung. The further characteristics of solitary nodules of pulmonary origin are described below.

A lesion of pleural origin, whether an encysted effusion or tumour, is seen on tangential view to have a broad base on the pleura of the chest wall, mediastinum or diaphragm and to have a smooth rounded or lobulated margin indenting the adjoining lung. Such findings may be seen in encysted pleural effusions (Fig. 7.27), benign tumours (e.g. fibromas) or malignant tumours (e.g. mesotheliomas, pleural secondary deposits). There is usually a small effusion at the costophrenic angle accom-

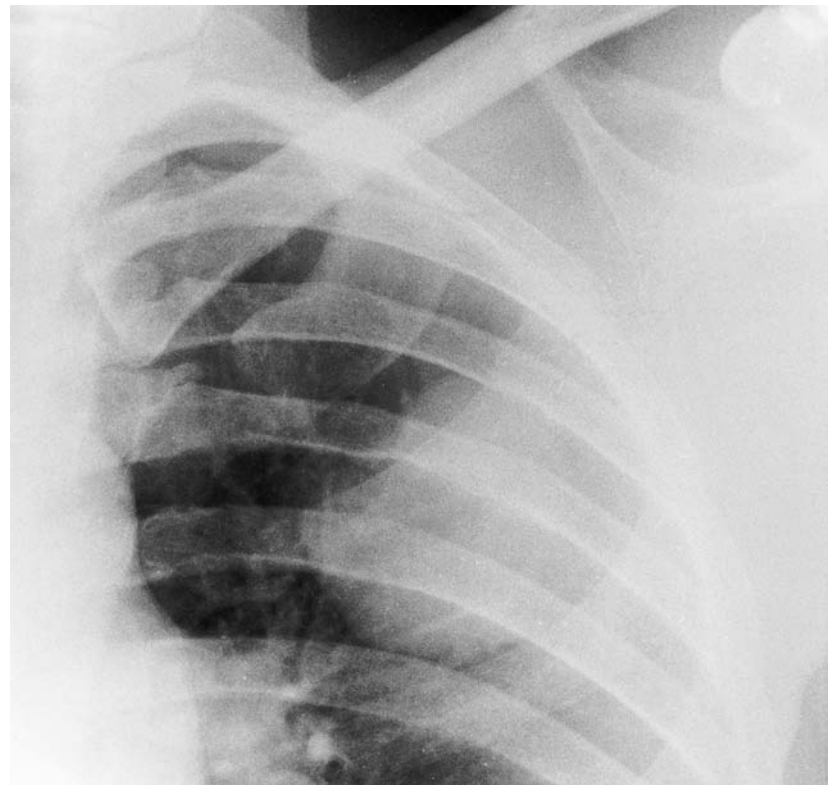
panying the D-shaped shadow of a loculated empyema. When viewed *en face*, pleural-based lesions may appear of relatively low density because they may be shallow, spreading out within the pleura rather than bulging the visceral pleura to any great extent. Typically also the lower margin of a 'hanging' pleural lesion indents, and is silhouetted by, the neighbouring lung to a greater extent than the tapering upper margin, so that the lower margin is more clearly defined than the upper.

Lesions of extrapleural origin have similar characteristics in profile and *en face* to the above, but it may be possible to establish their chest wall rather than pleural origin by noting abnormality of the adjacent ribs or extension of the swelling into the soft tissues of the chest wall. Thus an intercostal neuroma arising from one of the intercostal nerves may produce smooth pressure erosion of the inferior surface of the adjoining rib (Fig. 7.28), such smooth erosion being a manifestation of pressure change over a long period of time. In contrast, malignant primary bone tumours (e.g. sarcomas), blood-borne secondary cancer deposits in bone, lymphoma and plasmacytoma produce bone destruction that may be accompanied by an extrapleural extension of tumour with characteristics as described above. Haematomas due to rib fractures also give rise to extrapleural swellings. In assessing rib fractures, it should be noted whether the margins of the fractures are mineralized and clearly defined, as in simple fractures due to trauma or coughing, or are demineralized

and indistinct, with possible abnormalities of bone texture evident in ribs elsewhere, as in pathological fractures due to malignant bone disease. Certain lesions of extrapleural origin, such as lipomas, give rise to extrapleural shadows with no accompanying rib changes. CT readily demonstrates the low-density fat composition of a lipoma.

A mass of mediastinal origin is visible on an anterior radiograph when it causes a bulge in the normal mediastinal silhouette. As with masses of extrapleural origin, the margin of a mediastinal mass appears rounded and smooth where it abuts lung, any irregularities being smoothed out by the two overlying layers of pleura. A smooth swelling bulging from both sides of the mediastinal contour clearly has a mediastinal rather than pulmonary origin. If the mass produces a rounded swelling of one mediastinal contour only, it may be obvious from the visible portion of such a shadow that the mass is too large and too medially situated to lie in lung and must therefore have an origin in the mediastinum. It is often impossible to determine from an anterior radiograph whether a mediastinal mass is located in anterior, middle or posterior mediastinum. A lateral view is therefore mandatory since the range of diagnostic possibilities differs for these different compartments (see Chapter 49).

Primary lesions of the diaphragm, such as sarcomas, are rare; a much commoner problem is to determine the cause of a high or apparently high hemidiaphragm or portion of diaphragm. When confronted with such a problem, it is



**Fig. 7.28** Large intercostal neuroma associated with smooth erosion of lower border of fifth rib.

useful to consider in turn the structures from which such a shadow could arise (lung adjacent to diaphragm, pleura, diaphragm, subphrenic) and then to consider the pathological processes to which these could give rise (e.g. peripheral lung cancer, subpulmonary pleural effusion, tumour or eventration/paralysis of the diaphragm, diaphragmatic hernia). The features and diagnosis of a subpulmonary effusion as a cause of an apparent high diaphragm have been described above. Diaphragmatic paralysis is recognized on fluoroscopy or ultrasound: the entire hemidiaphragm moves sharply upwards on sniffing and inspiration. In eventration (weakness of the central tendon of the hemidiaphragm) the weak part also moves sharply upwards on sniffing but the margins of the hemidiaphragm usually move in a normal direction, so aiding differentiation from paralysis. Gas, faeces and fluid levels in bowel may be seen in the chest in a diaphragmatic hernia. In cases of doubt a defect of the hemidiaphragm can be further assessed by barium contrast studies, ultrasound or CT.

### Lung carcinoma

On the chest film lung carcinoma may manifest as the tumour mass itself, secondary collapse-consolidation from endobronchial obstruction by the tumour, pleural effusion, or spread giving rise to hilar and mediastinal lymphadenopathy, diaphragmatic paralysis or bone metastases. Lung carcinoma characteristically has a lobulated border, the margin often being spiculated from infiltration of tumour into surrounding lung. It may have a homogeneous consistency or be cavitated due to central necrosis. Such a cavity is usually eccentrically placed and the wall is of varying thickness, where areas of necrosis alternate with areas of continuing growth (Fig. 7.29). This continuing growth may give rise to a lobulated inner border, and the cavity wall typically remains of moderate average thickness (5 mm or more). The differential diagnosis in such cases is from other causes of cavitated lung lesions with walls of similar average thickness, most commonly lung abscesses and infarcts, and less commonly



**Fig. 7.29** Tomogram of large cavitating squamous carcinoma of lung: note the irregularity of the width of the cavity wall.

such conditions as rheumatoid nodules and Wegener's granulomatosis. Tuberculous cavities usually have rather thinner walls (2–3 mm), while the walls of bullae and staphylococcal pneumatoceles are of hairline thickness. Cavitated carcinomas are most commonly of squamous cell origin, either primary or secondary, but cavitation of tumours of other cell types does occur.

### Staging of lung carcinoma

CT is routinely used in the staging of lung cancer and assessment of operability. Dynamic scanning during infusion of intravenous contrast medium is performed to distinguish between normal hilar and mediastinal vascular structures and abnormal tissue from tumour extension. Such findings as mediastinal lymphadenopathy (Fig. 7.30) and unequivocal invasion of the chest wall may be shown. The role of CT in the staging process is as follows.

When CT shows an intrapulmonary tumour and no hilar or mediastinal lymphadenopathy, the patient may proceed directly to thoracotomy without the need for further staging by mediastinoscopy. More commonly, mediastinal nodes up to 1 cm diameter are seen on CT. Such nodes are considered normal since small reactive nodes are common in the general population. Although such small nodes may occasionally be malignant, the patient can again be offered surgery on the basis that preoperative biopsy of such nodes would necessarily be random with a very low chance of detecting malignancy.

CT does not distinguish malignant from inflammatory nodes; however, as a generalization, the larger the mediastinal nodes in patients with lung cancer, the more likely they are to be malignant. Nodes of 3 cm diameter are highly likely to be malignant but even at this size can

represent inflammatory reactive nodes, particularly in patients with pneumonia distal to a central tumour, in those people from areas of the USA in which histoplasmosis is endemic, or in dust-exposed workers in whom large anthracotic or silicotic nodes may be found. Patients cannot therefore be deemed inoperable solely by CT demonstration of enlarged mediastinal nodes; when such large nodes are detected the scan serves as a 'road map' for planning preoperative nodal sampling by mediastinoscopy, mediastinotomy or needle aspiration.

It is difficult to establish from CT whether a tumour is resectable when it lies in contact with vital mediastinal structures. A tumour is likely to be resectable (stage T3a or less) when less than 3 cm lies in contact with the mediastinum, it has less than a 90° circumferential contact with the aorta, or visible fat planes between it and vital mediastinal structures are preserved [13]. However, a contact with the mediastinum of greater than 3 cm or absence of visible fat planes does not necessarily imply inoperability and, since surgery offers the only chance of cure, exploratory thoracotomy should not be discounted in such situations.

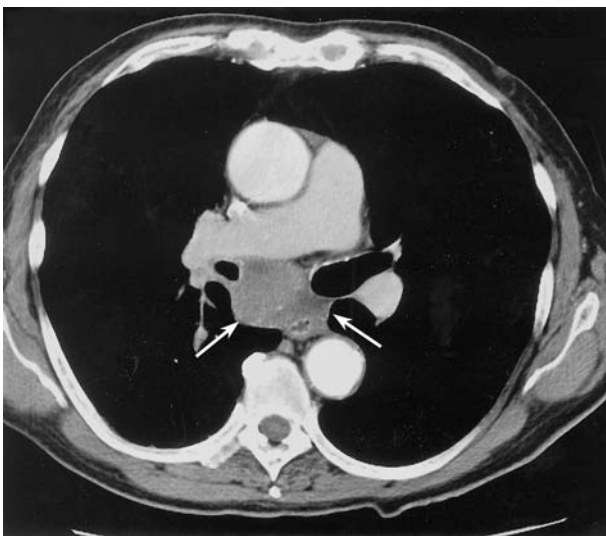
MRI has few advantages over CT in the preoperative staging of lung cancer. It shows enlarged mediastinal nodes and is generally no more accurate in distinguishing between contiguity of tumour with the mediastinum and mediastinal invasion. However, it is superior in identifying involvement of major mediastinal blood vessels and has an advantage in superior sulcus tumours in showing extension to the brachial plexus and subclavian vessels.

### Other solitary lung masses

#### Solitary lung metastasis

A solitary pulmonary metastasis, radiologically simulating a primary lung carcinoma, is occasionally seen in patients with known current or pre-existing carcinoma or sarcoma or other malignancy. The diagnosis is suggested when biopsy of the lesion, by bronchoscopy, fine needle aspiration or other means, reveals tissue corresponding histologically with that of the known tumour elsewhere. More often such metastases are multiple and chest CT usually reveals further deposits that have not been seen on the chest radiograph. However, demonstration of further nodules subpleurally in the peripheral lungs and elsewhere requires cautious interpretation since these may represent coincidental granulomas. This is particularly the case in areas where histoplasmosis is endemic.

If chest CT shows no further lesions and resection is contemplated, it is advisable to examine also the regions of lymphatic drainage of the original tumour by CT, the liver by ultrasound or contrast CT, and to perform a radioisotope bone scan if there is any biochemical abnormality to suggest skeletal spread. Thorough preoperative



**Fig. 7.30** CT of bronchial carcinoma showing large mediastinal node (arrows) between bronchi and oesophagus.

investigation may spare the patient a fruitless attempt at curative resection when there is demonstrable dissemination elsewhere.

### Sarcoma

Primary sarcoma of lung is rare. The diagnosis is suggested by a rapidly expanding mass with a smooth well-defined border. Lung involvement in Kaposi's sarcoma, occurring particularly in patients with AIDS, is diffuse and therefore does not enter the differential diagnosis of patients with solitary mass lesions. The radiological changes of lung Kaposi's sarcoma are bilateral, ill-defined, nodular opacities or rather coarse linear or reticulonodular shadowing. These may be obscured by coincidental *Pneumocystis carinii* or other pneumonia. Pleural effusions and hilar and mediastinal lymphadenopathy may also be present in Kaposi's sarcoma [14].

### Tuberculoma

A tuberculoma, formed of caseous material, may be a manifestation of primary or postprimary tuberculosis. Tuberculomas are most commonly located in the upper lobes, are round or oval, measure 0.5–4 cm or more in diameter, and have smooth, sharply defined margins. They may contain flakes of calcification or may become heavily and almost uniformly calcified. 'Satellite' shadows, small nodules of tuberculous origin in lung adjacent to the tuberculoma, are present in up to 80% of cases, and these and the presence of calcification provide the main clues to the diagnosis.

### Hamartoma

This benign tumour characteristically has a very smooth well-defined margin, reflecting its indolent nature and slow growth, compressing surrounding lung without infiltration. Hamartomas are commonly less than 4 cm in diameter, though occasionally much larger, and growth may be observed on serial films, adding to the difficulty of differentiation from carcinoma. Calcification is present in approximately 25% of cases, the configuration of calcification being described as resembling popcorn (Fig. 7.31). The tumour is usually peripheral and rarely produces endobronchial obstruction, so that distal consolidation is unusual. Areas of contained fat as well as calcification may be evident on thin-section CT, further aiding the preoperative diagnosis [15].

Calcification, which takes time to develop, may be seen in tuberculomas and hamartomas, and usually indicates the presence of a non-malignant lung lesion. However, lung cancers may arise in areas of pre-existing scarring with calcification, so that the presence of calcification needs to be interpreted with caution.



**Fig. 7.31** Large smoothly rounded hamartoma with central 'popcorn' calcification.

### Carcinoid tumour

About 80% of carcinoid tumours are located centrally in major or segmental bronchi, and may present radiologically as the tumour mass itself or, more commonly, as distal collapse–consolidation due to the effects of endobronchial obstruction. When the tumour mass is visible, it is typically spherical or oval in shape with a smooth well-defined border. It is usually 1–4 cm in diameter but can be much larger, and visible calcification is exceptionally rare.

### Mycetoma

A chronic, commonly tuberculous, cavity may become colonized by *Aspergillus fumigatus* or other fungus, the mycelium presenting as an intracavitary fungal ball. An early sign of the presence of the fungus, sometimes visible before there is any change in the cavity itself, is of progressive thickening of the overlying pleura. The fungal mass forms an enlarging ball within the cavity, characteristically with a crescent of air separating it from the cavity wall





**Fig. 7.32** Large post-tuberculous cavity containing aspergilloma: large arrows indicate crescent of air; small arrows show cavitation within part of aspergilloma.

(Fig. 7.32). The fungal ball may itself become necrotic and cavitate, may develop calcification within it, or may discharge its contents into the bronchi with consequent reduction in size or complete disappearance. Recurrent or life-threatening bleeding may occur from the inflamed walls of mycetoma-containing cavities. Surgery is hazardous and carries a real risk of spread of infection to the pleural space; this complication can be managed by embolization of one or more of the feeding bronchial arteries.

## Hila

The normal hilar shadows are formed by the pulmonary arteries and veins only, as previously discussed. Since there are a wide range of normal diameters for the two measurable hilar arteries (the main pulmonary artery on the left and the basal branch of the pulmonary artery on the right), plain film recognition of moderate pulmonary artery enlargement is unreliable. However, in any one individual, changes in pulmonary artery size can be recognized on serial films (for instance, in cor pulmonale or due to vessel plugging in pulmonary embolism).

True hilar enlargement must be distinguished from apparent enlargement, caused by a mass or consolidation in lung in the plane of the hilum. This can usually be resolved in the PA view, as a hilar mass will distort and cause partial loss of the normal D-shaped hilar silhouette while a normal hilar outline will be maintained and projected through a lesion in the overlying lung. A lateral view resolves any uncertainty. It is sometimes difficult to decide if a hilum is enlarged or if an enlarged hilum is due to vascular enlargement, lymphadenopathy or a primary tumour at the hilum. This dilemma is most readily

resolved by contrast CT, which may also demonstrate unsuspected mediastinal lymphadenopathy.

If hilar enlargement due to lymphadenopathy is suspected, a decision should be made as to whether this is unilateral or bilateral, since this influences the differential diagnosis. Thus rounded or lobulated shadows from unilateral hilar, or hilar and mediastinal, lymphadenopathy are likely to arise from a condition affecting the ipsilateral lung. Common causes of this are tuberculosis in young people and lung carcinoma in the middle-aged and elderly. Bilateral hilar, or hilar and mediastinal, lymphadenopathy would most commonly suggest a different group of causes. Important in this group are sarcoidosis and lymphoma, which can both also present with nodular infiltrations in the lungs, and sometimes small-cell carcinoma and lymphatic spread of other malignancies, e.g. colonic carcinoma. However, bilateral hilar node enlargement may be seen as a manifestation of primary tuberculosis in Asian patients. A common practical problem is to determine if a young adult with such appearances has sarcoidosis or lymphoma. A lateral film can be useful, since evidence of marked lymphadenopathy in the anterior mediastinum favours lymphoma, while in sarcoidosis this is rarely seen radiologically although the anterior mediastinal nodes can be pathologically involved in this condition.

Hilar node calcification is usually due to healed tuberculosis. It may also occur in silicosis, where it often assumes an eggshell pattern (see Chapter 54); similar appearances may be seen in sarcoidosis (Fig. 7.33). It has recently been recognized that this may be a sequel to acute hilar node enlargement in individuals with high exposure to quartz [16]. Similar appearances may be seen also after hilar radiotherapy for lymphoma.

## Diffuse lung disease

The range of possible radiological changes in response to disease is limited. A specific diagnosis can rarely be made from the radiographic appearances alone in a patient pre-



**Fig. 7.33** Bilateral eggshell calcification of hilar nodes in a patient with quiescent sarcoidosis. (Courtesy of Dr James Choo-Kang.)

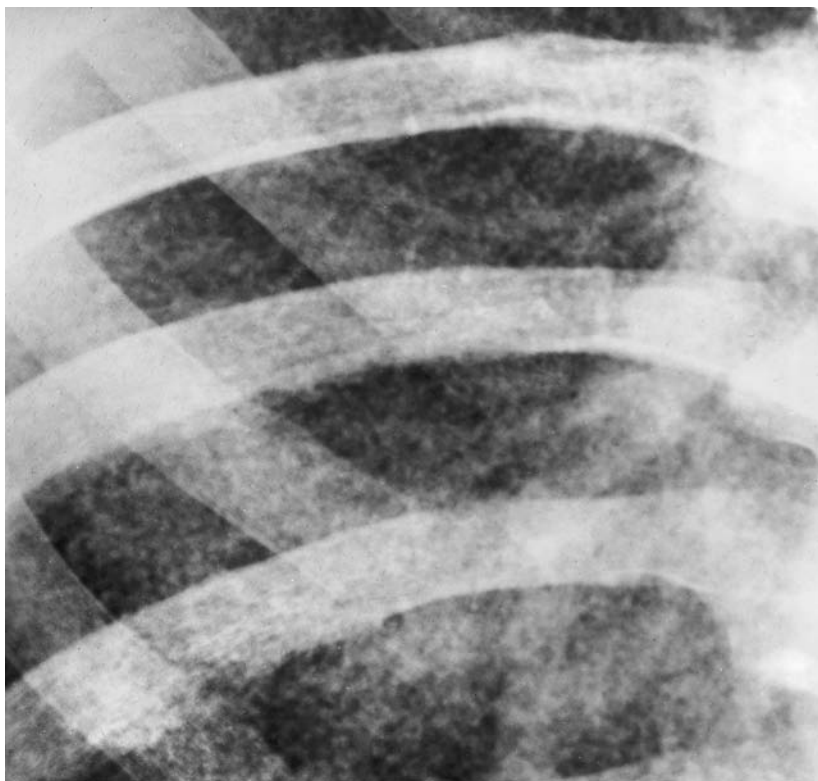
senting with diffuse lung disease. In most instances it is necessary to identify the pattern of radiographic abnormality and to consider the common causes for such appearances in the context of each specific clinical presentation.

In analysing a chest radiograph showing diffuse abnormality, it is necessary to determine the nature of the shadowing (e.g. nodular, reticular, ring shadows, line shadows or a combination), its distribution, its density (soft tissue or calcific), and whether there is involvement of extrapulmonary structures (e.g. rib metastases, hilar or mediastinal nodes). Further information may be provided by HRCT, the principles of which have been described above. The following is a summary of the main patterns of radiographic change and their commoner causes, although these sections are by no means exhaustive and are intended to serve as an introduction to which readers will add their own clinical experience.

### Nodular shadows

When nodular shadows are recognized, it is necessary to consider whether they are well defined or ill defined, their size range and their distribution.

In miliary tuberculosis the nodules are characteristically well defined, 3–5 mm in diameter and, as would be expected from their blood-borne origin, uniformly distributed throughout all three zones of both lungs (Fig. 7.34).



**Fig. 7.34** Uniformly distributed fine shadows of miliary tuberculosis.

Such appearances are also seen in other conditions, including sarcoidosis (when hilar and mediastinal lymphadenopathy may be present), blood-borne carcinomatosis, haemosiderosis and some types of pneumoconiosis, where the nodules tend to show relative sparing of the bases.

Widespread lung opacification, predominantly mid zone or mid and lower zone in distribution, in which nodular shadowing may be fluffier and less well defined than the above may be seen in atypical pneumonias (e.g. varicella, Fig. 7.35), pulmonary oedema and extrinsic allergic alveolitis. A particular diagnosis may be favoured by the presence of associated shadowing of other specific character (e.g. concurrent lymphatic lines in pulmonary oedema).

While some 80 causes have been described for diffuse shadowing produced by small nodules, the diagnostic possibilities diminish when larger nodules can be identified. Thus the nodules of miliary tuberculosis and haemosiderosis do not exceed an upper diameter of 5 or 6 mm. When multiple nodules of up to 1 cm diameter can be identified the commonest cause is carcinomatosis, although other conditions that may produce nodules of this size, generally of moderate number only and sometimes in clusters, include sarcoidosis, Caplan's syndrome and, in immunocompromised patients, fungal infection. With increasing size of lesion, the diagnostic possibilities reduce further. Multiple pulmonary masses of 3 cm diameter or more are usually due to dissemination of malignancy (metastases from carcinoma or sarcoma, Fig. 7.36), but other possibilities include fungal masses in immunocompromised patients, rheumatoid nodules, Wegener's

granulomatosis and progressive massive fibrosis in dust-exposed workers.

The lesions of progressive massive fibrosis are initially small but may enlarge to diameters of 8 cm or more (see Chapter 54). They are commonest in the upper and mid zones and may develop simultaneously yet asymmetrically on both sides. Initially, nodular shadowing due to simple pneumoconiosis is also visible; however, as the lesions enlarge and emphysema develops around them, these may become less obvious until only the fibrotic masses may be seen surrounded by emphysematous lungs. The lesions of progressive massive fibrosis are often irregular at first, although as they enlarge they tend to become oval or sausage-shaped, often with smooth well-defined lateral margins running roughly parallel with the overlying chest wall. Commonly peripheral at first, they migrate medially towards the hilum leaving grossly emphysematous lung between their surfaces and the chest wall (Fig. 7.37).

### Reticular shadowing

In fibrosing alveolitis, the predominant abnormality is characteristically fine reticular shadowing or, if coarser, a honeycomb appearance that is bilateral and maximal at the bases and periphery of the lungs (Fig. 7.38). Small nodules may be seen in conjunction with this reticulation, when the shadowing is described as reticulonodular, and there is often a ground-glass appearance that produces a haze in the affected basal regions. When the fibrosis is advanced, the adjacent heart border and diaphragm become indistinct and shaggy in outline, and the lung



**Fig. 7.35** Acute varicella pneumonia showing bilateral fluffy consolidation.



**Fig. 7.36** Multiple small nodules (arrows) of metastatic carcinoma.



**Fig. 7.37** Progressive massive fibrosis in a coal-miner: there is a background of nodular opacities seen best in the left upper zone with two areas of progressive massive fibrosis (arrows).

volume diminishes. Appearances similar to fibrosing alveolitis occur in asbestosis, rheumatoid lung, scleroderma and due to treatment with many cytotoxic and other drugs.

A number of CT changes have been described in asbestos lung disease and fibrosing alveolitis. In addition to reticular and honeycomb shadowing, subpleural short lines (<2 cm long) may be seen reaching, and perpendicular to, the pleura (Fig. 7.39). These represent fibrosis in the interlobular septa and peribronchiolar fibrosis. Traction bronchiectasis may be seen in advanced interstitial fibrosis, representing bronchial dilatation due to traction

generated by neighbouring lung fibrosis and contraction (Fig. 7.40). Long, curved subpleural line shadows, parallel with and within 1 cm of the pleura, have been described but are non-specific and may be seen also in patients with normal lungs, where they represent bands of linear atelectasis. Areas of increased density in the dependent posterior parts of the lungs can represent true fibrosis or may be due to normal hypoventilation and gravitational blood flow, since they may disappear on rescanning the patient in the prone position.

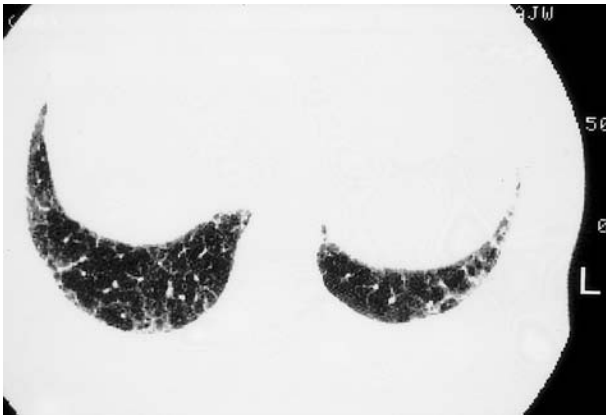
In patients with asbestosis, calcified and uncalcified pleural plaques may be present, seen as local or extensive areas of pleural thickening up to about 5 mm thick, usually bilateral and commonly involving the diaphragmatic pleura as well as the pleura of the chest wall and mediastinal pleura. Coarse band shadows, 2–5 cm long, may be seen extending deeply into the lung along the connective tissue septa or bronchovascular bundles from the surface of plaques. Such band shadows may represent an extension of the pleural fibrotic process into the lungs rather than a primary fibrosis of the lungs.

Pleural adhesions and fibrosis may give rise to round atelectasis, most commonly seen in asbestos workers with pleural plaques but also arising occasionally in other instances of chronic pleural thickening (e.g. after trauma). Round atelectasis represents chronic collapse of a region of lung from hypoventilation beneath an area of rigid thickened pleura. The CT features are of a round, lens-shaped or wedge-shaped opacity in continuity with thickened overlying pleura, with the supplying pulmonary vessels sweeping into the margins of the mass to give a comet-tail appearance (Fig. 7.41).

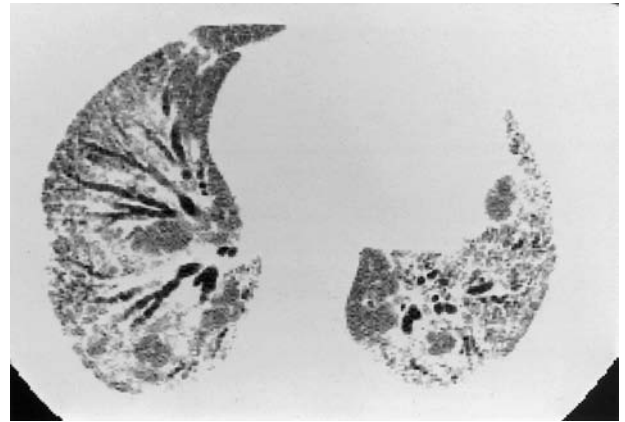
Round atelectasis is commonest in the posteromedial lung bases, produces volume loss of the affected lobe and opacifies uniformly on contrast CT. The main differential



**Fig. 7.38** High-resolution CT of patient with fibrosing alveolitis showing well-developed bilateral fibrosis, most marked peripherally.

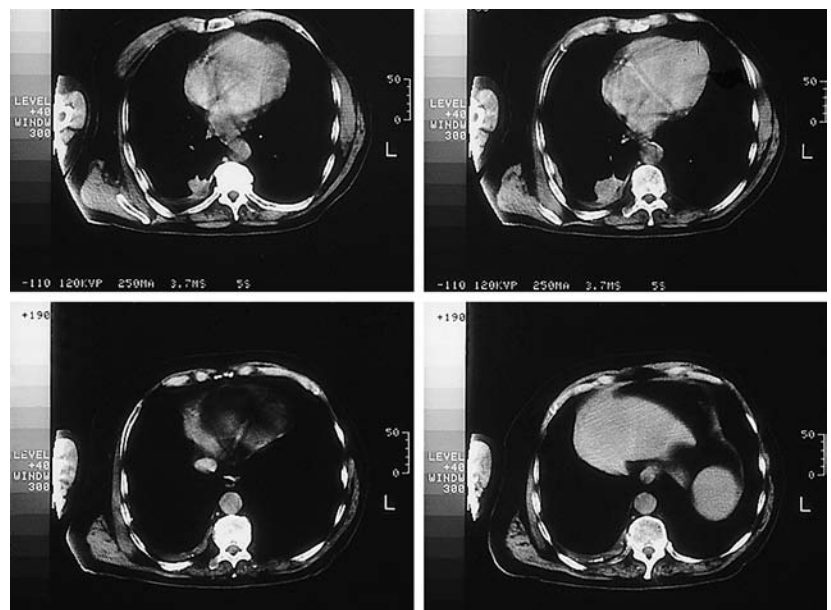


**Fig. 7.39** High-resolution CT of patient with fibrosing alveolitis showing strands of fibrosis extending perpendicularly from pleura into peripheral lung.

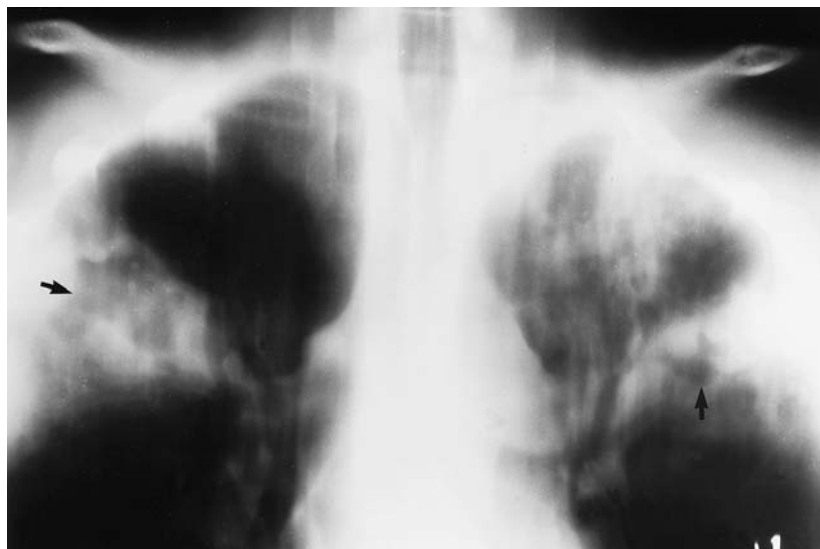


**Fig. 7.40** High-resolution CT in fibrosing alveolitis showing traction bronchiectasis caused by advanced honeycomb fibrosis.

diagnosis is from carcinoma, and the above features assist in the correct recognition of this benign condition. Consideration of the distribution of pulmonary fibrosis is important in differential diagnosis. The above-mentioned conditions are characterized by predominantly basal and peripheral fibrosis as described. In contrast, the fibrosis of chronic extrinsic allergic alveolitis occurs predominantly in the mid zones, with relative sparing of the apices and bases, and is mainly peripheral in distribution [17]. In the early stages of sarcoidosis widespread nodules and thickened interlobular septa may be present, while in the chronic burnt-out phase the fibrosis is predominantly central (in contrast to chronic extrinsic allergic alveolitis) in the upper and mid zones, with coarse honeycombing.



**Fig. 7.41** Round atelectasis in right paravertebral region: note underlying pleural fibrosis and calcification from asbestos exposure.



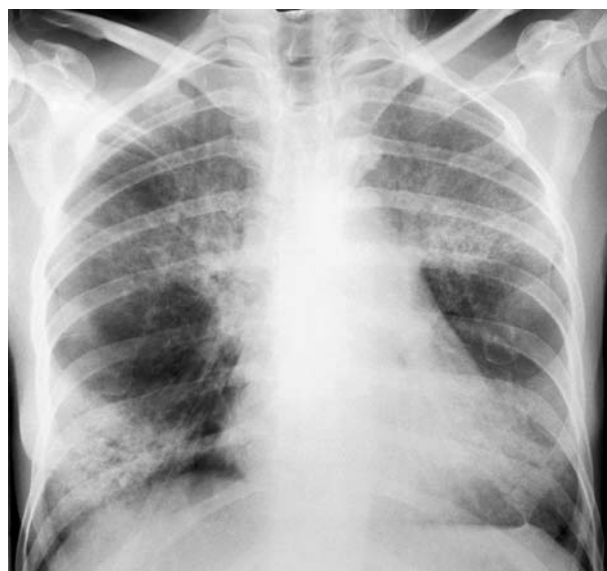
**Fig. 7.42** Tomography of extensive bilateral upper-lobe consolidation with cavitation (arrow) in postprimary tuberculosis.

### **Diffuse shadowing affecting particularly the upper lung regions**

In differential diagnosis the distribution of lung disease can be as important as the characteristics of any abnormal shadowing. Certain conditions that show preferential involvement of the upper regions of the lung deserve mention.

#### **Pneumonic infiltration at the apices**

A small number of conditions produce shadowing that simulates consolidation, sometimes with a visible air bronchogram, predominantly in the upper zones of one or both lungs. Of foremost importance is postprimary tuberculosis, which produces infiltrates particularly in the apical and posterior segments of the upper lobes and apical segments of the lower lobes. Cavitation within the areas of infiltration strongly support this diagnosis (Fig. 7.42). *Pneumocystis* may also present with unilateral or bilateral apical pneumonia (Fig. 7.43), also occasionally with cavitation (Fig. 7.44). Pulmonary eosinophilic pneumonia characteristically produces peripheral and apical infiltrations with sparing of the perihilar regions (Fig. 7.45), so that the radiographic appearance of this condition mimics the mirror image of pulmonary oedema, where the consolidation is central and perihilar. After radiotherapy to the supraclavicular nodes, most commonly 1–4 months after cessation of treatment, consolidation due to radiation pneumonitis may develop in the apices; this clears rapidly with steroid treatment but may progress to fibrosis with appreciable volume loss in the upper lobes.



**Fig. 7.43** Bilateral upper zone and right lower zone consolidation in *Pneumocystis* pneumonia.

#### **Fibroses affecting particularly the upper lobes and apices**

Linear or reticular scarring, with associated volume loss manifest by hilar elevation, tracheal deviation and crowding of the ribs is seen in the late or burnt-out stages of a number of conditions; in many instances there is no radiographic clue to the original causative disease. Fibrosis of this distribution is seen following tuberculosis, sarcoidosis, some forms of silicosis, radiotherapy to the lung apices as described above, in ankylosing spondylitis, sometimes in the late stages of asthma with bronchopulmonary aspergillosis, and following long-term use of the urinary





Fig. 7.44 Cavitation in *Pneumocystis* pneumonia.



Fig. 7.45 Peripheral consolidation characteristic of eosinophilic pneumonia.

antiseptic nitrofurantoin. The lung destruction may cause cavitation, and one or more cavities may in turn harbour an intracavitary mycetoma (see Fig. 7.32).

### Lymphatic (Kerley) lines

A careful search should be made on a chest film showing diffuse infiltration for lymphatic (Kerley) lines. Kerley A lines are seen as sharp line shadows (from hairline to about 1 mm in width and 1–3 cm long) lying midway between the hilum and lung periphery, and mainly point-

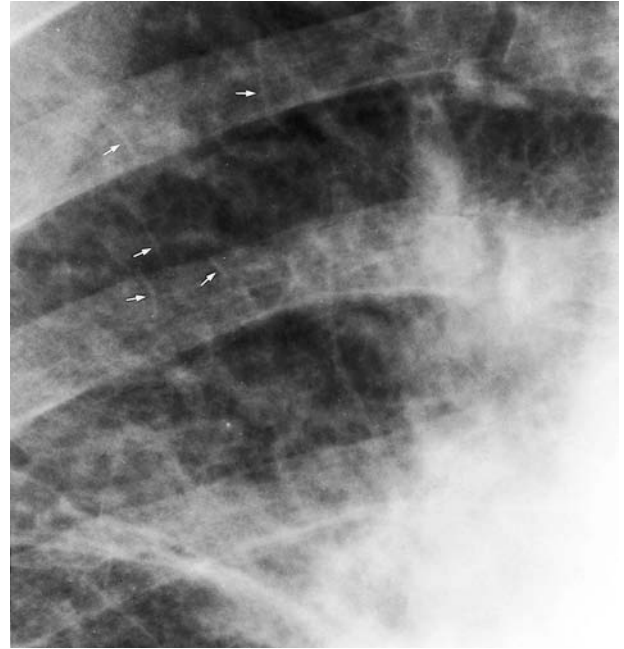


Fig. 7.46 Kerley A lines (arrows)

ing in the direction of the hilum (Fig. 7.46). Kerley B lines are similar thin line shadows, up to 3 cm long, that are seen peripherally and reach to the pleural surface at right angles to the chest wall (Fig. 7.47). Kerley A lines are produced by abnormally enlarged communicating lymphatics between bronchoarterial bundles and veins, and B lines by lymphatics in the interlobular septa. The importance of recognizing Kerley lines as a component of diffuse lung opacification is to limit the diagnostic possibilities. The most common causes are pulmonary oedema from cardiac insufficiency and malignant lymphatic infiltration (lymphatic carcinomatosis); in the one instance they represent lymphatic engorgement and perilymphatic oedema, and in the other malignant infiltration or lymphatic obstruction by proximal tumour. Kerley lines are also seen commonly in pneumoconiosis, where they represent interlobular dust deposition. A few hairlines simulating Kerley lines are seen rarely in pneumonia and sarcoidosis.

### Ring shadows

Multiple thin-walled ring shadows may be a recognizable finding on a chest radiograph showing diffuse disease. They are the cardinal sign of bronchiectasis and represent dilated bronchi seen end-on. They may be accompanied by parallel-line shadows representing the thickened walls of dilated bronchi viewed along their lengths, 'gloved finger' dense branching shadows produced by secretion-filled dilated bronchi, and loss of volume (manifest by crowding of lung markings in the affected region of lung),



Fig. 7.47 Kerley B lines.

hilar and mediastinal displacement and sometimes minor diaphragmatic elevation.

The chest radiograph in bronchiectasis may be normal, but if abnormal frequently underestimates the extent of the disease. HRCT is used for confirmation of the diagnosis and assessment of the extent of known bronchiectasis when a patient is being assessed for surgery. Dilated bronchi are recognized by a 'signet ring' appearance in which the diameter of the bronchus exceeds that of the neighbouring artery (Fig. 7.48). The lobar distribution of

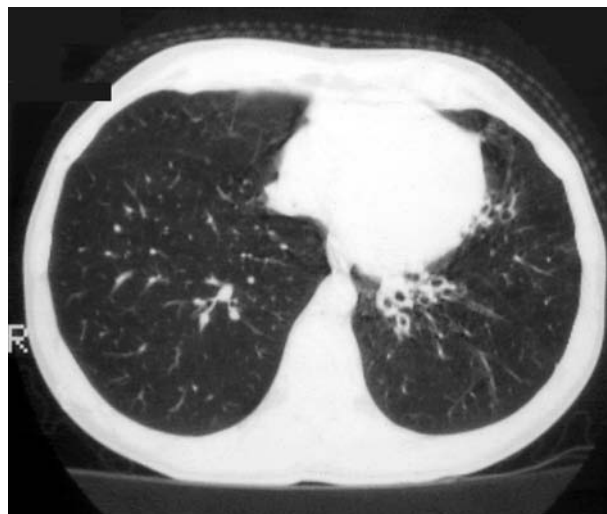


Fig. 7.48 High-resolution CT showing ectatic bronchi in left lower lobe adjacent to cardiac border.

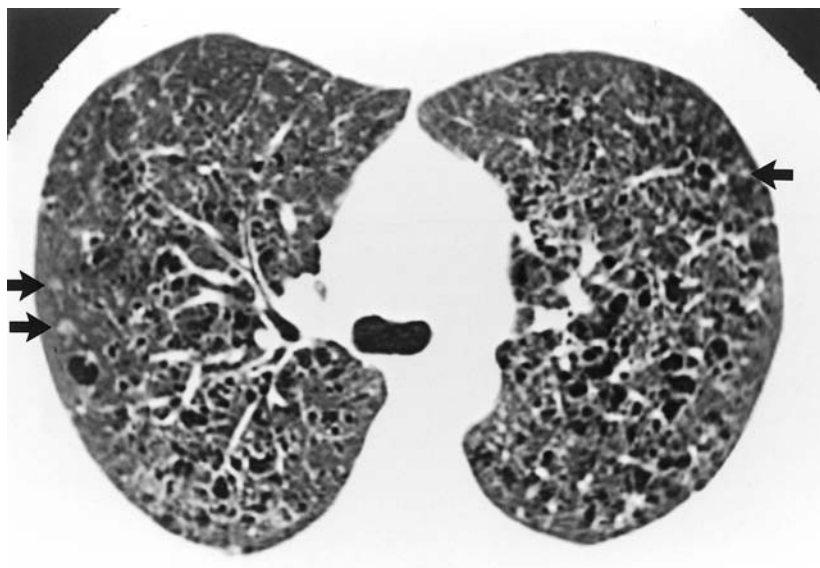


Fig. 7.49 High-resolution CT in Langerhans' cell histiocytosis (histiocytosis X) showing diffuse thin-walled ring shadows. Arrows indicate the granulomatous nodules that develop into cysts.

bronchiectasis is easily assessed by CT, although determination of the segmental involvement may be more difficult due to the anatomical distortion produced by bronchiectasis in affected neighbouring segments and lobes.

CT has replaced bronchography in the assessment of bronchiectasis, and there is currently no ideal bronchographic contrast agent on the market. In two studies comparing HRCT with bronchography, CT was highly sensitive and specific in confirming a diagnosis of bronchiectasis though somewhat less so in recognizing bronchiectasis at segmental level [18,19]. CT is therefore a

satisfactory and sensitive examination in confirming a diagnosis of bronchiectasis, and is appropriate for determining that a patient is unsuitable for surgery when widespread bilateral disease is shown. However, it is inferior to bronchography in demonstrating the segmental extent of bronchiectasis in patients who are considered suitable for surgery.

In cystic fibrosis the ring shadows of bronchiectasis are seen particularly in the upper lobes. Multiple thin-walled ring shadows may also be shown, particularly on CT, in Langerhans' cell histiocytosis (Fig. 7.49) and lymphangioleiomyomatosis.

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# MINIMALLY INVASIVE DIAGNOSTIC PROCEDURES

DOUGLAS SEATON

This chapter describes a number of largely diagnostic procedures that have been found to be useful in the practice of respiratory medicine. The content is not exhaustive because some procedures that have diagnostic implications are discussed in other chapters and have been omitted from the text that follows. Diagnostic imaging is dealt with in the preceding chapter.

## Bronchoscopy

Endobronchial examination was first carried out in the last decade of the nineteenth century for the purpose of removing inhaled foreign bodies, and as long ago as 1904 a rigid bronchoscope with provision for suction and illumination came into use [1,2]. About 60 years elapsed before the fiberoptic instrument was introduced into clinical practice, being first passed through a rigid bronchoscope and later through a nasopharyngeal airway or directly through the nose itself [3–5]. The realization that these instruments could be used without the assistance of an anaesthetist soon led to their widespread uptake by respiratory physicians for a variety of diagnostic and, at a later stage, therapeutic purposes.

### Indications (Table 8.1)

#### Diagnosis of lung cancer

The commonest indication for bronchoscopy is to confirm or exclude a diagnosis of lung cancer. A small isolated episode of haemoptysis in a young non-smoker is likely to be due to acute bronchitis and need not lead to endoscopic examination [6]. However, young patients with haemoptysis who began smoking at an early age should be considered candidates for bronchoscopy, as should patients with haemoptysis in whom any of the following three criteria of increased risk are fulfilled: (i) age exceeding 40 years; (ii) intermittent haemoptysis lasting more than 1 week; and (iii) any abnormality on the chest radiograph [7]. A negative bronchoscopy in the presence of persisting

haemoptysis may lead to the need for high-resolution CT (HRCT) of the lungs to exclude a small area of otherwise occult bronchiectasis and also a competent examination of the nose and throat by an otorhinolaryngologist to exclude a source of bleeding in those areas that respiratory physicians tend to pass the bronchoscope through in the shortest possible time.

#### *Cough*

A persistent cough, without haemoptysis, in a previously well patient with chest radiographic features that are either normal or unsuggestive of neoplasm is usually due to some inflammatory cause, such as sinusitis, asthma, bronchial hyperreactivity following acute bronchitis, or gastro-oesophageal reflux. It should be possible to reach such diagnoses from the history, physical examination and non-invasive investigations, including lung function testing, without recourse to bronchoscopy in the great majority of patients; methacholine (or other bronchial challenge) testing and oesophageal pH monitoring is undertaken in selected cases [8,9]. When, despite the foregoing, no satisfactory explanation for an intractable cough can be found, bronchoscopy is indicated in order to exclude an underlying tumour, particularly if the patient smokes tobacco.

#### *Abnormal chest radiograph*

Bronchoscopy is also indicated when the chest radiograph is abnormal, showing either an opacity consistent with a lung tumour or changes suggestive of bronchial obstruction, such as the appearance of early volume loss or undoubted collapse, unresolved pneumonia or hemidiaphragmatic paralysis, raising the possibility of phrenic nerve involvement by tumour [10]. The physician should be reticent in ascribing volume loss to previous radiotherapy for carcinoma of the breast as these neoplasms may metastasize endobronchially, sometimes years later.

**Table 8.1** Principal uses of fiberoptic bronchoscopy.

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<i>Diagnostic</i>
Diagnosis of lung cancer
Chest radiographic abnormality
Haemoptysis
Persistent or recurrent cough
Paralysed vocal cord
Positive sputum cytology
Staging of lung cancer (see Chapter 41)
Diagnosis of diffuse lung disease
Identification of infecting agents
Immunocompromised host
Immunocompetent host
 <i>Therapeutic</i>
Insertion of endotracheal tube
Tamponade for bleeding*
Foreign body removal*
Aspiration of secretions*
Relief of tracheobronchial obstruction
Laser therapy
Insertion of stents
Brachytherapy

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\* May be better carried out with rigid-tube bronchoscope.

### ***Vocal cord paralysis***

The finding of a paralysed vocal cord calls for careful endoscopic inspection of the bronchial tree, whether or not posteroanterior and lateral chest radiographs are normal [11]. Normal bronchoscopic findings may need to be followed by CT examination of the mediastinum, extending up to the neck in order to follow the course of the corresponding recurrent laryngeal nerve. The vocal cord palsy may be regarded as idiopathic once these investigations have been completed with negative results.

### ***Positive sputum cytology***

Occasionally expectorated sputum is found to contain neoplastic cells on cytological examination even though the chest radiograph itself provides no clear localizing features [12]. The oropharynx and larynx should be examined by an otolaryngologist in such cases, as the cells have been picked up by sputum *en passant*. If this examination is normal, bronchoscopy may find tumour, usually squamous cell carcinoma, that is often central, although the author has also seen peripheral lesions develop in this situation. When bronchoscopy is negative it is usual practice to repeat the examination at 3-monthly intervals. For several years some workers have advocated a meticulous examination of the bronchial tree down to subsegmental level with a small-diameter endoscope and the application of fluorescent bronchoscopic techniques using intravenous substances (such as haematoporphyrin derivative) that may be taken up by tumour and which fluoresce

under an appropriate light source, although the technique has not yet reached the stage of widespread practical application [13,14].

Even when a clinical diagnosis of lung cancer is virtually certain in terms of radiographic and other findings, bronchoscopy is still indicated, unless the patient is *in extremis*, in order to obtain histological confirmation of whether the tumour is primary non-small-cell or small-cell lung cancer or metastatic and to assist in the process of staging (see Chapter 41). Without this information, the good ship 'clinical conviction' will sometimes founder on the rocks of reality!

### **Diagnosis of diffuse lung disease**

Transbronchial lung biopsy, carried out through the fiberoptic bronchoscope, is one of a number of possible methods by which lung tissue may be sampled, and the respective merits of this technique compared with various forms of needle, trephine, thoracoscopic or open biopsy are discussed later.

The decision about whether an invasive procedure such as transbronchial lung biopsy should be used has to be weighed up in terms of risk and benefit. The risks are well known and are spelt out in a section that follows. Although relatively small, they may be unjustifiable when the diagnosis can be made with near certainty without histology. Sarcoidosis is sometimes a case in point when it presents with a diffuse pulmonary infiltrate occurring in an asymptomatic, immunocompetent patient with bilateral hilar lymphadenopathy, absent crackles on auscultation and normal measurements of lung function. Histological confirmation could be obtained several weeks later and without risk to the patient by means of a Kveim test. On the other hand, the same disease may present with an identical pulmonary infiltrate without hilar lymphadenopathy in a patient with an impaired gas transfer factor and worsening exertional dyspnoea. Therapeutic action is then urgently called for and diagnostic confirmation cannot wait. Although an argument can be made for the 'blind' use of corticosteroid therapy in such situations, in that the prognosis of many such diffuse lung diseases is related more closely to response to steroids than to histological appearance, it is nevertheless standard practice to obtain tissue in these circumstances, a procedure likely to put the diagnosis on a firm footing and that should at the very least avoid the unusual but potentially disastrous confusion of sarcoidosis with miliary tuberculosis.

The specimens obtained by transbronchial lung biopsy are necessarily small and the diseases that lend themselves best to diagnosis by this technique are those with a highly characteristic histological pattern that is repeated diffusely throughout the lungs so that there is little room for sampling error. These include relatively common

conditions such as sarcoidosis and lymphangitis carcinomatosa and rarer conditions such as eosinophilic pneumonia and pulmonary alveolar proteinosis, the latter being characterized by the finding of a strongly eosinophilic and typically periodic acid–Schiff (PAS)-positive granular material. Lymphomatous or leukaemic infiltration is less easy for the histologist to identify on small biopsies but may sometimes be suggested. Appropriate staining may also identify particular pathogens, such as *Pneumocystis carinii* in the immunocompromised host (see Chapter 52) or mycobacteria in the caseating granulomas of miliary tuberculosis.

Small transbronchial samples may be insufficient to establish a definite histological diagnosis in diffuse lung disease such as cryptogenic fibrosing alveolitis (interstitial pulmonary fibrosis). The material sampled in such cases may be found to contain non-specific inflammatory or fibrotic changes that may be described by the histologist as being 'consistent with' rather than 'diagnostic of' fibrosing alveolitis. Such a report may provide little additional practical information as the clinician may well have been able to reach such a provisional diagnosis on the basis of the history, physical signs, lung function findings and the result of HRCT of the lungs, and these patients would be likely to receive treatment with a trial of high-dose corticosteroids anyway. A larger piece of tissue is diagnostically more reliable than transbronchial biopsies in providing a definitive diagnosis in such conditions where the histology may be either 'difficult' on a small sample or distributed in a patchy fashion, so that sampling error may occur. Open or thoracoscopic lung biopsy may therefore be of greater value in cryptogenic fibrosing alveolitis if histology is considered essential, although often it is not and in each centre the expertise and interests of local personnel are likely to be important factors in determining the most appropriate diagnostic route [15–17].

Some, but not all, transplant centres use so-called 'surveillance bronchoscopy' with transbronchial lung biopsy in order to detect the development of obliterative bronchiolitis in lung transplant recipients [18,19].

### Identification of infectious agents

The fibreoptic bronchoscope may be used to obtain microbiological evidence of lower respiratory tract infection by the examination of (i) aspirated bronchial secretions, washings or lavage fluid, (ii) endobronchial brushings or (iii) transbronchial lung biopsies. Other techniques, of varying degrees of invasiveness, used to sample the lower respiratory tract for evidence of infection include percutaneous needle or trephine biopsy of the lung, open or thoracoscopic lung biopsy, and transtracheal aspiration. The place of each different approach is considered later in this chapter. It is stressed that most bacterial infection of the lung can be treated without recourse to such procedures,

antibiotics being selected empirically on the basis of probability with possible modification in the light of response or subsequent microbiological data (see Chapter 13).

Such empiricism is more likely to fall down in patients whose immune systems are compromised by coexisting disease. Peculiar difficulties are created in this group by the wide variety of unusual organisms that may be responsible for pneumonic infection, which commonly defy diagnosis by ordinary means and may therefore elude effective treatment unless special efforts are made to identify the responsible microbes. One such opportunist is the fungal organism *P. carinii*, which may be successfully diagnosed by fibreoptic bronchoscopy using bronchial lavage, transbronchial biopsy with touch preparations and bronchial brushings, these procedures demonstrating cysts in bronchial secretions or lung tissue (see Chapter 52) [20,21]. These methods may yield positive results in patients with AIDS even if the chest radiograph is normal, and it has been recommended that efforts to confirm the diagnosis should be made in such patients when symptoms suspicious of respiratory infection are accompanied by a fall in the single-breath carbon monoxide transfer factor, a low  $\text{SaO}_2$  on exercise and an increased alveolar–arterial oxygen gradient [22,23].

Cytomegalovirus (CMV) may also be detected by transbronchial lung biopsy in immunocompromised subjects either by the demonstration of intranuclear and intracytoplasmic inclusion bodies in lung tissue or by the culture of CMV from lung tissue [22]. A wide variety of other organisms may be isolated from bronchoscopic sampling using appropriate microbiological techniques, including *Mycobacterium tuberculosis*, atypical mycobacteria and fungi [22]. Invasive aspergillosis has been diagnosed following examination of lavage or transbronchial lung biopsy material, although definite confirmation sometimes requires an open or thoracoscopic procedure [24–26]. Coccidioidomycosis is also detectable by transbronchial lung biopsy [27]. Tuberculosis may be diagnosed in patients who are not producing sputum by direct smear or culture of material obtained from bronchial brushings, transbronchial biopsy or bronchial lavage fluid [28,29]. The finding of more usual bacterial pathogens must be treated with caution as these may be picked up from the nasopharynx during the passage of the bronchoscope, as has been shown in normal volunteers [30]. Techniques have been developed in which the bronchoscopic brush is protected in order to avoid such contamination [31]. Microbiological aspects of sampling via the bronchoscope are discussed in a later section.

### Bronchoalveolar lavage

The fibreoptic bronchoscope acts as a suitable conduit for the injection and aspiration of saline in bronchoalveolar lavage (BAL), a procedure discussed later in this chapter.



## Bronchography

The fiberoptic bronchoscope became useful as a means of facilitating bronchography in patients in whom bronchiectasis (see Chapter 28) was suspected. It had the advantage of permitting more selective application of contrast medium than could be achieved by other methods [32,33], but has been superseded by HRCT of the lungs, following which propylidone has been withdrawn from the market. Although bronchography is still possible with contrast media such as Iotrolan 300 [34], it is now rarely performed.

## Therapeutic applications

Although primarily used for diagnostic purposes, fiberoptic bronchoscopy has a number of therapeutic applications.

- 1 Insertion of an endotracheal tube for general anaesthesia in patients in whom extension of the neck may be dangerous (e.g. atlanto-axial subluxation in rheumatoid disease), the tube being 'piggy-backed' over the flexible bronchoscope once it has been inserted [35].
- 2 Tamponade of endobronchial bleeding, either with the end of the bronchoscope itself or by using a Fogarty or other purpose-designed balloon catheter (see below) [36].
- 3 Removal of foreign bodies [37,38].
- 4 Aspiration of secretions in acute inflammatory lobar atelectasis where physiotherapy has proved unsuccessful in achieving this end [39]. It has to be said that the rigid bronchoscope is better suited to the last three applications as a result of its stronger suction capability and the fact that its large channel also permits the easier removal of inhaled foreign bodies and the packing of a bleeding bronchus under direct vision [40].
- 5 Relief of tracheobronchial narrowing by:
  - (a) laser treatment, which may be administered through the channel of a fiberoptic or rigid bronchoscope in the palliative treatment of lung cancer (see Chapter 41), this having been reviewed elsewhere [41,42];
  - (b) placement of stents [43,44]; and
  - (c) delivery of endobronchial radiotherapy, a technique known as brachytherapy [45,46].

Although external beam radiation is usually brought to bear for the palliative relief of symptoms caused by malignant involvement of the trachea or a large bronchus, this is not always possible as the narrowing may be critical so that any additional oedema after treatment may make a bad situation worse. In this predicament the options that may be available to the physician include (i) the abandonment of resuscitative measures and the use of morphine, (ii) the temporary use of a low-density helium-oxygen (4:1) mixture to reduce the work of breathing, or (iii) intervention by an expert in surgical disobliteration (e.g. diathermy resection), stenting, laser treatment or

brachytherapy. A number of large centres are becoming experienced in treating this difficult group of patients by a combination of these measures [47] and the results of controlled trials of one regimen versus another may yet be forthcoming [41].

Patients who have been stented require close follow-up and are likely to require repeated bronchoscopies. Stents may become obliterated by inspissated respiratory secretions, granulation tissue or continued growth of tumour and they occasionally migrate or erode through the tracheobronchial wall. Wire stents are usually 'permanent', whereas those that have an external siliconized plastic surface are potentially removable and replaceable. The accurate placement of stents may be undertaken by an experienced thoracic surgeon using the rigid bronchoscope and general anaesthesia [48], although expandable metal stents are being inserted with increasing frequency by physicians using local anaesthesia [49].

Surgical disobliteration or laser therapy may produce rapid palliation of the effects of large airway narrowing, although not without risk. However, neither approach can be used if the narrowing has arisen as a result of extrinsic compression or if the problem is one of an intramural 'shelving down', in which case stenting or brachytherapy may be more appropriate, the latter treatment having some effect on extramural tumour but being slow in delivering benefit, the response taking about 1 month. Brachytherapy itself carries a risk of fatal haemoptysis, the average figure from the literature being about 8% [41].

## Procedures for fiberoptic bronchoscopy (Table 8.2)

Having determined an indication for bronchoscopy, the patient's consent is obtained. This is more likely to be forthcoming if a reassuring explanation of the painless nature of this routine examination is given in terms that the patient will understand and if questions are invited. Such verbal explanation may be reinforced by a sensitively worded written pamphlet, the contents of which the patient may read at leisure. Bronchoscopists who hand out such leaflets without having read them themselves for a

**Table 8.2** Fiberoptic bronchoscopy: diagnostic methods.

Visual inspection
Proximal endobronchial sampling
Bronchial washing
Forceps
Brush
Curette
Needle aspiration
Extrabronchial and distal sampling
Transbronchial lung biopsy
Transbronchial needle aspiration
Bronchoalveolar lavage

decade or more are occasionally embarrassed when the patient subsequently points out a deviation from the script.

Most bronchoscopies are carried out electively on a day-case basis, the patient being asked not to eat or drink for 4–6 h beforehand, so that for an afternoon procedure a light breakfast is permissible. Advance provision must be made to get patients home safely as the law is unlikely to regard them as being capable of safe driving if they have received sedative medication.

### Supplemental oxygen

It is usual to give the patient supplemental oxygen via nasal cannulae and to monitor the saturation by pulse oximetry. If it is decided, at an earlier assessment, that a high concentration of inspired oxygen is likely to be needed, this can be achieved using a high flow mask with a reservoir bag, a hole having been made in the front of the mask beforehand using a leather punch or other suitable tool. The patient can then breathe high-flow oxygen through nasal cannulae while the instrument is being passed, after which the reservoir mask may be 'rail-roaded' down the shaft of the instrument and into place on the patient's face.

### Premedication

Intramuscular atropine is usual, although its use has been based more on long-standing practice than substantiated evidence of clinical benefit, so that its routine application has been questioned [50]. The traditional adult dose is 0.6 mg. The anticholinergic action of atropine may reduce secretions in the airways as well as diminishing the chance of reflex vasovagal phenomena such as bronchoconstriction and bradycardia [51].

### Sedation

Most bronchoscopists give their patients sedation [52], although whether this is necessary has been the subject of debate for many years [53,54]. Morphine (half-life about 2.5 h) may be given 20–40 min before the procedure in order to produce a sense of euphoria, reduce anxiety and suppress coughing. The standard adult dose is 10 mg intramuscularly, although this may be reduced to 5 mg in small or elderly patients.

Other advocates of narcotic agents prefer the short-acting opiate alfentanil (half-life about 1.5 h) [55], this being given intravenously either before or after the application of topical anaesthesia to the upper respiratory tract [56]. Some studies suggest that this agent is a better cough suppressant than other sedatives, including intramuscular morphine (as papaveretum) [57], intravenous diazepam (as Diazemuls) [57] and midazolam [58].

Many bronchoscopists prefer to use an intravenous benzodiazepine [52]. As well as sedating, these compounds produce an amnesic effect that, paradoxically, may be greater when the more rapidly metabolized midazolam (half-life about 2.5 h) rather than diazepam (half-life about 20 h) is used [59]. It should be borne in mind that this effect may prevent the patient from retaining information given after the bronchoscopy has been completed. One practice is to give 2.5 mg midazolam by slow intravenous injection over about 30 s (1 mg for those aged over 70 years), giving further small increments after 1–2 min until the patient feels drowsy. Diazepam, being half as potent [60], may be given as an alternative in similar fashion at about twice the dose, i.e. 5 mg initially for the younger and 2 mg for the older patient. An average total dose for midazolam in a younger patient might be about 5 mg and for diazepam 10 mg, although requirements are variable and some bronchoscopists use high doses to produce complete amnesia [60,61]. One group found that 2 mg lorazepam taken orally 1.5 h before bronchoscopy reduced the patient's perception of the unpleasantness of the procedure the next day compared with placebo [62].

Any sedative is better omitted altogether if the forced expiratory volume in 1 s ( $FEV_1$ ) is less than 1 L, if the  $Paco_2$  is raised, or indeed if the patient's respiratory function gives any cause for concern. It is common experience that elderly patients tend to display greater equanimity when subjected to bronchoscopy than do some young adults, who as a group may be more likely to benefit from sedation. It is the author's practice not to sedate any patient routinely but to offer sedation to patients under the age of 65 years if their ventilatory capacity is near normal. It is as well to be more selective in other groups and to omit sedation altogether in the very elderly and frail patient. Extreme caution is advised if sedation is given to elderly patients and it should always be remembered that it is entirely possible to carry out fiberoptic bronchoscopy without any sedation at all [53,63], many patients responding adequately to the explanation and reassurances of an experienced operator and the endoscopy staff.

Should respiratory depression occur with any of the opioids, their effect can be rapidly antagonized by 100–200 µg of naloxone hydrochloride as an intravenous bolus repeated with 100 µg every 2 min until the desired response is achieved. Up to 10 mg may be given safely but such high doses are unlikely to be necessary and, if approached, another cause for the patient's condition should be considered. The half-life of naloxone is 60–90 min and patients who have responded should continue to be closely monitored if a longer-acting opiate has been used [64].

The benzodiazepines are effectively antagonized by intravenous flumazenil, the usual dose being 300–600 µg. It has a short half-life of about 1 h so that it may also need

to to be repeated if resedation develops [64], being given as 200 µg over about 15 s initially, thereafter at 100-µg dose increments at 1-min intervals to a maximum of 1 mg. Flumazenil itself may produce feelings of nausea and agitation [65].

Withdrawal reactions may occur if either of these antagonists are used in patients who are chronic takers of opiates or the more commonly prescribed benzodiazepines. Some endoscopists use antagonists routinely at the conclusion of their examination [66]. Adequate endoscopy staff levels are essential if patients who have received sedation are to be adequately monitored while recovering from bronchoscopy and proper facilities for resuscitation should be readily available.

### Topical anaesthesia

The great advantage of fiberoptic bronchoscopy is that it can be carried out under topical anaesthesia. In earlier days rigid bronchoscopy was similarly applied, this being an unforgettably unpleasant procedure for most patients and one that is nowadays obsolete.

A 10-mg benzocaine lozenge may be given to the patient to suck at the time of premedication. About 20–40 min after premedication the patient is usually transferred to a couch, although the procedure may be carried out equally well in a hospital bed from which the head has been detached. The patient is propped comfortably in a semi-recumbent position by means of a foam wedge and/or pillows. Many operators prefer to work from the front as this enables them to talk to their patient more comfortably. Those who prefer to pass the instrument standing behind the patient find it easier if the patient is relatively flat, sup-

ported by only two pillows. An adjustable fluoroscopic table is needed if X-ray screening is to be used.

There are various ways in which the topical anaesthetic may be delivered. One method is to spray a 4% lidocaine (lignocaine) solution into both nostrils using an atomizer, with the advice to the patient to 'sniff it back' and a warning about its foul taste. Alternatively, the nasal mucosa may be anaesthetized with 2% lidocaine gel containing 20 mg/mL, about 5 mL being applied directly from the tube into each nostril (200 mg) using the conical applicator supplied by the manufacturer; there is some evidence to suggest that this is less unpleasant for the patient [67] and that plasma levels may be lower when the gel is used [68].

A 4% lidocaine solution may also be sprayed directly into the patient's mouth in the direction of the fauces. The patient is then asked to say 'aaah' in order to elevate the soft palate and two or three metered-dose sprays of 10% lidocaine (20–30 mg) may be directed at the cords using a removable and sterilizable angled nozzle (Fig. 8.1). An accurate aim usually produces coughing, at which point the spray is rapidly withdrawn from the mouth. It is the author's practice to further anaesthetize the cords and upper respiratory tract with about 5 mL of 4% lidocaine solution (200 mg) given by transcutaneous cricothyroid injection. The cricoid cartilage is usually easily palpated by the operator's forefinger with the patient's neck slightly extended, it being the first prominence above the cartilagenous tracheal rings. Immediately above it and below the next prominence, which is the thyroid cartilage, is a shallow depression that marks the cricothyroid membrane. This area is wiped with an alcohol swab and the patient warned that 'the voice box is going to be numbed'.



**Fig. 8.1** Some equipment used in fiberoptic bronchoscopy. Left to right: atomizer (local anaesthetic), bite block, lidocaine metered-dose spray with angled nozzle, slides and screw-top jar for fixative, specimen trap for suction line.

The patient is requested not to swallow (in order to avoid movement of the larynx) and warned that coughing is likely but is asked to try to hold the cough for a few seconds. The patient is then asked to 'lift up your chin and look at the ceiling' in order to achieve extension of the neck and a 23-gauge needle attached to the loaded syringe is smoothly inserted in the midline. If correctly positioned it will meet no resistance and withdrawal of the plunger will be rewarded by bubbles of air indicating a proper intratracheal position. The local anaesthetic is then injected as rapidly as possible. A small proportion of patients can contain their cough until the syringe has been emptied but most cannot. As soon as the cough occurs the needle is rapidly withdrawn to avoid trauma. If less than 3 mL has been injected, then the remainder can be injected by reinserting the needle, coughing being less frequent with the second application. Many bronchoscopists prefer to anaesthetize the cords under direct vision from above while advancing the bronchoscope ('spray as you go'), while others have delivered the lidocaine using a nebulizer and pump [69]. Any of these methods is satisfactory and a matter of personal preference; in the author's experience, cricothyroid anaesthesia is the least unpleasant for the patient and there is some evidence to suggest that it results in less patient discomfort and coughing [70,71].

Serious adverse effects from the use of lidocaine at bronchoscopy appear to be unusual but it should be used sparingly as epileptic seizures have been reported [72]. The safe dose for infiltration is said to be 3 mg/kg [64], although much higher levels than this were routinely used topically according to a survey of British bronchoscopists [52], the average dose given being about 350 mg. A significant quantity is presumably removed through the suction channel of the bronchoscope. That which is not is absorbed from both mucosal surfaces and the gut, in which case first-pass metabolism occurs in the liver. Absorption is particularly rapid from the lower respiratory tract, the pharmacokinetics at this site apparently approaching that following intravenous administration [72]. Peak levels may occur up to 1.5 h after its use and toxicity may occur at plasma levels of 5 µg/mL or more [64]. The amount of lidocaine used should be kept to a minimum in patients with liver disease [72]. Topical cocaine solution, although a good anaesthetic agent, is less commonly used than lidocaine and is more likely to produce cardiovascular side-effects, including dysrhythmias [73,74].

### Passing the bronchoscope

Having anaesthetized the upper respiratory tract, the shaft of the bronchoscope is well lubricated with 2% lidocaine gel and is advanced into a nostril under direct vision, being passed along the floor of the nose through the

widest visible opening between the turbinates, which project inwards from the lateral margin of the nasal cavity. Gentle pressure is all that is required if the space is adequate and the instrument should never be forced. If the bronchoscope does not advance easily it should be withdrawn and the other nostril tried. In a significant proportion of patients, the nasal approaches are too narrow to permit the bronchoscope to pass, in which case the patient is asked to hold a bite block (see Fig. 8.1) between the teeth or gums and the instrument is introduced into the oropharynx through it. It is necessary for the bronchoscopist's assistant to gently hold this in place with two fingers spread on either side of the orifice in order to avoid damage to the shaft should the bite block become displaced, which might allow the patient to bite directly into the bronchoscope. As the instrument is advanced, the tip is flexed downwards and the epiglottis and larynx come into view (Fig. 8.2). The position and movement of the vocal cords with respiration is noted and the patient is asked to say 'eeee', so that full apposition of the cords can be observed and vocal cord paralysis confirmed or excluded.

A unilateral paralysed cord lies in an 'intermediate' position and does not fully adduct. The left cord is involved more often than the right because of its longer course through the mediastinum. Involvement of the right recurrent laryngeal nerve by tumour implies that the lesion extends into the neck. Lung cancer is the commonest cause in respiratory practice but a diagnosis of idiopathic vocal cord paralysis [75] is sometimes reached following normal bronchoscopy and negative radiographic procedures, including CT of the mediastinum and neck. Bilateral vocal cord paralysis produces a narrow glottic chink and laryngeal stridor, usually occurring as a

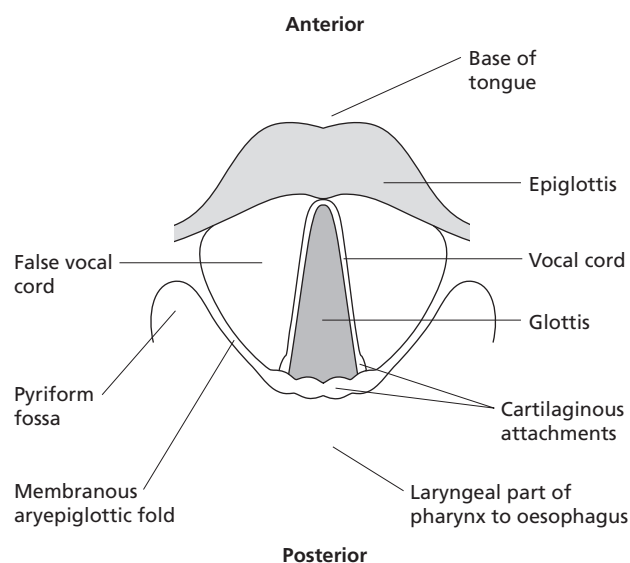


Fig. 8.2 Bronchoscopist's view of the larynx.

complication of previous thyroid surgery [75]. Stridulous inspiratory noises are also sometimes produced by patients with 'functional upper airway obstruction' [76,77]; more rarely sarcoidosis of the upper respiratory tract may produce this symptom, sometimes involving the epiglottis and laryngeal structures but usually sparing the cords [78]. The author has seen a case of bilateral vocal cord palsy occurring in association with rare neuromyopathic disease.

The tip of the bronchoscope is centred with regard to the vocal cords and quickly advanced through the opening during inspiration. The tip should not be forced through and if the cords appose it should be withdrawn and further attempts made. Additional 2.5-mL aliquots of 2% lidocaine (50mg) may be instilled down the suction channel of the bronchoscope if needed, using boluses from 5-mL syringes made up to volume with air in order to allow for the instrument's dead-space and to rapidly empty all the local anaesthetic from its channel. The passage of the bronchoscope through the vocal cords is one of the least pleasant parts of the procedure, and a transient sensation of apnoea, about which patients may be forewarned, is common.

Some bronchoscopists have preferred to use the oropharyngeal rather than the nasal approach and introduce an endotracheal tube 'piggy back' over the bronchoscope once the trachea has been entered [79]. This method has the principal advantage of allowing removal of the bronchoscope so that the tip can more easily be cleaned if vision becomes obscured by tenacious secretions.

Once the cords have been passed any further lidocaine is given through the suction channel as 2% solution. If cricothyroid local anaesthesia has been used, there is usually little further coughing other than when the tip of the bronchoscope is manoeuvred into the upper lobes before which additional local anaesthetic does not go amiss. The local anaesthetic action of lidocaine is about 20 min and allowance of a safety margin of 1 h after bronchoscopy is quite long enough, after which the fully awake patient's craving for a cup of tea may be satisfied.

#### **Further advancement of the instrument and endoscopic appearances**

A good appreciation of normal and abnormal endoscopic appearances can be gained by logging sufficient 'flying hours'; however, even with experience the distinction between likely benign and malignant change is not always clear and is subject to error. Atlases of bronchoscopic appearances that contain clear images have been published [80] and are helpful as they accurately document the appearances of some of the rarer conditions with names designed to impress colleagues, such as tracheo-bronchopathiaosteochondroplastica. Such conditions are

infrequently encountered and might give rise to confused wonderment if not seen before.

It is also all too easy, even for an experienced bronchoscopist, to lose his or her bearings during the course of an examination, particularly in the more distal reaches of the bronchial tree, and there is no disgrace attached to the deliberate withdrawal of the instrument back to a familiar landmark, such as the carina, in order to reorientate. Vision not uncommonly becomes obscured by mucus or blood on the end of the instrument. This may be removed by flexing the end of the bronchoscope and wiping it on the membranous part of the tracheal wall or by injecting 5 mL normal saline down the channel. It is rarely necessary to withdraw the bronchoscope to wipe the end.

#### ***Trachea***

This is sometimes surprisingly tortuous in the elderly, often being bowed in from the left by the aortic arch, which runs its course anterior to the carina before looping round the lateral aspect of the lower third. The first third of the trachea is extrathoracic. It is as well for the beginner to remember that the endoscope is a solid 'space-occupying lesion' and not be tempted to pass it through a trachea that is grossly narrowed by disease or indeed to biopsy tracheal lesions that are causing a significant stenosis in case they become oedematous and cause the narrowing to become critical.

The trachea may be involved by primary neoplastic disease. All of these tumours are unusual and most are malignant, squamous carcinoma probably being found most frequently, followed by adenoid cystic carcinoma (formerly known as cylindroma), and less frequently carcinoid tumour, adenocarcinoma and small cell carcinomas. Benign tracheal tumours are even more rare and include papillomas, neurofibromas, neurilemmomas and leiomyomas. Direct spread of malignant disease to the trachea from elsewhere is more common and this may occur from mediastinal lymph nodes, lung, thyroid and oesophagus. Inflammatory narrowing may result from the trauma of endotracheal intubation and tracheostomy may also produce stenoses.

Non-neoplastic tracheal pathologies are rare and include Wegener's granulomatosis, which may cause subglottic stenosis [81,82], and tracheal amyloidosis [83,84]. Isolated, pale, almost pearl-coloured cartilagenous spurs or projections are not uncommon especially in the elderly and they defy attempts at biopsy, as do the remarkable stalactite- and stalagmite-like projections of tracheo-bronchopathia-osteochondroplastica, which continue down beyond the carina [85]. The trachea may be narrow in the transverse diameter, as in the so-called 'inverted-U' normal variant, but in relapsing polychondritis may be excessively narrow, assuming the slit-like appearance of the inside of a scabbard [86].

### *Tracheobronchial mucosa*

This is normally smooth and pink, and the main carina and subcarinae (bronchial or segmental spurs) are usually sharp. The more recent generations of fiberoptic bronchoscope provide excellent vision and a high degree of tip manoeuvrability so that all numbered segmental bronchi (see Fig. 8.3) may be inspected or even entered with little difficulty. The right upper lobe bronchus arises much sooner and usually more acutely than its opposite number on the left, so that the beginner often passes its orifice unawares. Once entered, three segmental bronchial openings can usually be identified without much difficulty. The acute angulation required to enter either upper lobe often causes patients to cough, despite the application of local anaesthetic, and it is considerate to forwarn them of this just before undertaking the manoeuvre. An accessory right upper lobe bronchus occasionally arises from the distal trachea. The tyro may be surprised by the relatively small diameter of the middle lobe bronchus as it arises anteriorly, directly opposite and not much wider than the apical (superior) segmental bronchus of the right lower lobe. The left upper lobe is easier to enter, the lingular division bronchus presenting itself first, greater angulation being required to enter the upper division bronchus. The apical segment of the lower lobe on the left is also easily identified. The basal segmental bronchi on both sides are easy to inspect and the novice will soon cease to be distracted by their variable anatomy.

Inflammation is indicated by areas of mucosal reddening and by mucosal oedema with resultant blunting of interlobar or intersegmental spurs. There may also be increased production of mucus and mucosal gland ducts may be prominent as visible 'mucous pits' in the bronchial wall. Suppurative lung disease may be marked by purulent endobronchial secretions, which may be sucked out more easily if a larger channel instrument is being used. Despite the fact that histological evidence of endobronchial disease is common in sarcoidosis, having been reported in 20–70% of cases [87], visible nodular 'cobblestone' or infiltrative changes are seen much less frequently, although these are occasionally very evident and bronchial stenoses may also be produced [88]. Fungal infections, such as invasive aspergillosis or candidiasis, may produce diffuse infiltrative mucosal changes in immunosuppressed patients, the former characterized by necrotic change [89], the latter by a 'white carpet' appearance. Florid endobronchial involvement has been documented in histoplasmosis [90]. Tuberculosis may also unusually produce florid endobronchial inflammatory appearances that may mimic tumour [91,92]. Endobronchial changes due to tuberculosis, comprising hyperaemia, caseating masses and the protrusion of extra-bronchial lymph nodes, may also be seen in patients infected with human immunodeficiency virus (HIV) [93].

Neoplastic changes are variable in appearance. A centrally placed tumour may be clearly visible as an endobronchial mass of tissue that may partially or totally occlude the lumen in which it is situated. Such lesions may be smooth-walled or more irregular and cauliflower-like. Occasionally they arise from a stalk, the base of which may be impossible to locate. They may be a pinkish colour or may be covered by white or grey material, biopsies of which may reveal only necrotic slough. A similar slough-like appearance may be produced by large mucous plugs that are sometimes found occluding a bronchial orifice in allergic bronchopulmonary aspergillosis and the gross appearance of these may be mistaken for tumour. Carcinoid tumours are sometimes quite rounded and smooth, commonly sitting at the bifurcation of a more proximal bronchus. Their reputation for bleeding is an encouragement to the bronchoscopist to spray the suspect lesion with a bolus of 5 mL 1:20000 epinephrine (adrenaline) solution before taking a biopsy [94]. Endobronchial involvement by lymphoma [95,96] may sometimes consist of single or multiple nodules or mass lesions, some of which may protrude from bronchial orifices in polypoid fashion. Almost 50% of patients with AIDS who had cutaneous Kaposi's sarcoma (KS) were found to have endobronchial involvement at necropsy [97]. Endobronchial KS was found in 15% of 580 HIV-positive patients coming to bronchoscopy over a 10-year period [98], and may occur in the absence of mucocutaneous KS elsewhere [97,99]. It may be evident as reddish areas of discoloration in the mucosal wall, which may be multiple and not unlike submucosal haemorrhages, or as a raised violaceous lesion that may unusually cause bronchial obstruction. KS is a vascular tumour so that biopsy may produce haemorrhage; biopsy is often unnecessary if KS is evident elsewhere. Endobronchial metastases may be seen from many different primary cell types, breast and colonic carcinoma being particularly common. Others include genitourinary tract and thyroid tumours, malignant melanoma, sarcomas (including KS) and lymphoma [80,100,101].

Some tumours may declare themselves less obviously as bronchial narrowing that shelves down gradually like a funnel so that conventional biopsy forceps slide off the bronchial surface tangentially in annoying fashion. Such 'shelving down' appearances are sometimes due to extrinsic compression rather than intramural invasion, in which case biopsies may yield normal tissue. Earlier bronchoscopes were limited in that biopsy tools could be passed into some of the upper lobe segments only with difficulty and sometimes not at all. The friction characteristics and flexibility of more modern instruments are such that the forceps and brush tools may be advanced with the tip of the bronchoscope held in a greater degree of flexion so that the upper lobes are usually more readily sampled. The sampling tools should not be forced through the flexed end of the bronchoscope or damage to the instrument may



THE IPSWICH HOSPITAL NHS TRUST  
RESPIRATORY MEDICINE DEPARTMENT

**BRONCHOSCOPY**

Date:

Personnel:

Method: Transnasal ☐

Per Oral ☐

Endotracheal Intubation ☐

Under Fluoroscopy ☐

Premedication:

Anaesthesia: Parenteral ☐

Topical ☐

Supplementary Oxygen:

Abnormalities noted (check if normal)

		Hospital Reg. No.	
Surname			
First names			
Address		M/F	
		M/S/W	
Ref:		D. of B.	
G.P.			
Con.		Ward	

Diagnosis:

Bronchoscope type:

Vocal cords.....

Trachea.....

Motion with Phonation.....

Carina.....

Right Lung

Mainstem bronchus (A).....

Upper Lobe bronchus (B).....

B1 Apical.....

B2 Posterior.....

B3 Anterior.....

Intermediate bronchus (C).....

Middle Lobe bronchus.....

B4 Lateral.....

B5 Medial.....

Lower Lobe bronchus.....

B6 Apical.....

B7 Med. Basal.....

B8 Ant. Basal.....

B9 Lat. Basal.....

B10 Post Basal.....

Left Lung

Mainstem bronchus (A).....

Upper Lobe bronchus (B).....

Upper division bronchus.....

B1-B2 Apico-posterior.....

B3 Anterior.....

Lingula division bronchus.....

B4 Superior.....

B5 Inferior.....

Lower Lobe bronchus (D).....

B6 Apical.....

B8 Ant. Basal.....

B9 Lat. Basal.....

B10 Post Basal.....

Follow up/Results:

Specimens taken:

Washings.....

Brushings.....

Endobronchial biopsy.....

Transbronchial biopsy.....

Images taken:

Complications:

Comments:

Signed:

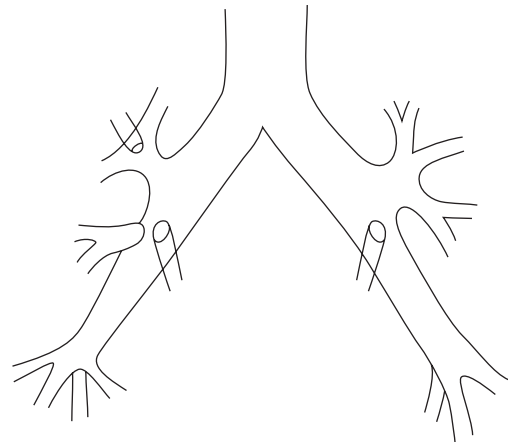


Fig. 8.3 Example of a fiberoptic bronchoscopy report sheet.

result, and sometimes it is necessary to protrude the biopsy tool just beyond the end of the bronchoscope before applying full flexion with the target area in view. Occasionally a tumour that is radiographically large and centrally situated is frustratingly accompanied by entirely normal endoscopic appearances, presumably arising at segmental level and surrounding rather than invading the proximal bronchial tree.

In cases of haemoptysis it is sometimes possible to see a little blood issuing from a bronchus that subtends a more distal tumour that is itself not endoscopically visible. When cricothyroid puncture is used, a small amount of blood may be spilt into the lower parts of the bronchial tree and this may be difficult to distinguish from more distal bleeding.

### **Procedures for sampling through the fiberoptic bronchoscope** (see Table 8.2, p. 151)

Cooperation between the histopathologist, the microbiologist and the clinician is extremely important. The pathologist needs to be aware of the sampling techniques used in order to be able to advise how best to process the specimens and the microbiologist should be aware of the clinical background, particularly when bronchoscopy is used to determine the nature of presumed opportunistic infection in an immunocompromised patient. Teamwork is essential in this situation if the procedure is to be of full value to the patient.

### **Endobronchial biopsy**

Clear endobronchial tumour is easy to biopsy but the bronchus that funnels down gradually presents more of a problem. Such narrowing may sometimes be more easily biopsied using a 'spear forceps', the sharp point of which may be used to impale the bronchial wall in order to provide an anchorage so that the jaws of the forceps are less likely to slip off the area of interest (Fig. 8.4). Other innovations are biopsy forceps with a 'swinging jaw' or 'rat tooth' design, both of which may prevent such slippage. Alternatively, a double-hinged curette may be used to scrape the surface of the lesion, the curettings obtained being submitted for cytology. Endobronchial biopsy material obtained by forceps under direct vision is carefully teased off the cup of the instrument and placed in 10% formalin fixative. Visible tumour may be covered by slough and attempts should be made to clear this first using the biopsy forceps in order to improve the yield. Similarly, attempts should be made to wash away blood clot following biopsy before taking the next sample, in order to avoid filling the forceps with thrombus. Three or four biopsies of a plainly seen tumour usually suffice [102,103], although one study reported that five biopsies were needed to achieve a greater than 90% probability of obtaining at least

one positive sample in cases of carcinoma [104]. Sometimes a tantalisingly large piece of tissue is obtained, in which case the operator may choose to leave the closed forceps just protruding beyond the end of the bronchoscope so that the whole instrument and intact biopsy can be removed as one, rather than fragmenting the biopsy by withdrawing it through the narrow biopsy channel.

Biopsy material is often friable and as an alternative to putting it directly into fixative it can be gently teased off the forceps, using a wooden cocktail stick or equivalent, into a Petri dish (or similar shallow receptacle) containing normal saline or Ringer's solution. Larger pieces that are most suitable for histology may then be carefully transferred to the formalin fixative in the tip of a syringe. Any tissue debris that remains in the saline may be fragmented into tiny pieces too small to be processed as tissue biopsies and may be decanted into a further container and submitted as a sample for cytology.

### **Transbronchial lung biopsy**

Transbronchial (sometimes referred to as 'bronchoscopic') lung biopsies are made beyond the limits of direct vision and may be conveniently carried out under fluoroscopic control using a C-arm (Fig. 8.5) or other suitable device, although some bronchoscopists have been content to work without any such assistance [105]. Where there is diffuse disease that is bilateral, the tip of a larger-channel bronchoscope may be wedged into a laterally placed segmental bronchus in either lower lobe, as these usually accept the forceps comfortably. At this point, 5 mL of 1:20000 epinephrine solution is injected into the chosen segmental orifice in the belief that this diminishes the likelihood of serious bleeding [106]. The largest possible toothed biopsy forceps (Fig. 8.6) are then passed through the same segmental opening, while the end of the bronchoscope remains wedged into that segment; the progress of the forceps is followed by fluoroscopy, the shaft of the bronchoscope nearest the patient being held by the assistant, with gentle inward pressure, so that the bronchoscopist is free to advance the forceps. If the forceps reach the extreme periphery of the lung, pleuritic pain may be felt and the forceps are withdrawn a few centimetres to reduce the chance of pneumothorax. If the forceps are arrested early on in their journey, another basal segment is tried instead, as too proximal a biopsy runs a small risk of damaging a larger blood vessel. When the forceps appear to be well situated towards the lung periphery, the patient is asked to 'take a deep breath in and hold it' and the assistant is given the instruction 'open'. The forceps can often be seen to open on the fluoroscopy screen, and they are then pushed gently forwards until resistance is felt, whereupon the patient is asked to 'let all your air out' and the assistant is given the instruction 'close' when expiration is seen to be complete. The forceps are then firmly

withdrawn. An elastic tug followed by a feeling of 'give' is sensed and lung tissue may be seen to be pulled and to recoil back into place on the screen. This is usually a sign that a satisfactory biopsy has been obtained. The biopsy material is then placed in fixative for histopathology or normal saline for microbiology.

Transbronchial lung biopsy depends for its success on the forceps having invaginated and torn away lung tissue as well as bronchial mucosa (Fig. 8.7). A pale fluffy-looking specimen that floats is likely to be a good one, although one that sinks need not mean failure. While the assistant is attending to the specimens, the bronchoscopist holds the end of the bronchoscope firmly wedged up against the segment just sampled so that any local bleeding is contained. The procedure is then repeated in the same segment so that the bronchoscope continues to tam-

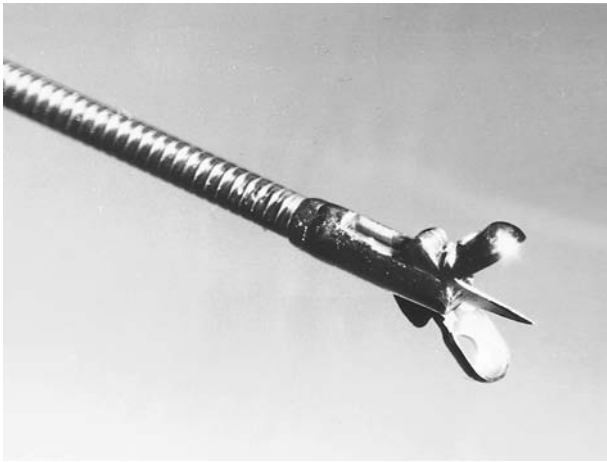


Fig. 8.4 Spear fiberoptic bronchoscopic forceps.

ponade effectively. In diffuse disease, three adequate-looking samples are probably sufficient for histology [107], although some work has shown an increase in positive histological yield with up to six biopsies [103]. Milman and colleagues [108] found no significant increase in yield when taking more than four biopsies in 93 cases of diffuse non-malignant disease. By the time all the biopsies have been taken, vision has usually been obscured by local bleeding and it is wise to keep the instrument wedged in the segmental bronchus for at least 5 min in order to enable clot to form and to prevent bleeding once the instrument is removed. A small amount of local bleeding is to be expected, although there is a danger that this might become uncontrollable if proper precautions are not followed. The patient's chest may be finally screened for evidence of a pneumothorax. It is our practice to keep patients who have had transbronchial lung biopsies in hospital overnight, with a repeat chest radiograph the next morning to exclude pneumothorax as a result of a 'slow leak'. In practice, pneumothoraces are seldom a problem; when they do occur, they are usually shallow so that active treatment may not be required. There are certainly reported series in which transbronchial lung biopsy for diffuse lesions has been carried out without fluoroscopy and as a day-case procedure [105]. Transbronchial biopsy should not be carried out bilaterally at the same session because of the small but real risk of bilateral pneumothoraces.

The same technique may be used to biopsy mass lesions that are situated peripherally (i.e. beyond bronchoscopic vision), provided that they are of sufficient size to be seen fluoroscopically and that the forceps can be directed towards them. The resolution of some equipment is such that lesions on standard chest radiographs become



Fig. 8.5 Fluoroscopy table with C-arm and screening equipment.

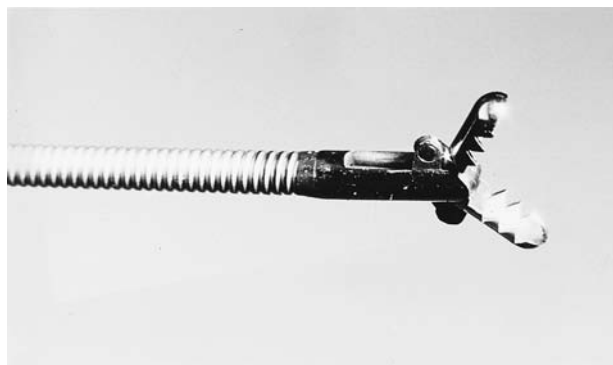


Fig. 8.6 Crocodile fibreoptic bronchoscopic forceps.

frustratingly less clear on the fluoroscopy screen and they may become impossible to localize on the lateral projection. However, such biplanar screening can aid in positioning the forceps in relation to the lesion in the anteroposterior view and the lateral projection can at least confirm to the bronchoscopist that the forceps are directed anteriorly or posteriorly as he or she would wish. As usual, before exposing the patient to even a small risk, the bronchoscopist needs to consider how the result of the examination is likely to influence management. There is little purpose in attempting the procedure for suspected neoplasm if the lesion will still be resected even though the result of the biopsy is negative.

It is possible to carry out transbronchial lung biopsies on patients who are being ventilated mechanically [109]. The risks should be expected to be greater in an intensive care situation because of the increased likelihood of associated problems in critically ill patients. These include serious hypoxaemia, bleeding and pneumothorax (particularly with positive end-expiratory pressure), and fluoroscopy should be used in this situation.

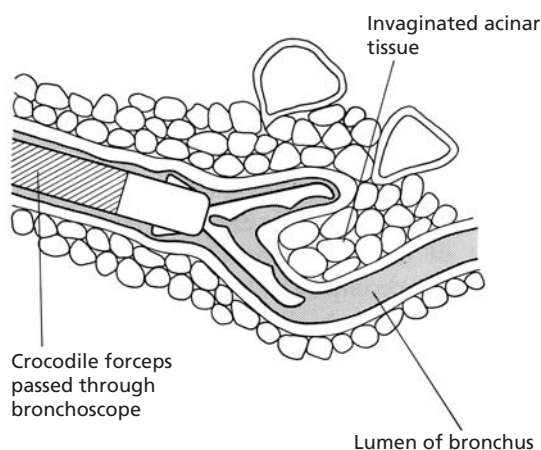


Fig. 8.7 Transbronchial biopsy: mechanism whereby acinar tissue may be obtained (see text for description of method).

### Bronchial brushings

Various types of bronchial brush may be used to collect both cellular and microbiological material, using direct vision when collecting from proximal areas of suspicion or fluoroscopic screening when sampling more peripheral sites. Brushes are now disposable and are contained in a plastic sheath. When tumour is seen proximally, forceps biopsy should be used first in the author's opinion, as a brush stroke may cause enough local bleeding to obscure the lesion and made subsequent biopsies problematical. When bronchial brushings are to be submitted for cytology, the brush is smeared directly on to a microscope slide using a circular motion; the brush is rotated firmly on to a small area of the slide using a second slide, this manoeuvre being carried out for about 5 s in order to minimize drying artefacts, each slide being immediately fixed in 95% ethanol contained in a Coplin jar [110]. Alternatively, the brush may be agitated in a tube of normal saline or Ringer's solution, which is then promptly submitted for cytological studies or microbiological culture.

### Bronchial washings and bronchoalveolar lavage

The earliest applications of BAL were therapeutic, with the intention of removing inspissated bronchial secretions from patients with severe attacks of asthma. This practice failed to gain general acceptance but is used in modified form as 'whole lung lavage' under general anaesthesia in the treatment of alveolar proteinosis (see Chapter 51). Later the technique was modified for diagnostic and research purposes using smaller volumes of lavage fluid as a safe and effective method for sampling selected areas of peripheral lung [111].

### Clinical approach

The instillation of normal saline down the channel of the fibreoptic bronchoscope and the retrieval of some of it into a 'trap' (see Fig. 8.1) by suction is used in routine practice, being frequently combined with other sampling methods such as biopsy and brushing. When the volume of saline is small (e.g. 10–20 mL) and is sprayed into the vicinity of a visible lesion, this procedure may be described as *bronchial washing*; samples are usually submitted for cytological examination in the laboratory, where they may be passed through an 8- $\mu$ m Millipore filter or centrifuged in order to make smears or other cellular preparations so that a search may be made for neoplastic cells. At the end of the procedure the channel of the bronchoscope may be rinsed out into a container with 10–20 mL normal saline so that cellular debris lost from brushes or biopsy forceps may be similarly sampled.

In certain circumstances larger volumes of fluid may be instilled in order that more peripheral lung tissue can be

sampled. The usual clinical reasons for doing this are (i) to look for neoplastic cells in the case of a suspicious peripheral opacity that is beyond the visual range of the bronchoscope; (ii) to look for acid-fast bacilli where there is a suspicious-looking peripheral infiltrate and when it has not been possible to demonstrate these organisms in sputum (occasionally a cavitating lesion suggestive of tuberculosis turns out to be neoplastic, so that it is as well to collect some aliquots of fluid for cytology as well); and (iii) to search for opportunistic organisms such as *P. carinii* in cases where there is a more diffuse infiltrate in a patient who is immunocompromised (e.g. AIDS, after transplant, acute leukaemia, myeloma, etc.) [112,113]. When this organism is suspected, an upper lobe is often chosen as this may provide a greater yield.

In general there is little if any purpose in submitting such samples for 'routine' aerobic or anaerobic culture of the more usual pathogens that cause pneumonia or infective exacerbations of bronchitis, since these microbes frequently colonize the nose and oropharynx and may well be picked up by the passage of the instrument through these microbiologically fertile territories, the suction channel becoming contaminated by all manner of organisms *en route* so that subsequent cultures do not necessarily reflect intrathoracic disease. These organisms may be sought in the lungs only if special precautions have been taken to avoid such contamination, as may be achieved by the use of a 'protected brush' (such as that designed by Wimberley) or if a semi-quantitative calculation of the microbial load is made by techniques that record numbers of colony-forming units (cfu). Such methods are not yet widely used in routine clinical practice but do have applications particularly in cases of severe nosocomial pneumonia on intensive care units (see Chapter 13). As a generalization and where BAL is used,  $>10^5$  cfu has been taken as a threshold indicating probable pneumonia,  $<10^4$  cfu indicating probable absence of pneumonia [114].

The volume of fluid used to sample more peripheral lung, for the usual purposes outlined above, is commonly in the order of 60 mL (given as two 30-mL aliquots) and frequently gives a return on suction of about 10–15 mL. Much larger volumes have been used, mainly for research purposes, but such high volumes are of no benefit for clinical diagnostic purposes. When 60 mL or more is used the technique can fairly be described as 'bronchoalveolar' rather than 'bronchial' washing and by convention the term *bronchoalveolar lavage* is used. The technique in clinical practice requires the tip of the bronchoscope to be wedged into a segmental or subsegmental bronchus thought to subtend the area of interest and the given volume of fluid to be injected down the channel, immediately being retrieved with low-pressure suction. Less irritation and coughing may occur if the bronchus is first rinsed with a small volume of 2% lidocaine; initial concerns about its bacteriostatic properties do not seem to

have been borne out in practice as the concentration is low [115]. Further modifications to the technique are made when BAL is used for research into either the cellular constituents of lavage fluid or the nature of epithelial lining fluid and some of these are mentioned below.

Occasionally BAL fluid may yield unusual findings consistent with rare pathologies, such as clumps of amorphous lipoproteinaceous material that may be found in alveolar proteinosis [116] or large numbers of alveolar macrophages that are found to contain haemosiderin using Perl's stain for ferric iron, suggesting pulmonary haemosiderosis, although somewhat similar cellular appearances may occur when there has been pulmonary haemorrhage due to other causes [117].

It is clearly of crucial importance for the bronchoscopist to work closely with those colleagues in the microbiology, cytopathology and histopathology laboratories and it is helpful to have a 'lead person' in the laboratory who is willing and able to take responsibility for coordinating efforts across departmental divides, according to the nature of the particular clinical problem that has to be solved. It is the responsibility of the clinician to make sure that sufficient information is passed to the relevant laboratory personnel, otherwise all endoscopic efforts may be thwarted.

### Research aspects

Much work has been carried out over the years to investigate whether the use of larger volumes of BAL fluid than are used in routine clinical practice would help to characterize and also yield useful diagnostic and prognostic information about various forms of diffuse lung disease, such as cryptogenic fibrosing alveolitis, extrinsic allergic alveolitis and sarcoidosis [118–121]. Much of this work has centred around the determination of the main cellular constituents and their relative proportions in BAL fluid in normal subjects and comparison of these with the findings from the lungs of groups of patients with known pathology. The fluid lining the epithelial layer of the respiratory membrane has also been a subject of interest for some researchers [122]. Although much interesting data have been collected, these have unfortunately not had a major bearing on routine clinical decision-making; indeed a sceptic has unfairly suggested that this line of research is likely to be about as much use as trying to determine the workings of an elephant by studying its bath water.

When large-volume BAL is being undertaken for research purposes in the evaluation of diffuse lung disease, care must be taken to avoid trauma to the bronchial mucosa so that samples accurately reflect peripheral cell counts and are not contaminated by bleeding. There is at present no universally standardized method and thus results from one centre are not necessarily

ily strictly comparable with those from another, although attempts have been made to rectify this in both Europe and North America [123,124]. The choice of segmental bronchus is not critical provided that the abnormality under investigation is diffusely distributed; in this case it may be preferred to wedge the tip into the middle lobe or lingular bronchus since a greater volume of fluid may be retrieved from either of these sites. Others prefer to sample a laterally disposed basal segment, although the choice may be influenced by the radiographic disposition of shadowing when the radiograph is abnormal.

For research purposes, sterile, non-bacteriostatic, normal saline is used, either at room temperature or warmed to 37°C and buffered to a pH of 7.4 by the addition of a calculated volume of 8.4% sodium bicarbonate solution (0.55 mL to 1 L normal saline). Aliquots of 20–60 mL are injected down the suction channel and immediately reaspirated using low-pressure suction. A total of between 60 and 550 mL has been used, 120–180 mL being commonplace [118–121,125–128]. Larger volumes than 300 mL are unlikely to be necessary and these increase the chance of febrile episodes following the procedure [129]. With gentle suction a proportion of the volume used may be recovered after each instillation, the fluid being ideally aspirated into a container that reduces cellular adherence to its walls, such as a silicon-lined glass bottle or a polyethylene or polycarbonate vessel. The fluid then needs to be transported to the laboratory on ice with minimal delay.

Most attention has centred around differential cell counts, the total cell counts per unit volume having been found to be unhelpful. Thus relatively high percentages of lymphocytes have been found in BAL fluid in many patients with extrinsic allergic alveolitis (hypersensitivity pneumonitis). A similar finding has been recorded in a lower proportion of cases of sarcoidosis, whereas the differential counts in cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) and fibrosing alveolitis associated with systemic sclerosis or other connective tissue diseases tend to show an excess of neutrophils sometimes also with increased eosinophils [120,121,130,131]. Recent work also suggests that the cell populations in BAL fluid are not homogeneous in a given patient with cryptogenic fibrosing alveolitis and that they may vary according to the extent of the abnormalities on HRCT in the lavaged lobe [132].

BAL had been proposed as one of a number of methods for determining the 'activity' of sarcoidosis (see Chapter 39) in order to try to separate those cases that if left untreated develop fibrosis and permanent impairment from those which resolve spontaneously. It has been claimed that a T-lymphocyte count of greater than 28% (especially if combined with a positive gallium scan) is an indication of an active alveolar inflammatory process or 'high-intensity alveolitis', so that fibrosis can be expected, whereas with lower counts the converse is more likely

[133]. Unfortunately some patients with sarcoidosis who have hilar lymphadenopathy only and clear lung fields on the radiograph may fulfil the lavage criteria of 'high-intensity alveolitis' and yet be followed to apparently complete resolution, so that this lavage parameter cannot be relied upon as a sound base for therapeutic decisions regarding corticosteroid therapy [121]. This is further borne out by the observation that patients with sarcoidosis who have evidence of fibrosis on lung function testing and who have normal lymphocyte counts in lavaged fluid may yet respond to corticosteroid treatment.

In patients with cryptogenic fibrosing alveolitis it has been similarly suggested that a relative increase in the BAL lymphocyte count in lavaged fluid may be an indication of steroid responsiveness, possibly carrying a better prognosis [134]. The clinical usefulness of this observation is again questionable as some patients with cryptogenic fibrosing alveolitis with relatively high neutrophil counts also respond to steroids [121]. A better clinical response to steroids or cyclophosphamide has also been correlated with a relatively low eosinophil count on BAL [121].

Further research into the significance of lavage fluid cell counts has extended to counts of T-lymphocyte subsets but whether this will prove clinically helpful has yet to be shown [135].

### Per-bronchoscopic needle aspiration

The development of various needle devices that can be passed down the channel of the fiberoptic bronchoscope has provided another method for obtaining samples of the cellular content of suspected areas of neoplastic involvement [136]. A number of such needles have been designed [137]. One version consists of a hollow rigid 19-gauge needle attached to the distal end of a flexible wire, this sampling needle containing a solid 22-gauge needle 'core'; the whole arrangement is housed in a plastic catheter, the proximal end of which has a side-port, allowing suction to be applied, along with a slide mechanism that facilitates manual advancement of the needle beyond the end of the catheter [137,138]. This allows a bronchoscopist who has mastered the technique to advance the larger hollow cutting needle over the smaller solid needle in order to enter a centrally placed extrabronchial lesion, such as an enlarged subcarinal node. The sample is retrieved by applying suction to the side-port and the central solid needle prevents the cutting needle from becoming obstructed by tissue from the tracheobronchial wall itself. The contents of the cutting needle may then be expelled, either by positive pressure from a syringe on the side-port or by advancing the solid central needle, in order to obtain specimens for histology or cytology according to their size. The yield from cytological samples may be better if they are placed on a microscope slide and fixed immediately in alcohol [137].

There are three main applications of per-bronchoscopic



needle aspiration. The first involves the sampling of central (carinal, paratracheal and hilar) lymph nodes or other mediastinal lesions by puncturing the tracheo-bronchial wall in the manner described above [137,138]. This technique has therefore been used by *aficionados* in the staging of lung cancer in order to avoid the need for mediastinoscopy [139,140], prior CT of the mediastinum indicating the position of the enlarged nodes to be sampled [140,141]. Caution must be exercised before discharging a patient with a positive mediastinal needle sample as being surgically inoperable since false-positive results, although uncommon, may occur due to the potential for contamination of the needle by neoplastic cells from various areas, including those that have been carried up in bronchial secretions from more distal parts of the tracheobronchial tree [142,143].

The second use is to sample peripheral 'mass shadows' using the same type of fluoroscopic control as that described above for transbronchial lung biopsy [144]. Once the lesion has been 'found' a smaller-gauge flexible needle is advanced and retracted while suction is applied. Such flexible needles have the advantage of allowing access to lesions that are inaccessible to a rigid needle, such as those situated in the apical segments of the upper lobes. It has been reported that yield may be increased if needle aspiration is combined with other sampling methods such as conventional transbronchial biopsy with forceps [145]. There is some evidence to suggest that transbronchial needle biopsy may be better than transbronchial biopsy and brushing at retrieving neoplastic cells from nodular smooth-walled peripheral lesions compared with irregular-walled more infiltrative lesions [146].

The third use is to sample proximal endobronchial lesions that have to be approached by the bronchoscope at a narrow angle so that the operator may find them awkward to biopsy should conventional forceps fail to find a proper purchase and slip off. Such mural tumours are less easily biopsied and needle aspiration may be effective in this situation [102]. The needle may also offer a potential advantage over forceps when a tumour is apparently covered by slough but this has yet to be demonstrated.

Apart from the potential problem of false positivity, other difficulties may arise with needle aspiration.

- 1 The fear of false negatives leads to a reluctance to diagnose benign conditions, so that a further more invasive procedure is likely to follow anyway.
  - 2 There may be difficulties distinguishing different histologies (e.g. non-small-cell vs. small-cell cancer), especially on cytological samples.
  - 3 There is a potential risk of haemorrhage, either into the bronchial tree or mediastinum.
  - 4 Incautious use of the biopsy tool may damage the bronchoscope.
- Transbronchial needle aspiration biopsy is probably the least widely used of the various fiberoptic bronchoscopic

techniques; about 12% of 871 North American respiratory physicians who responded to a questionnaire claimed to use it routinely in 1991 [147]. This relatively poor uptake probably reflects not only concerns about the problems just listed but also the difficulties in learning a technique that inevitably increases the complexity of already busy lists. It has been estimated that a training experience of about 50 procedures is required to achieve acceptable results [148].

## Diagnostic yield of fiberoptic bronchoscopy

### Lung cancer

#### Visible endobronchial tumour

The diagnostic yield from biopsy of bronchoscopically visible tumours that occupy the lumen of the bronchus is, in the best analyses, over 90% [103,149–151]. The number of biopsies taken to achieve this should be three or four [102,103] and it is possible that increasing the number of biopsies might correct any tendency towards a lower yield in a relatively inexperienced operator, although this has not been shown. The yield for bronchial brushings/washings submitted for cytology in the same situation may be almost as high as biopsy given expert cytopathological support [149,152], which is not available in all institutions. There is good evidence that the positive yield is increased if specimens are submitted for both cytology and histology [153–155]. A British study in a group of 125 endoscopically visible tumours found positive biopsy results in 76%, positive bronchial washings in 50% and positive brushings in 52%. Biopsy and brushings together gave a yield of 97%, biopsy and washings a yield of 95%, but washing and brushing together a yield of only 74% [155]. There was usually more than one positive in each case, so that biopsy gave the only positive in 22%, brushing in 5% and washing in 2% [155]; the clear message is to combine the different techniques. False positives may occur with cytology but are rare [152].

Small biopsy samples such as those obtained by fiberoptic bronchoscopic biopsy result in appreciable histological inaccuracies if attempts are made to type according to the World Health Organization's classification of lung cancer and a simplified classification comprising either 'small cell carcinoma' or 'non-small-cell carcinoma, not further specified' has been suggested in its place for this type of small biopsy [156].

#### Visible intramural tumour

The yield from the technically more uncertain biopsy of bronchoscopically visible tumours that are intramural rather than endobronchial is predictably less good. A positive yield of 55% in 31 such cases has been reported [102]. However, this was increased to 87% when the biopsy was

supported by transbronchial needle aspiration and 97% when bronchial washings and brushings were submitted for cytology as well [102].

### *Peripheral tumour*

The diagnostic yield in the case of peripheral tumours beyond bronchoscopic vision is bound to be lower and more variable. Factors that influence yield include the skill and experience of the bronchoscopist, the time available for the procedure, the availability of supporting fluoroscopic facilities and their competent operation, the size of the lesion and whether it is a primary or secondary deposit. The yield has also been noted to be lower if the lesion has a sharp rather than an irregular border [157].

Previous bronchoscopic experience has been shown to influence the rate of positivity following biopsy of visible endobronchial tumour [104] and it can therefore be inferred that the same factor is likely to operate at least as strongly in the technically more difficult biopsy of peripheral lesions.

The absence of fluoroscopy turns attempts to biopsy a peripheral lesion into a much more haphazard affair as even the most experienced operator can do no more than choose what appears to be the correct bronchopulmonary segment and hope, having no idea whether the end of the forceps has reached the lesion or not. An arrangement by which screening can be carried out in two planes is necessary so that the patient is moved in relation to the X-ray beam by means of a rotating C-arm or some other device. One early study demonstrated an increased diagnostic yield from 30% without screening to 80% when screening was available [158]. The results of two large studies, one of which used fluoroscopy [159] and the other not [155], showed that biopsy achieved a positive result in 61% with fluoroscopy vs. 37% without, bronchial lavage a positive result in 52% with vs. 38% without and bronchial brushing a positive result in 52% with vs. 29% without. When all three techniques were used the success rate was 86% with fluoroscopy compared with 57% without [155,159].

Unsurprisingly, the size of the lesion influences yield: the positive yield is lowest with lesions less than 2 cm in diameter, usually 35% or less [160–162], small lesions being easily lost as a result of relatively poor fluoroscopic resolution. They are also likely to be subtended by fewer bronchi, thereby reducing the chance of the forceps, brush, curette or needle reaching them, for once these instruments have been placed in a bronchial segment or subsegment the bronchoscopist loses control over the route that they take. Combined sampling techniques and the use of fluoroscopy enhances the yield, one series reporting a higher overall positive yield for lesions of 2 cm or less of 54% increasing to 87% for those over 5 cm, using an approach that combined brushing, transbronchial biopsy and transbronchial needle aspiration [157].

The overall yields for biopsy and brushing of peripheral

lesions has been reported to vary widely between 30 and 90% [163]; for biopsy alone in such lesions, one study reported positive results in 46%, the yield increasing to 60% with brushing as well [164]. A further study reported a positive yield from biopsy alone in 75% of cases [103]. Positive yield was likely to be increased if six or more biopsies were taken [103]. The use of bronchial washings and brushings may augment the yield from transbronchial lung biopsy alone [163], as may per-bronchoscopic needle aspiration. Using a technique of needle aspiration, positive results in over 70% of tumours 2 cm or more in diameter have been reported compared with a 33% yield for smaller lesions [163].

The yield is lower for peripheral metastatic tumours that are beyond bronchoscopic vision, positive results for transbronchial lung biopsy being reported in 50% of cases of metastatic cancer compared with almost 70% for peripheral primary lung cancer [149]. Similar yields have been found by other workers [165]. On the other hand, lymphangitis carcinomatosa, being diffuse, is usually readily diagnosable by transbronchial lung biopsy assuming that the patient is fit enough to undergo the procedure [166].

## **Diffuse non-neoplastic lung disease**

### *Sarcoidosis*

Transbronchial lung biopsy is a very useful technique when it is considered important to obtain lung tissue to confirm a diagnosis of sarcoidosis (see Chapter 39). The success rate of this method in all stages of sarcoidosis has been reported to lie between 60 and 90%, the yield being greater when an infiltrate is visible on the radiograph [167–169]. One such study found that four transbronchial lung biopsies achieved a yield of 90% [170]. Endobronchial biopsies may also give the diagnosis in sarcoidosis [171] and these should be taken if mucosal lesions are seen. It has been claimed that such changes may be seen in up to 10% of patients with all stages of sarcoidosis [80]. Endobronchial changes consistent with sarcoidosis may be found histologically in 20–70% of cases [87] but random biopsy of normal-looking mucosa will probably not increase the diagnostic yield from transbronchial biopsy significantly.

### *Other diffuse non-infectious disease*

With the possible exceptions of alveolar proteinosis, in which alveoli contain a typical strongly eosinophilic and PAS-positive granular exudate, and idiopathic pulmonary haemosiderosis, in which alveoli contain numerous haemosiderin-laden macrophages, diffuse lung diseases of a non-infectious nature, other than sarcoidosis [171] and lymphangitis carcinomatosa [166], are much less likely to be reliably made on small pieces of tissue such as those

provided by transbronchial lung biopsy. Frequently the histopathological reports on such samples describe non-specific changes that could represent the end-stage of innumerable inflammatory processes or at best may report changes that are 'consistent with' whatever diagnosis the clinician was considering rather than being 'diagnostic' of a given pathology.

Wall, Gaensler and colleagues [15] carried out a prospective trial in such cases to ascertain the reliability of transbronchial lung biopsy in comparison with open lung biopsy; 53 patients underwent transbronchial lung biopsy and the procedure was diagnostic in only 20 (38%); over half these patients had sarcoidosis. The remaining 33 patients in whom the tissue diagnosis following transbronchial lung biopsy was uncertain were submitted to open lung biopsy, which achieved a specific diagnosis in 92%. These diagnoses bore little relationship to those put forward after transbronchial biopsy. The conclusion from this was that transbronchial diagnoses of cryptogenic fibrosing alveolitis (interstitial pneumonitis, interstitial pulmonary fibrosis), chronic inflammation, 'non-specific reactions' and fibrosis were unreliable and often misleading [15]. Other studies in which a comparison has been made between transbronchial and open lung biopsy have shown good agreement in a higher proportion of patients (62%) but have been much smaller, involving only 16 patients [172,173].

Although there is a lack of consensus concerning the best method by which lung tissue should be sampled to confirm the diagnosis and assess the degree of activity in cryptogenic fibrosing alveolitis, the argument is strong for carrying out open (or thoracoscopic) lung biopsy when it is considered necessary to obtain tissue [174]. In practice, once the balance of the risks as against the potential benefits of invasive investigation have been discussed with the patient, treatment is often started without histology when the diagnosis of cryptogenic fibrosing alveolitis seems highly probable on the basis of the whole clinical picture, including the result of HRCT.

Diffuse lung disease in patients with HIV is usually indicative of secondary infection but may occasionally be due to lymphocytic or non-specific pneumonitis, which can only be diagnosed by transbronchial or some other form of lung biopsy [175].

## **Pulmonary infection**

### ***Mycobacterial infection***

When active tuberculosis is suspected, fiberoptic bronchoscopy may be carried out in those patients who are unable to raise an adequate sample or in whom sputum is negative on direct staining for acid-fast bacilli [28,29,176–180]. Mycobacteria may be more easily detected if auramine staining with fluorescence rather than Ziehl–Nielsen staining is used. Material that can be examined

includes bronchial lavage fluid, endobronchial biopsies (where lesions are seen), bronchial brushings, transbronchial lung biopsies and postbronchoscopy sputum. The immediate positive yield in patients shown subsequently to have active tuberculosis is about 50% by acid-fast staining of transbronchial lung biopsies or other material [177,181]. One study found that of 56 positive bronchial brushings, 63% were immediately positive on direct smears and 37% only on culture [28]. Other studies have reported that tuberculosis is diagnosed by culture of fiberoptic bronchoscopy material, such as bronchial brushings (brush agitated in normal saline) or transbronchial lung biopsy, in about 30–50% of patients [177,178]. Miliary tuberculosis that is negative on sputum smear can also be diagnosed bronchoscopically, the highest yield coming from transbronchial lung biopsy followed by bronchial brushing and bronchial lavage [182]. There is some evidence to suggest that sputum induction using nebulized hypertonic saline may provide a diagnostic yield as good as bronchoscopy, the clear implication being that this simpler and less invasive test should be tried first [183].

The diagnosis of tuberculosis may sometimes be made by biopsy of endobronchial lesions found in patients with tuberculous hilar or mediastinal lymphadenopathy in the absence of lung parenchymal abnormalities [184]. The diagnosis can also be made by transbronchial or transcarinal needle biopsy of the enlarged lymph nodes themselves [184]. Endobronchial abnormalities are also not uncommon in patients with active lung parenchymal tuberculosis, being found in one-third of cases in one series [185]. Bronchoscopy was found to add little to the diagnostic yield in a hospitalized group studied in Dar es Salaam, a resource-poor area where tuberculosis is endemic, this disease being the most common cause of pulmonary infection (irrespective of HIV serological status), accounting for over 75% of disease in both HIV-positive and HIV-negative groups whereas *P. carinii* pneumonia was found in only 1% of the HIV-positive group [186].

In Taiwan, despite the high prevalence of tuberculosis, cancer was still found to be the commonest cause of a solitary pulmonary nodule, although tuberculosis accounted for 24% of such cases. Fluoroscopically guided brushing and transbronchial lung biopsy yielded the diagnosis of this infection in 55% of those in whom it could not be made by sputum smears [162].

*M. tuberculosis*, *M. avium-intracellulare* and other 'atypical' mycobacteria may also be isolated from immunocompromised patients [98,187,188]. A survey of patients with AIDS in England and Wales found that 4.6% had tuberculosis [189], and non-tuberculous mycobacteria may be detected with increasing frequency as AIDS progresses [190,191]. Visible endobronchial changes have been found in about 25% of HIV-infected patients with pulmonary tuberculosis [93]. Combined transbronchial biopsy and BAL has been claimed to have a sensitivity of 90% in diag-

nosing *M. avium-intracellulare* infection in patients with AIDS [126]. The finding of this organism in such circumstances is generally considered to be of pathological significance [192].

### Fungal infections

*P. carinii* pneumonia (see Chapter 52) may occur in many conditions in which the patient's cellular immunity is compromised, such as leukaemia, lymphoma, during the use of cytotoxic and other immunosuppressant agents for both neoplastic and non-neoplastic disease, and following organ transplantation [23]. This fungal organism is also recognized as the most important opportunist pathogen causing pneumonia in AIDS, accounting for 65–85% of cases in developed countries [112,192,193]. Fiberoptic bronchoscopy has been shown to be a highly effective means of establishing the diagnosis of *P. carinii* pneumonia in such patients. In a series of 171 patients with AIDS, from whom 127 isolates of *P. carinii* were obtained, it was reported that the sensitivity of BAL was 89% compared with 97% for transbronchial lung biopsy [126]. Where both procedures were used, a sensitivity of 100% was achieved. The authors stressed the importance of both adequate lavage and experienced and competent laboratory personnel. Fiberoptic bronchoscopy has also been found to produce a high diagnostic yield in *P. carinii* pneumonia by other workers [112,127,194]. There has been a trend to rely increasingly on the less invasive BAL, with a decline in the transbronchial lung biopsy rate, as it has become clear that BAL has a high diagnostic accuracy and a low rate of false negatives for *P. carinii* in experienced hands [98] as well as lower morbidity [194]. The yield may be higher if the upper lobes are lavaged [194]. The sediment obtained from BAL fluid is now usually examined using a direct immunofluorescent test, employing monoclonal antibodies against *P. carinii*, which demonstrates brightly stained cysts. Transbronchial lung biopsies may also be subjected to various conventional silver stains, such as Grocott–Gomori's methenamine silver stain for cysts and the modified Wright–Giemsa (or Diff Quik) stain for trophozoites, which may show them as minute dots in the alveolar spaces. The commencement of treatment for *P. carinii* pneumonia before bronchoscopy does not appear to prevent subsequent detection of the organism, as the cysts persist for days or sometimes even weeks after treatment, but prophylactic aerosolized pentamidine may reduce the yield from BAL so that the addition of transbronchial lung biopsies may be appropriate in this circumstance [194].

The recovery of fungi other than *P. carinii* from BAL fluid can cause difficulties in immunodeficient patients with apparent pneumonia, as it may not be clear whether such isolates are colonists or the genuine invasive cause of fungal pneumonia. *Aspergillus fumigatus* in particular is ubiquitous and is a common lung saprophyte. Purists

insist on histological evidence of lung parenchymal invasion by transbronchial biopsies coupled with a positive culture result, although clinicians often treat on the basis of strong suspicion, such as the finding of large numbers of fungi in the BAL fluid. Transbronchial lung biopsies are not always possible in such cases, as these patients not infrequently have thrombocytopenia as well as neutropenia. Various organisms other than *Aspergillus* species may be implicated, including *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Candida albicans* and the Mucoraceae causing pulmonary mucormycosis (see Chapter 21). A test for cryptococcal antigen may be run on BAL fluid and is useful in patients with HIV infection, who are particularly susceptible to infection by this organism [195].

### Viral infections

CMV is the commonest cause of viral pneumonia in patients who are immunosuppressed by drugs and in those with HIV infection. This virus has a tendency to cause infection in a recipient 6–8 weeks after transplantation of solid organs and, more particularly, bone marrow [194]. It has been suggested that such infection may be a factor in causing obliterative bronchiolitis in lung transplant recipients, although this remains controversial [18]. CMV was isolated from 43% of initial bronchoscopies in 171 patients with AIDS [126]. This organism may sometimes be a colonist rather than an invader and its clinical significance as a cause of pneumonia has been frequently questioned [98,196,197]. CMV may be cultured from bronchoalveolar washings and from transbronchial lung biopsies, although this may take several weeks and thus other methods have to be used. Evidence of infection, but not necessarily disease, may be provided by the typical 'owl's-eye' inclusion bodies on transbronchial lung biopsies. Positive immunofluorescent testing (by detection of early antigen fluorescent foci) of infected cells in BAL fluid or transbronchial lung biopsies may help to put the diagnosis on a firmer footing within a short time. CMV has also been detected in such specimens by the polymerase chain reaction technique.

Bronchoscopy is not ordinarily used to diagnose the microbial cause of pneumonia in immunocompetent patients [198] other than in those situations mentioned in the preceding paragraphs, with the exception of severe ventilator-associated pneumonia on intensive care units, in which case a protected brush is sometimes used [199,200] or semi-quantitative bacterial counts may be applied using numbers of colony-forming units as a diagnostic yardstick [114] (see p. 161 and Chapter 13).

### Complications of fiberoptic bronchoscopy and transbronchial lung biopsy

The general safety of fiberoptic bronchoscopy may lull the

operator into a false sense of security, for sudden complications do occur and rare fatalities are recorded in both the literature and physicians' memories. Such catastrophes can be guarded against by correct application of technique and by bronchoscopists and their staff being in a state of preparedness, so that when difficulties do arise they are dealt with swiftly and decisively.

### Mortality

Retrospective postal surveys rely on the accurate recall of events that the respondent might prefer to forget and therefore underestimate the total number of deaths. One such survey reported a mortality rate of 0.01% from 24 501 bronchoscopies, another found 0.02% from 48 000 investigations, and a third 0.04% from 39 564 procedures [52,201,202]. Prospective studies from single centres have naturally been much smaller and have recorded higher mortalities of 0.1% of 908 bronchoscopies and 0.5% of 205 bronchoscopies, the authors of the last work implying that the high mortality rate might have been related to the fact that the procedures were carried out by medical staff in training [150,203].

Of the multicentre series, the two deaths reported by Credle and colleagues [201] both occurred during the procedure in seriously ill and intubated patients. The 12 deaths in the series by Suratt and colleagues [202] were accounted for by two reactions to the topical anaesthetic (tetracaine) prior to the procedure, two massive bleeds from previously slowly bleeding tumours and two myocardial infarctions; of the remainder, chronic respiratory insufficiency, severe pneumonia, carcinoma and heart disease were coexisting factors. The most common cause of mortality associated with fiberoptic bronchoscopy in the series by Simpson *et al.* [52] was cardiovascular (myocardial infarction or left ventricular failure), accounting for 5 of 13 deaths; of the remainder two were attributed to haemorrhage, two to 'bronchospasm', two to 'advanced neoplasia', one to aspiration pneumonia and the other to a general anaesthetic. This study also found a higher incidence of deaths in teaching hospitals but attributed this to the observation that patients in teaching hospitals were 1.64 times more likely to undergo transbronchial biopsy during the procedure [150].

A retrospective postal survey of 2628 transbronchial lung biopsies found a mortality rate of 0.5% for this procedure, the most common cause being haemorrhage which accounted for nine of a total of 13 deaths [204]. Of these deaths eight occurred in patients who either had diseases or were taking drugs known to affect coagulation; of the remaining deaths two were associated with refractory hypotension, one with severe hypoxaemia and others occurred as a result of tension pneumothorax [204]. The estimated 3387 transbronchial lung biopsies in Simpson *et al.*'s series were associated with a mortality rate of 0.12% for this procedure; three of these four deaths were due to

haemorrhage (two in patients with leukaemia), the remaining death being attributed to pneumothorax in a patient with advanced neoplastic disease [52].

### Morbidity

Retrospective studies of fiberoptic bronchoscopy have found a major complication rate of 0.08–0.3%, 'major complication' having been defined as one considered to endanger life or requiring urgent therapeutic intervention [52,201,202]. Prospective studies report higher major complication rates of 1.7–5% [150,203]. Major complications have been found to occur 20 times more frequently when transbronchial lung biopsy is used rather than standard fiberoptic bronchoscopy, the figures being 0.12 and 2.7% respectively [52]. The two most important complications of transbronchial lung biopsy are pneumothorax and haemorrhage.

### Pneumothorax

Two series found that pneumothorax was the most common serious transbronchial complication, occurring in 5.5% and 2.9% of 2628 and 3387 procedures respectively [52,204]. The use of radiological screening reduced the incidence of this complication by almost 40% from 2.9 to 1.8% in one series [52]. The incidence of pneumothorax was 15% in one small series in which fluoroscopy was not used [205]. Small air leaks need no intervention other than observation, although intercostal tube drainage may be anticipated in 40–65% of cases and delayed pneumothorax may occur some hours later, presumably due to slow leaks [52,108,206,207]. Fatalities have occurred (see above). Pneumothorax may be more common when transbronchial biopsy has been carried out for diffuse rather than localized disease but need not be related to the number of biopsies taken [108]. HIV-infected patients with *Pneumocystis* pneumonia already have an increased incidence of secondary spontaneous pneumothorax [208] and these patients also appear to run a greater risk of iatrogenic pleural leaks; in one series 9% of 100 HIV-infected patients undergoing transbronchial lung biopsy developed pneumothorax and over half of them required tube drainage [126].

### Haemorrhage

This is the second most common serious complication of transbronchial biopsy and the most feared. The definition of a 'serious' pulmonary haemorrhage is problematical and subjective. One study recorded bleeding estimated to exceed 50 mL in 1.3% of 2628 cases; another reported that 0.5% of 3387 transbronchial biopsies were accompanied by 'major' bleeding [52,204]. Series in which transbronchial lung biopsy has been carried out in immunocompromised patients suggest a higher incidence of

significant endobronchial bleeding of about 5% [209]. A series that reported the complication rate of transbronchial lung biopsy in 24 thrombocytopenic patients (platelet range  $7\text{--}60 \times 10^9/\text{L}$ , mean  $30 \times 10^9/\text{L}$ ) reported serious endobronchial bleeding with a minimum estimated blood loss of 80 mL in four patients (17%), one of whom (4%) died of haemorrhage. Most of these patients had leukaemia and 67% died later as a result of the underlying condition [209]. The minimal platelet count necessary prior to performing transbronchial lung biopsy or bronchial brushing in peripheral lung is unclear but the requirement of a count greater than  $50 \times 10^9/\text{L}$  is usual [209]. There needs to be a compelling reason for the investigation at platelet counts below this level. There is little evidence to demonstrate the efficacy of measures to prevent alarming intrabronchial haemorrhage following transbronchial biopsy but the following are recommended.

1 Use of a routine 'clotting screen' before biopsy, e.g. platelet count, prothrombin time, activated partial thromboplastin time (and a bleeding time if a history suspicious of a haemorrhagic tendency is obtained). Platelet function may be impaired in a qualitative rather than a quantitative sense by aspirin and other drugs, plasma cell dyscrasias, other myeloproliferative disorders and systemic lupus erythematosus [209]. When a coagulopathy is suspected or confirmed, it seems prudent to carry out these screens within 12 h of bronchoscopy. Haematological advice should be taken about the finding of a systemic coagulopathy, which should be corrected with appropriate replacement, such as fresh frozen plasma, vitamin K, etc., before biopsy is undertaken.

2 Correction of thrombocytopenia (6–12 fresh platelet packs for a count of less than  $50 \times 10^9/\text{L}$ ).

3 Avoidance of biopsy or brushing in patients with uraemia (see pp. 169–170), which also impairs platelet function.

4 Local application of 5 mL of 1:20 000 epinephrine solution before biopsy.

5 Use of the 'wedge technique', where the bronchoscope tip tamponades a bleeding segment [210,211] (see p. 159).

6 Availability of a balloon catheter of suitable size for passage down the suction channel (e.g. Fogarty no. 4 or purpose-designed bronchoscopic balloon catheter) in order to tamponade a bleeding bronchus [212,213]. If such a catheter is not available in the presence of massive haemorrhage, asphyxiation may be prevented by isolating the bleeding lung with a single-lumen endotracheal tube passed into the other main bronchus. Such 'blind' intubation until resistance is felt usually places the tube in the right main bronchus, allowing ventilation of the middle and lower lobes. It may also be possible to selectively intubate the left main bronchus when the right side is bleeding, by passing the tube with the patient's head turned to

the right and with appropriate positioning of the bevel of the tube [214]. It is also usual to place patients on their side, with the bleeding lung most dependent in order to protect the other lung.

7 Availability of a competent rigid bronchoscopist with appropriate instrumentation for suction and per-bronchoscopic tamponade is also an advantage, although such a person (now usually a thoracic surgeon) will not be readily available in many smaller units [52,215].

Clearly the risk of haemorrhage is much higher in some patients than others, and aggressive bronchoscopists performing a biopsy in pursuit of opportunistic organisms or other diagnoses in perilously ill, immunosuppressed patients with uraemia, leukaemia or other blood dyscrasias are more likely to encounter serious haemorrhage than those whose practice is more mundane [204,210]. In such cases bronchial lavage without biopsy often gives a high yield with minimal risk. Severe haemorrhage may also occur as a result of endobronchial biopsy of visible tumour, although this is unusual. Vascular tumours such as KS have a propensity to bleed when interfered with and injudicious transbronchial needle biopsies by the less-experienced operator in the vicinity of centrally placed major vessels may court disaster.

### *Complications of sedation and topical anaesthesia*

One survey found that about half of all life-threatening complications were related to either premedication or topical anaesthesia [201]. Topical anaesthetics may cause epileptic seizures and cardiac dysrhythmias as already described [72,201]. Premedication also usually employs sedative drugs that may result in hypoventilation, as described in an earlier section. In another large survey, 7 of 10 episodes of life-threatening hypoventilation followed the use of intravenous sedatives [52]. It is conventional to guard against hypoventilation by reducing the dose of a sedative or omitting it altogether in patients who may be at risk, such as the elderly or those with significant pre-existing impairment of lung function. Where there is doubt about the advisability of a sedative, it is best omitted and patients often tolerate the procedure without one [216].

A maximum dose of 300–400 mg of lidocaine has been recommended for topical anaesthesia [217,218] and despite the fact that this dose is sometimes exceeded in practice [52], serious reactions occurred in only two patients in one series of 39 564 bronchoscopies [52]. Nevertheless, caution is advisable as both fatalities and serious complications have been described, and blood levels of 30–50% of an intravenous dose of local anaesthetic may follow the application of the same dose to a mucous membrane [201,202,219]. There is evidence to suggest that the topical application of lidocaine to the airways may also result in some airflow limitation [220].



Laryngospasm may occur, possibly as a result of inadequate anaesthetization of the larynx, although this is not clear. It was the most frequently reported complication in one series and may cause the bronchoscopy to be hurriedly abandoned [201].

#### *Other respiratory and cardiovascular complications*

Although the safety of fibreoptic bronchoscopy in mild asthma has been stressed [221,222], serious reactions in asthmatic patients are a well-recognized complication of the procedure [223,224]. The series of Dreisin *et al.* [150] recorded severe bronchospasm in three of four asthmatic subjects, with death in one. In the series of Credle and colleagues [201], six asthmatic patients had similar reactions and two required intubation. A UK postal survey recorded three major complications and two deaths ascribed to bronchospasm [52]. Various untested recommendations have been made in order to avoid serious bronchial reactions in asthmatic patients [118]. Such precautions include the administration of an intravenous bolus of 100 mg hydrocortisone before the procedure, intramuscular atropine 0.6 mg as premedication, 2.5–5.0 mg nebulized salbutamol before bronchoscopy, the limitation of lavage fluid to 200–300 mL with its heating to body temperature, and the provision of oxygen while monitoring pulse oximetry, a practice that is now routine.

Cardiovascular complications range from minor vasovagal episodes to serious cardiac dysrhythmias, myocardial infarction and pulmonary oedema, of which the last two were the most common causes of death in one postal survey [52]; 27 life-threatening cardiovascular complications occurred in 48 000 bronchoscopies surveyed in the USA [202]. Although published data to support the efficacy of preventive measures in these circumstances are sparse, sensible precautions involve the ready availability of equipment for cardiopulmonary resuscitation and the avoidance of hypoxaemia by means of pulse oximetry and appropriate provision of supplemental oxygen. Bronchoscopy should be avoided in patients with unstable cardiovascular symptoms. It may be carried out in patients who have had a myocardial infarction within the previous month provided that a strong indication exists [225,226].

Hypoxaemia has long been recognized as a potential complication of fibreoptic bronchoscopy, one study having found an average fall in  $P_{aO_2}$  of 2.7 kPa (20 mmHg) in 18 subjects [227–229]. A correlation between hypoxaemia and cardiac events has also been found, transient atrial and ventricular ectopic activity being most evident with maximum desaturation when the bronchoscope was in the region of the larynx [230]. Although such problems are rarely of clinical significance, the provision of supplemental oxygen and pulse oximetry as a routine is sensible [231]. Cardiac monitoring is also carried out routinely in some centres but is by no means universal.

**Table 8.3** Relative contraindications to fibreoptic bronchoscopy and biopsy under topical anaesthesia (see text).

Uncooperative patient
Uncorrectable hypoxaemia/hypercapnia
Unstable myocardium
Uncorrectable bleeding tendency
Tracheal stenosis
Poorly controlled asthma

#### *Miscellaneous complications*

Episodes of fever following fibreoptic bronchoscopy are described but supportive evidence of infection is unusual and bacteraemia rare [232]. The older literature suggests that bronchoscopic instrumentation in the vicinity of a large lung abscess may be hazardous as it carries the potential risk of rupture of the abscess with subsequent flooding of the bronchial tree by a sufficient volume of pus to overwhelm the suction channel.

#### **Contraindications to fibreoptic bronchoscopy and biopsy**

Contraindications to fibreoptic bronchoscopy are listed in Table 8.3; some have already been alluded to in the preceding section. Few of them are absolute. As fibreoptic bronchoscopy is normally carried out with only topical anaesthesia and sedation, a reasonable level of patient cooperation is required, otherwise the procedure is a waste of time and the instrument at risk of damage. Severe respiratory impairment present before bronchoscopy is likely to be worsened and it is our practice to carry out arterial blood gas analysis in patients whose  $FEV_1$  is less than 1 L or who have diffuse lung disease with tachypnoea at rest or on minimal exertion. If the  $P_{aO_2}$  is less than 9.0 kPa (about 70 mmHg) and if it cannot be safely corrected to this figure by supplemental oxygen, then this may be regarded as a contraindication to bronchoscopy, as is a raised  $P_{aCO_2}$ .

A myocardial infarction or serious cardiac dysrhythmia within 3 months would prompt a careful evaluation of the need for the examination and is a reason to monitor the cardiac rhythm during and following the procedure. Bronchoscopy may be carried out within 1 month of a myocardial infarction provided that a strong indication exists [225,226]. Unstable angina or uncontrolled left ventricular failure would clearly necessitate postponement of the procedure.

Thrombocytopenia or any other uncorrected bleeding tendency, including the presence of uraemia (which impairs platelet function), renders biopsy hazardous. As mentioned in the preceding section, transbronchial lung biopsy may be carried out when the need is pressing provided that steps are taken to correct the problem. Thus

6–12 units of platelets should be given for platelet counts of less than  $50 \times 10^9/L$  and haematological advice should be taken about the correction of bleeding diatheses. A blood urea of greater than 11 mmol/L (blood urea nitrogen 30 mg/dL) has previously been regarded as a marker of haemorrhagic risk [233]. More recently, greater tolerance of renal insufficiency has been shown, a serum creatinine of greater than  $260 \mu\text{mol/L}$  (3 mg/dL) being considered a relative contraindication to transbronchial lung biopsy by one group [234]. Such perturbations may lead to the request for a bleeding time, which if greater than 15 min is also regarded as a contraindication until corrected [209], although good data on the positive correlation between bleeding time and haemorrhagic risk in transbronchial lung biopsy are sparse [235].

Fibreoptic bronchoscopy may be carried out in controlled asthma provided that precautions are taken, and this condition should be regarded only as a relative contraindication to the procedure. Severe tracheal stenosis is more safely inspected by rigid bronchoscopy and to take biopsies in an area of critical tracheal narrowing is to court disaster.

### Infection control in fibreoptic bronchoscopy

It has been suggested that for the purposes of infection control in bronchoscopy all patients should be assumed to be potential HIV carriers, so that precautions should be applied routinely [118]; such advice clearly makes good sense.

### Protection of instruments

Fibreoptic bronchoscopes are costly and should be handled only by properly trained staff [231]. One firm of distributors used to be in possession of the wreck of an instrument fused to the inside of its carrying case after the bronchoscopist had made the mistake of leaving it on an intensive care unit only for it to be later removed and placed in an autoclave, as though it had been made of steel!

### Protection of staff

The chance of the spread of HIV infection from saliva is considered to be very small; however, occasional cases of HIV transmission have been reported from the splashing of blood on to broken skin or mucous membranes [236]. Care should be taken with the cricothyroid application of anaesthetic because of the small chance of self-inoculation. Seroconversion following needlestick injury after drawing blood in patients who are HIV or hepatitis B positive is thought to be about 0.9% in the former and 6–20% in the latter, so that bronchoscopists who do not have immunity should receive hepatitis B vaccine [237]. In order to avoid unnecessary risk, it has been recommended

that staff involved in bronchoscopy should wear water-impermeable gowns/aprons, gloves and masks. In addition, goggles or other protective eye-wear should be worn to avoid the theoretical transmission of the virus from contaminated material that might splash into the face of the bronchoscopist from the suction channel of the instrument when the patient coughs. Any accidental exposure to the blood of a patient known to be HIV positive may, after an appropriate risk assessment of the incident, be dealt with by a 4-week course of three antiretroviral drugs according to current published guidelines [238]. All pathological specimens are handled with the usual precautions applied to blood samples, being bagged in plastic before delivery to the laboratory. All disposables are bagged for incineration [239,240]. Contaminated surfaces may be cleaned effectively with a 10% solution of domestic bleach (sodium hypochlorite).

### Protection of patients

It is important that fibreoptic bronchoscopes and their accessories are thoroughly cleaned in order to prevent the transmission of infection [241], particularly as the instruments are used increasingly for diagnostic purposes in susceptible patients who are immunocompromised. Furthermore, potential pathogens identified in bronchoscopic washings may in fact be contaminants if bronchoscopic cleaning techniques are imperfect and this may lead to the inappropriate treatment of patients with potentially toxic antimicrobial agents. *Mycobacteria* and *Pseudomonas aeruginosa* were found to be the organisms most commonly transmitted in one study [241]. The bronchoscope may become contaminated from tap water by environmental organisms such as *M. chelonae*, *M. fortuitum* and *M. xenopi* and by fungi such as *Rhodotorula rubra* and *Blastomyces dermatitidis* [242].

It is most important that fibreoptic bronchoscopes are routinely first cleaned *before* being disinfected, these procedures being carried out by a trained nurse or other assistant both at the beginning of a list and between procedures [242,243]. Removable valves from the proximal end of the suction channel are dismantled and hand-washed and brushed using neutral detergent. The bronchoscopic channel should be similarly hand-brushed with detergent. Prior dispersion of particulate matter from complex components, such as biopsy forceps and cleaning brushes, by placing them in an ultrasonic cleaner with detergent for 10 min has been claimed to be helpful and is often carried out routinely in well-equipped units. It is stressed that these manual cleaning procedures must be carried out before disinfection as some disinfectants fix proteinaceous debris (which may subsequently act as a nidus for infection) and such material is not effectively removed by washing machines. A solution of neutral detergent is also sucked through the biopsy channel several times, between

which a cleaning brush is pulled up and down the channel to remove blood and particulate matter. Further disinfection is usually achieved using a freshly prepared 2% alkaline solution of glutaraldehyde in which modern bronchoscopes and biopsy implements may be totally immersed for 20 min, the solution being first drawn into the suction channel using a syringe. It is now a requirement that glutaraldehyde be used under a fume hood because of its irritant properties and propensity to cause asthma. This part of the process is now frequently carried out in washing machines, although personnel should be aware that these machines may themselves become contaminated; thus they should be regularly serviced and not be considered immune from periodic inspection by the infection control team.

After this cleaning and disinfection procedure has been followed, the shaft of the instrument and its channel are then wiped and rinsed through with sterile water (which does not contain environmental mycobacteria) or 70% alcohol, all parts being well dried before reassembly or storage [244]. North American guidelines for infection control in flexible endoscopy have also been published [245]. Recent evidence has been published showing that many units in the UK do not fully adhere to guidelines on disinfection procedures [243].

When tuberculosis is suspected, immersion of the bronchoscope for 1 h has been recommended [246], although the usual practice of thorough cleaning followed by a 20-min immersion in 2% glutaraldehyde is probably adequate [242,243,247]. *M. avium-intracellulare* is more resistant to glutaraldehyde than *M. tuberculosis* [248] so that when immunocompromised patients are to undergo bronchoscopy, 2% glutaraldehyde immersion of the bronchoscope for 1 h rather than the usual 20 min has been suggested [244]. Earlier publications recommended prolonged immersion of bronchoscopes in glutaraldehyde following their use in HIV-infected patients [239]. However, HIV has been shown to be destroyed by 2% glutaraldehyde within 2 min even in the presence of serum [236]. Hepatitis B virus has similarly been shown to be inactivated by 2% glutaraldehyde in less than 10 min [236].

Stabilized buffered 0.35% peracetic acid solution is a new, less irritant, more rapidly acting and more expensive alternative to 2% glutaraldehyde that is currently undergoing evaluation. Fibreoptic bronchoscopes may be gas sterilized using ethylene oxide but this is rarely necessary and indeed carries the disadvantage of requiring up to 7 days to allow for the dispersal of gas that has become adsorbed on to the plastic parts of the instrument; furthermore ethylene oxide may sometimes cause damage to the shaft of the bronchoscope.

The risk of infective endocarditis in susceptible patients appears to be very low or negligible following fibreoptic bronchoscopy so that antibiotic prophylaxis is not mandatory [249].

**Table 8.4** Indications for rigid bronchoscopy (see text).

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Surgical assessment of lung cancer operability
Foreign body suspected
Inspection of tracheal stenosis
Emergency control of profuse endobronchial bleeding
Removal of copious or viscid endobronchial secretions
Paediatric bronchoscopy (paediatric fibreoptic bronchoscopes are available)

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### **The place of rigid bronchoscopy under general anaesthesia**

The rigid bronchoscope has by tradition been the instrument of the thoracic surgeon and a postal survey carried out in 1983 found that only 24 of 231 respiratory physicians who responded made use of the rigid instrument [52]. Despite this, the rigid bronchoscope used under general anaesthesia retains an important role (Table 8.4), sometimes because the rigid instrument itself is preferable and sometimes because general rather than topical anaesthesia is indicated [52,250].

The principal advantages of the rigid bronchoscope relate to (i) its wide channel through which large biopsies and foreign bodies can be more easily grasped and removed and (ii) its superior suction capability. It has also been claimed that extrinsic involvement of the carina by nodes can be inferred by using the rigid bronchoscope as a lever. The principal disadvantages of the rigid bronchoscope are its lack of manoeuvrability and the requirement for a general anaesthetic if a particularly unforgettable experience is to be avoided.

Fibreoptic bronchoscopy in children using topical anaesthesia is not only a frightening procedure but may also interrupt normal ventilation significantly, as the bronchoscope acts as a space-occupying lesion in the relatively small volume provided by the child's glottis and trachea, although this spatial problem has been reduced by the availability of smaller, purpose-designed, paediatric fibreoptic bronchoscopes [251–253]. However, these are unsuitable for removing foreign bodies and cannot deal with brisk bleeding. In general, bronchoscopy in the adult or paediatric patient who is uncooperative is best performed under general anaesthesia if a tiresome fiasco is to be avoided.

The rigid bronchoscope was first developed to remove foreign bodies and has retained its pre-eminence in this field [38,255]. Similarly the rigid bronchoscope is necessary for the endoscopic removal of a broncholith. The flexible bronchoscope may be used to remove small foreign bodies that may be beyond reach of the rigid instrument and a number of accessories are available for this purpose [38]. These include wire baskets or claws, with alligator forceps and balloon catheters [38]. The fibreoptic instrument may also be useful if the rigid bronchoscope cannot be used because of trauma to the face or neck.

The emergency treatment of profuse haemoptysis may be delivered using a rigid bronchoscope that provides a channel for stronger suction, enabling the bronchoscopist to pack the bleeding bronchus with gauze tape or to otherwise tamponade it by means of a Fogarty or similar balloon catheter. The fiberoptic bronchoscope suffers from the dual disadvantage of immediate loss of vision with anything more than the most trivial bleed and of a suction capacity that is immediately overwhelmed by a large volume of blood. Nevertheless, when a bleed occurs during fiberoptic bronchoscopy it is possible to tamponade the bronchus with a balloon catheter as previously described on p. 168 [255]. The author has seen torrential bleeding during rigid bronchoscopy result in fatality despite the advantages that this instrument possesses in this situation.

Tumours involving the trachea or protruding above the level of the carina are often anticipated, as a result of the presence of stridor and because of the typical appearance of a flow-volume loop or FEV<sub>1</sub>-time curve. These are better inspected by the rigid instrument as the flexible instrument can cause respiratory embarrassment in the presence of critical airway narrowing, whereas the hollow-tube bronchoscope does not. Biopsies should not be undertaken with either instrument where narrowing is judged to be critical as only a little oedema or haemorrhage may seriously worsen the obstruction. Other serious causes of tracheal narrowing are also best inspected using the rigid instrument, which may also be used to pass a tracheal dilator or in stenting of the trachea or a main bronchus [44]. Rigid bronchoscopy may also be used in the treatment of large airway tumours by laser [42].

## Lung biopsy

Lung biopsy is carried out in order to establish a histological or microbiological diagnosis in a patient with either diffuse or localized lung disease, provided that the diagnosis cannot be established with a reasonable degree of certainty by other less invasive means. The procedure should be undertaken if it is anticipated that the information obtained will usefully influence the management of the patient, either by encouraging the initiation of potentially beneficial treatment or by discouraging potentially harmful empirical therapy.

Lung biopsy may be closed or open. Closed lung biopsy may be carried out percutaneously with various types of needle or trephine by any physician competent in the technique. Nowadays it is more commonly performed by radiologists who are trained to guide the needle to the most appropriate place under fluoroscopic, CT or, in the case of subpleural lesions, ultrasound control [256,257]. In the case of closed lung biopsy, it should be remembered that a negative biopsy of a 'mass lesion' does not always exclude malignancy and that preoperative investigation using these techniques is not necessary if surgical excision will be carried out regardless of a negative result.

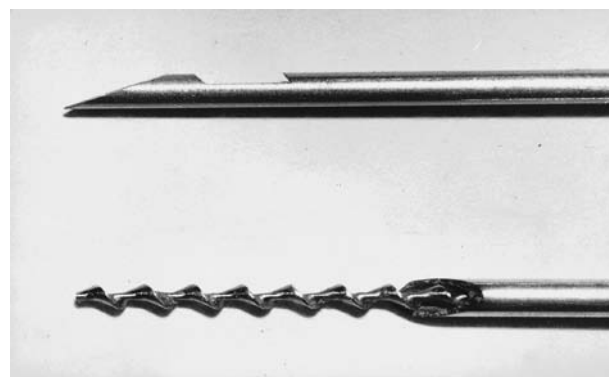
Before undertaking any type of lung biopsy it is wise to check the haemoglobin and to request a 'clotting screen' and measurement of urea and creatinine; the patient's blood group should also be determined and serum saved. An uncorrectable bleeding diathesis is a clear contraindication to biopsy (see pp. 169–170). Bilateral procedures are never carried out at the same session because of the risk of double pneumothoraces. Impaired lung function increases the risk of the procedure and a compelling reason would need to be found to justify the risk of lung biopsy in a patient with an FEV<sub>1</sub> of less than 1 L. Other contraindications to closed needle biopsy include uncontrollable cough and pulmonary hypertension.

## Transbronchial lung biopsy

This procedure has been fully discussed in the section on bronchoscopy (see pp. 157–160).

## Percutaneous fine-needle biopsy

Two techniques in use are aspiration biopsy and screw-needle biopsy. Aspiration biopsy needles are, by convention, smaller than 20 gauge (usually 22 gauge) and obtain cellular material for cytological examination, in contrast to the 'cutting' or 'core' biopsy needles described later that are designed to obtain a core of tissue suitable for making multiple conventional histological paraffin sections. One technique employs a thin spinal-type or longer Chiba needle, with an external diameter of approximately 1 mm, that is introduced together with a central stylette into the area under investigation, suction being applied and the needle withdrawn with a small harvest of cellular debris [258,259]. Various designs of circumferentially sharpened needles have been used with lengths up to about 20 cm, similar to those available for lumbar puncture, although modifications such as the provision of a lateral slot towards the tip of the needle may retrieve more material for diagnostic purposes (Fig. 8.8). Many dif-



**Fig. 8.8** Fine percutaneous aspiration needle (above) with a lateral slot towards its tip designed to increase the sample size. Screw-type fine biopsy needle (below) with a coaxial system enabling the screw-like stylette to trap larger clumps of cells.

ferent types of needle have been designed, some relying on a coaxial system in which the lesion is located with a slightly larger outer needle, multiple passes being then made through this with a thinner inner aspiration needle. More specialized needles of the type developed by Nordenstrom that are modifications of this coaxial system are also available [260,261]. These are also thin (1 mm) but differ in that a screw-like stylette traps larger clumps of cells (Fig. 8.8).

These types of needle are used to sample discrete peripheral lesions beyond bronchoscopic vision, more often than not to confirm a diagnosis of neoplastic disease [262]. The size of peripheral lesion that may be successfully biopsied is a function of the skill of the operator and the resolution of the radiographic equipment. Biopsy of lesions greater than 2 cm in diameter should be achievable with a reasonable level of expertise; lesions of 1–2 cm may be attempted but lesions of less than 1 cm require CT or biplanar imaging equipment and a very high degree of proficiency [263]. More centrally placed hilar and mediastinal masses may also be biopsied [264]. Less frequently, needle aspiration has been used in serious and unresponsive cases of pneumonia when the aetiological agent is uncertain [265].

### Techniques

The area of interest is predetermined from recent posteroanterior and lateral chest radiographs and by CT, the latter being helpful in planning the biopsy approach. The patient may be sedated provided that no contraindications exist and is positioned prone or supine according to whether a posterior or anterior approach is planned. The area under investigation is then identified under radiographic control, usually by CT guidance or ultrasound in the case of lesions abutting the chest wall with no separation by aerated lung. Biplanar or C-arm fluoroscopy may also be used to locate the lesion. If single-plane fluoroscopy without a C-arm is all that is available, then the vertical distance between the skin surface and the lesion can be predetermined by measurement on the lateral chest radiograph and this distance measured off against the biopsy needle and marked with either a ligature or plastic clip, so that the needle may be advanced to the correct depth; the area of skin through which the needle will enter is marked under fluoroscopy using a metal pointer and skin pencil. Fluoroscopic guidance may be an advantage in biopsy of lesions in the lower third of the lungs, where respiratory excursions are greater, as it provides imaging in real time.

The area is then cleaned and local anaesthetic (about 10 mL of 1% lidocaine) applied to the skin and chest wall down to the pleura. A nick is made in the skin with a scalpel blade to allow easy passage of the needle. The position of the lesion is again checked fluoroscopically and the needle inserted into the abnormal area, usually using an

approach that is perpendicular to the chest wall and under intermittent fluoroscopic control. Some resistance may be felt when the needle contacts relatively dense tissue such as tumour but this may not be discernible.

In the case of aspiration biopsy of presumed solid lesions, the stylette is removed when the needle tip is judged to abut the edge of the lesion, the bevel of the needle being covered with the gloved finger to reduce the possibility of air embolism. A 10-mL syringe is then attached to it and forceful suction applied as the needle is advanced into the lesion. Suction may be continued as the needle is 'jiggled' up and down a few times and rotated or 'drilled' within the lesion but is turned off as the needle is slowly withdrawn from the chest, the aim being to draw material into the tip of the needle rather than the barrel of the syringe itself [264]. Once removed from the chest, the contents of the needle can be displaced on to a microscope slide either with the needle stylette or by blowing a little air through the needle from the syringe. Some prefer that a cooperative patient should suspend respiration when the needle is being advanced into the lung, while others prefer to permit quiet breathing in order to avoid the risk of a sudden respiratory excursion while the needle tip is in the chest. When fine-needle aspiration is being used to obtain microbiological information in 'difficult' pneumonias, the syringe may be primed with a few millilitres of non-bacteriostatic, sterile normal saline that is expelled into the area of suspicion before negative pressure is applied [265].

The technique of screw-needle (Nordenstrom) biopsy differs in that the biopsy device is a 22-cm needle, the last 1.5 cm of which is screw-like, inserted through a 1-mm diameter, 16-cm cannula that is itself held in a specially designed handle so that the instrument may be manipulated in a narrow X-ray beam without exposing the operator's hand to radiation. The cannula and screw are inserted together, with the screw in the sheathed position. When the edge of the lesion to be biopsied is reached, the screw is rotated clockwise between finger and thumb, drawing itself into the lesion while the rest of the instrument is held in the same position. The cannula is then advanced over the screw and the whole withdrawn together. As with other needling techniques, the manoeuvre and its effect can be safely and conveniently practised using an apple. A technique has been described by which three screw-needle biopsies may be taken with only one passage of the outer cannula [261]. Screw-needle biopsy allows a larger sample to be obtained than is possible with the tip of a standard aspiration needle and firmer more organized tissue to be successfully biopsied, whereas this might not be achieved with aspiration devices.

A chest radiograph is obtained after the conclusion of the procedure to exclude pneumothorax or intrapulmonary bleeding and the patient is advised to report the development of any new symptoms. The film may be repeated at 4 h or the following day as slow pleural air leaks sometimes occur, although this practice is often

omitted unless the patient is symptomatic. Patients who are having fine-needle biopsy carried out on a day-case basis should have the procedure done in the morning in order to allow a period of observation on the ward. They should also have someone to accompany them home and to remain with them overnight, with an agreed hospital point of access should difficulties arise. It is safer for the patient to remain in hospital overnight if these conditions cannot be met.

### Processing the specimen

As with BAL, retrieval of the specimen is only the first stage of the diagnostic process and the most competent technical performance may come to nothing unless there is a good degree of communication and cooperation between the operator and colleagues in the pathology or microbiology departments. The aspirated material should be placed on a labelled slide and spread evenly with the end of a second slide, before being fixed immediately by placement in 95% alcohol in a Coplin jar. Ideally, this should be done under the supervision of a cytologist or, if this is not possible, according to an agreed and tried protocol. For aspiration needle biopsy the cellular contents of the needle may be expelled on to a slide using the syringe. Smears are also made from material adherent to the screw when the Nordenstrom needle biopsy device has been used. Some debris may also be obtained by blowing air through the needle with a syringe. One advantage of having expert and readily available cytopathological comment on the smears is that the biopsy can be repeated at the same session if no neoplastic cells are initially identified in a lesion considered clinically to be a tumour [266]. Few facilities enjoy this luxury.

Where microbiological rather than cytological information is sought the procedure is the same, except that the material obtained is stained and cultured for microorganisms rather than submitted for cytology. Some of the aspirated material (in saline) may be inoculated into appropriate broth or solid media for culture according to microbiological advice and the needle and syringe may also be rinsed out with a liquid culture medium. Appropriate stains may be applied as described on pp. 165–166.

### Complications

#### *Pneumothorax*

This is the most common complication of fine-needle biopsy of the lung, occurring in between one-fifth and one-third of patients [261,263,264]; the sudden onset of sharp chest pain should alert the operator to this possibility. The majority of these pneumothoraces are shallow and require no treatment, but the placement of an intercostal drain may be necessary in 1–13% of cases [261,263,264,267,

268], the incidence of pneumothorax having been found to fall as the experience of the operator increases [261]. It should be borne in mind that the pleura will be punctured more than once if the needle crosses an interlobar fissure and thus the chance of pneumothorax is increased. Biopsy of lesions abutting the pleura rarely causes pneumothorax, although the chance of pneumothorax increases in needle biopsy with increasing distance of the lesion from the chest wall or if the lesion is small so that more needle passes are required to locate it [269]. Some but not all have found that pneumothorax is more likely in the presence of an obstructive impairment of ventilatory capacity [270–272]. When this complication does arise in an emphysematous patient, intercostal tube drainage is more likely to be required [269]. It has been claimed that if the patient breathes pure oxygen before lung biopsy, the frequency of a complicating pneumothorax is reduced [273]. However, Poe and colleagues [274] observed an unaltered risk after breathing oxygen, although the size of the pneumothorax was reduced and the rate of absorption increased. It is the experience of some authors that the rate of complicating pneumothorax may be reduced if the patient lies ‘puncture site down’ for 1 h after the procedure [275]. The equipment necessary for dealing with a pneumothorax should always be available when any form of closed lung biopsy is carried out.

#### *Haemorrhage*

Severe haemorrhage into the lung is the most feared complication of closed lung biopsy. This is rare with fine-needle biopsy, although small haemoptyses are not uncommon and radiographic evidence of a small pulmonary haematoma after the procedure is sometimes seen. Haemoptysis of sufficient size to require treatment is rare [261,262]; the various management options are dealt with in a previous section (see pp. 167–168). Significant bleeding into the pleural space may also occur [276]. Chest wall bleeding is prevented by avoidance of the intercostal arteries, the needle being inserted over the upper margin of a rib, attention also being paid to the surface anatomy of the internal mammary arteries, which run vertically 3–4 cm to the left and right of the sternum, posterior to the costal cartilages.

#### *Air embolism*

Air embolism complicating needle biopsy has been recorded as a possible cause of loss of consciousness, convulsion and cerebral infarction on rare occasions [277–279]. Theoretically it is possible for air to enter a pulmonary vein through the needle if this is unoccluded or for air to pass from a punctured bronchus into an adjacent damaged vein once the needle has been withdrawn, especially if coughing occurs. This potentially fatal complica-



tion, which may be managed with hyperbaric oxygen therapy [278], has been estimated to occur in about 1 in 2000 cases [263].

#### *Tumour seeding*

The possibility that an operable tumour might be seeded into the chest wall or pleura, although apparently remote with fine-needle biopsy, is nevertheless well reported and should therefore be carefully considered before biopsy of an apparently 'operable tumour' [280–283].

#### **Diagnostic accuracy**

A diagnosis is frequently reached in experienced hands. Success or failure depends not only on the nature of the case under investigation (almost always neoplastic disease in the published series) but also on the combined skill and experience of the operator and the cytology service. Those centres with a high level of expertise with the techniques described may obtain diagnostically useful material in 75–95% of cases, the highest yields being obtained in malignant lesions [21,261–263,284,285]. Such results are not achieved when the investigation is undertaken in less than optimal conditions. Thus although false-negative results in neoplastic disease may be only 5 or 6% in the best series, figures that are themselves cause for concern, the rate of false negativity in more usual circumstances may be higher. A large series of 683 patients with solitary pulmonary nodules found a false-negative rate of 18% of 203 patients in whom a diagnosis of malignancy was ultimately confirmed histologically by other means [284]. There was a false-positive rate for malignancy of 1.5% in the same series. A precise histological diagnosis is problematical but it is usually possible to make the distinction between small-cell and non-small-cell lung cancer [286]. The material obtained from fine-needle aspiration of benign nodules is more often undiagnostic, the reported accuracy ranging between 46 and 68% [287].

#### **Contraindications**

Fine-needle biopsy of the lung is contraindicated in patients who are unable to cooperate either as a result of illness or for other reasons. Uncorrected bleeding disorders or other conditions associated with an increased tendency to bleed, such as uraemia or pulmonary hypertension, are also contraindications. The presence of severe respiratory impairment to the extent that even a shallow pneumothorax might be dangerous would present an unacceptable risk. Other contraindications include bullous emphysema, the possibility of the opacity under investigation being either a vascular anomaly or a hydatid cyst, and the use of positive pressure mechanical ventilation.

#### **Mortality**

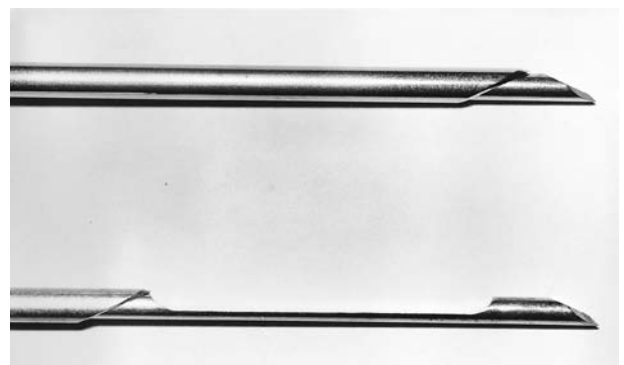
The reported mortality rate is very low, in the order of 0.1% [262,268].

#### **Cutting-needle biopsy**

Various manually operated cutting needles have been designed to remove a core of tissue from the lung; the modified Vim disposable cutting needle is one example (Fig. 8.9). It is the general view that the use of such wide-gauge needles (approximately 2 mm) is associated with greater morbidity and mortality than fine-needle biopsy, particularly if they are used to obtain tissue from patients with diffuse lung disease. This may be because a specimen of air-filled lung tissue is difficult to obtain with a conventional cutting needle without tearing surrounding lung and disrupting blood vessels in the process. Although some practitioners continue to use these larger manually operated cutting needles, mainly in patients with relatively superficial localized malignant disease, a variety of automated cutting needles that offer a number of advantages have been introduced in recent years [288].

#### **Techniques**

The radiographic determination of the position of the lesion and the preparation of the patient, including positioning under fluoroscopic or CT control, are as described for fine-needle biopsy. If the manual technique is used, the modified Vim biopsy needle (Tru-cut) is inserted in the closed position. Once the tip of the needle has entered the lesion the inner stylet is advanced to its limit using one hand, exposing a 20-mm specimen notch (the 'open' position). While the stylet is held steady in the first hand, the outer cutting sheath is then advanced rapidly over the stylet using the other hand so that the needle is once again closed, this time within the lesion, and the biopsy is secured. The needle is then immediately removed and the



**Fig. 8.9** Tip of cutting biopsy needle in open and closed positions.

specimen retrieved. The manipulations of the needle are carried out either during breath-holding, if the patient is judged able to cooperate, or during normal tidal breathing. The whole manoeuvre, once practised beforehand, need only take a few seconds. Where there is macroscopic doubt about the adequacy of the sample, and provided that there are no complications, the procedure may be repeated once or twice.

A fine-bore (1.2 mm) manually operated cutting needle has also been produced, the design being based on a modified Menghini technique. The needle (Vacu-cut) is inserted through the chest wall in a 'closed' position, after which a central trocar is retracted to induce a partial vacuum in the body of the needle, which is advanced and rotated into the lesion under radiographic control [289].

The first large series of automated biopsies described the use of an adapted 14–20 gauge Tru-cut needle that was single-handedly fired using a spring-loaded trigger device (Biopty) by which the central stylet was advanced by a spring, followed a fraction of a second later by the outer cutting sheath of the needle [290]. This device has the advantage of being easy to manipulate and fire with one hand, leaving the other hand free to hold an ultrasound probe in appropriate cases [290]. Such powered cutting-needle biopsy guns are widely used to obtain tissue from a variety of organs. One of the advantages of such needles for lung biopsy, compared with their non-automated counterparts, is the relatively small diameters available (usually 18 or 20 gauge) that nevertheless produce satisfactory cores of tissue 16 mm in length with a clear-cut edge, the shearing effect being minimal as a result of the very high speed with which the biopsy is taken [288,291].

Samples may be transferred from these needles to a Petri dish containing normal saline and thence to 10% formalin fixative. Staining is carried out in the light of prior discussion with the histopathologist and microbiologist, according to the nature of the case, and as well as haematoxylin and eosin might in appropriate circumstances include auramine, Ziehl–Nielson and silver methenamine stains for acid-fast bacilli, fungi, etc.

At the conclusion of the procedure chest radiographs are taken to exclude pneumothorax, as for fine-needle biopsy.

## Complications

### *Pneumothorax*

As with fine-needle biopsy, pneumothorax is the most frequent complication and has been reported to occur in 11–32% of cases in series that used non-automated cutting needles which crossed aerated lung [292–294]. The lower figure was obtained in those lesions where the vast majority were within 3 cm of the pleural surface [294]. One large

series of 220 biopsies, carried out using the Franklin–Silverman needle, in patients with diffuse disease found pneumothorax in 32% [295]. Complications are unusual in the case of pleurally based lesions, no pneumothorax occurring in 133 such lesions that were biopsied with non-automated large cutting needles in one series [294]. Death as a result of tension pneumothorax has been reported; however, as with fine-needle biopsy it is unusual for intercostal tube drainage to be required [296]. The fine-bore 1.2-mm modified Menghini needle (Vacu-cut) produced pneumothorax in 28% of a small series of 29 patients, three patients (10%) requiring placement of a small-bore tube for drainage [289]. A combined series of automated cutting-needle biopsies of 25 pleural lesions and 32 lesions surrounded by aerated lung produced pneumothorax in 15.6% of cases, active treatment being required in only one (3%) [297].

### *Haemorrhage*

Bleeding is not uncommon and is usually detected as a small haemoptysis or increased radiographic shadowing in the region of the biopsy. Occasionally more substantial bleeds occur [295]. One large study recorded haemoptysis in 18% of 220 biopsies of diffuse disease, one of which was fatal. A more recent series recorded haemorrhage, usually minor, in 20% of cases biopsied for localized disease. Haemoptysis estimated to be more than 50 mL was recorded in 5.6% of a total of 89 patients, one patient requiring a transfusion for a large haemothorax [292]. A review of 13 deaths caused by percutaneous lung biopsy found that 10 followed the use of cutting-needle or trephine (see below) techniques, despite the fact that these procedures accounted for a minority of most large series [298]. It is largely as a result of such sudden and catastrophic bleeds, which once witnessed are not easily forgotten, that the transbronchial lung biopsy technique was developed [299–301]. Such complications probably occur more frequently when the cutting needle is used in diffuse disease and when penetration is deep, although whether it is safer to restrict penetration to 3 cm beneath the pleura (or to 8 cm from the skin surface) is controversial [292,302]. It is intuitive that a more superficial stab is less likely to cause serious harm than a deep one.

### *Miscellaneous complications*

Other complications are uncommon and as described for aspiration lung biopsy. There is a remote possibility of air embolism. The seeding of the needle track by neoplastic cells occurred in 2 of 69 cases of confirmed malignancy (2.9%) in one series and has the potential to convert an operable case into an inoperable one [292]. This complication has been reported more frequently following cutting-needle biopsy than with fine-needle aspiration biopsy.

Infection of the pleural space is a rarely described complication [294].

### Diagnostic accuracy

Cutting-needle biopsy has not usually been recommended for diffuse lung disease because (i) the yield of tissue from non-automated cutting needles has been inadequate for definite diagnosis in one-quarter of cases or more, and (ii) the rate with which serious complications occurs is higher than for alternative diagnostic methods such as transbronchial lung biopsy and thoracoscopic or open lung biopsy [292,300–303]. A small study in which an automated cutting needle was used in 15 patients with diffuse lung disease produced a histological diagnosis in 79%, a 1.2-mm diameter needle being used in 14 of them; a complicating pneumothorax occurred in the one remaining patient (7%) in whom a 2-mm diameter needle was used [304].

There is no doubt that use of the older non-automated cutting needle can achieve a reasonable degree of accuracy in peripheral mass lesions. Comparisons between different series are not necessarily justifiable, but positive yields of 61–96% have been claimed where the lesion was considered malignant [292,296,302,305]. The series claiming the highest positive yield for localized opacities failed to obtain clinically useful information in 8% of cases, the pathological process being declared non-malignant in 18% of 89 patients [292]. A high degree of accuracy has been achieved for lesions that exceed 2 cm in diameter [292]. Lesions smaller than this require a high level of skill and adequate fluoroscopic, CT or ultrasound support. A small series in which the fine-bore 1.2-mm modified Menghini needle (Vacu-cut) was used under fluoroscopic control achieved a positive diagnosis in 89% of 18 malignant pulmonary tumours and in 80% of five non-malignant lesions [289].

The earliest large series of automatic cutting-needle biopsies (Biopsy gun) used ultrasound control to obtain 404 biopsies from a variety of organs including 18 lung biopsies in which the sensitivity was 87.5% for malignancy [290]. Further series using the same or similar techniques supported by ultrasound, fluoroscopic or CT guidance have produced consistently good results for localized lesions of pleura, chest wall, lung and mediastinal contents [288,291]. Although fine-needle aspiration biopsies are very sensitive at detecting neoplastic cells, they are dependent on cytological expertise and are less good at providing a tissue-specific diagnosis, whereas cutting needles provide a core of tissue for both conventional staining and immunohistochemical methods and are more likely to provide information about the precise pathological process in both benign and malignant disease, including lymphoma and KS [287,291,297]. A retrospective study of CT-guided transthoracic biopsy com-

pared the use of an 18-gauge automated cutting needle gun and a 20-gauge aspiration needle and concluded that the cutting needle increased diagnostic accuracy with no obvious increase in complication rate [306].

### Contraindications

The contraindications to cutting-needle biopsy are the same as those listed under fine-needle biopsy.

### Mortality

The majority of reported deaths that have occurred in patients as a result of percutaneous lung biopsy have been caused by various types of non-automated cutting needle, and have been a consequence of sudden and massive endobronchial haemorrhage. Various published series using different types of cutting needle (Vim–Silverman, Franklin–Silverman, Vim disposable, Jack) reported four deaths in 1079 patient procedures, giving a mortality rate of 0.37% [292,295,302,305,307–312]. The largest single series of modified Vim (Tru-cut) cutting-needle biopsies recorded two deaths in 382 procedures, giving a mortality rate for this implement of 0.52% [307]. In addition, there are a number of case reports of deaths including two procedures that were carried out for diagnostic purposes in peripheral mass lesions where both of the patients died from haemorrhage [298].

### Drill or trephine biopsy

A mechanically driven rotating cutting needle designed to biopsy various tissues was first described over 50 years ago. In the thorax this technique was confined to biopsy of localized lesions in the lung periphery and pleura until Steel and Winstanley [313], using modified apparatus, published the results of 38 drill biopsies carried out in patients with diffuse lung disease, a positive diagnosis being made in about 71%. The technique has a small and dwindling number of devotees, having been largely supplanted by transbronchial or thoracoscopic biopsy in diffuse disease and by the more modern automated cutting or aspiration needle methods in the case of localized disease.

### Technique

Steel's technique uses a Desoutter pneumatic drill (Fig. 8.10) driven by air compressed to 690 kPa (100 lb/in<sup>2</sup>) supplied from a standard cylinder via a reducing valve. This rotates a 3-mm external diameter trephine with a sharpened cutting edge and internal rifling. The speed of rotation at this pressure is about 15000 r.p.m., so that the cutting edge moves at a speed of 1.6 m/s as it slices through lung. The patient is prepared as described for

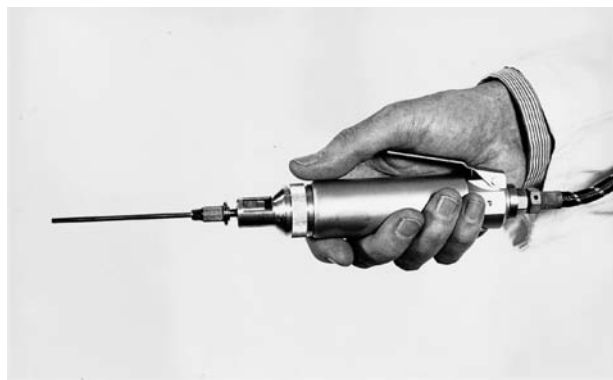


Fig. 8.10 Pneumatic trephine biopsy drill.

fine-needle biopsy, except that where the lesion is diffuse it is convenient to carry out the procedure with the patient sitting and leaning forward with arms resting on a support. The eighth intercostal space posteriorly in the region of the tip of the scapula may be used. The skin must be marked if a localized lesion is to be biopsied, and in such cases the procedure is carried out using intermittent fluoroscopy with the patient in either a prone or supine position [314]. The lesion has to be within about 4 cm of the visceral pleura because the hollow trephine is only 7.5 cm long (compared with 13.5 cm for a Tru-cut). The skin is prepared and local anaesthetic applied down to the pleura as previously described. The high-pitched noise that the drill makes when running is then demonstrated to the patient in order to avoid causing undue alarm. The trephine is flushed with 3.8% sodium citrate contained in a 20-mL syringe; if microbiological studies are required, normal saline may be used, about 5 mL being left in the syringe [313]. A small skin incision is made with a scalpel and the trephine with stylet in place is advanced to the pleura. Its position should be checked fluoroscopically in the case of localized lesions. If the position is judged to be satisfactory, the stylet is removed, the lumen of the needle being occluded with the gloved finger, and the drill is attached by its Luer fitting. Some authors found modifications helpful to prevent the slippage that may occur with the Luer fitting when the drill is in action [296,315]. Once the drill, which is not sterile, has been handled, a 'no-touch' technique has to be followed to prevent contamination of the trephine. Unless a gloved assistant is used, this involves the use of another sterile trephine if the procedure has to be repeated.

The patient is asked not to move, cough or breath deeply while the drill is in action. The drill is operated by pressing a lever and the trephine advanced 3–4 cm over the space of 2–3 s. The drill is then disconnected, being replaced with the 20-mL syringe to which suction is applied as the trephine is withdrawn from the lung. The liquid in the barrel of the syringe is used to eject the sample into a Petri dish, and from thence it is placed in for-

malin fixative for staining according to prior discussion with the pathologist. Any small pieces of tissue and residual saline may be submitted for microbiology and/or cytology as described above for the other biopsy procedures. A chest radiograph is obtained routinely at the end of the procedure in order to exclude haemorrhage and pneumothorax, as with other types of lung biopsy.

### Complications

The same complications occur with drill biopsy as for fine-needle aspiration and cutting-needle biopsy. Pneumothorax occurs with a reported frequency of 30–40% [300], although one study found pneumothorax in only 7% of 190 procedures [316]. These required placement of an intercostal drain in 40–60% of cases [314,316]. Substantial haemoptyses were uncommon, occurring in about 2% of cases, but as with other forms of percutaneous lung biopsy fatal haemorrhage may occur, albeit rarely [21,316,317]. Minor haemoptysis occurred in 7% of procedures [316]. As with cutting-needle biopsy, needle track spread of tumour has been described [313,314].

### Diagnostic accuracy

In practiced hands, adequate material has been obtained from drill biopsy in over 80% of cases [300,316], and claims have been made that the size of the specimen is superior to that obtained from any other type of percutaneous biopsy and that lung architecture is better preserved. Those series that compared the diagnostic yield of drill biopsy with transbronchial lung biopsy and cutting-needle biopsy (Vim–Silverman needle) obtained better specimens and a commensurately higher diagnostic yield with the drill, which was claimed to be preferable to earlier manually operated cutting needles for diffuse pulmonary disease and in patients who had large solid mass shadows within 4 cm of the pleural surface [296,318]. However, the development of modern automated cutting needles and thorascopic lung biopsy techniques have largely negated these advantages.

Three large series comprising 339 patients reported diagnostic results in about three-quarters of all cases, of whom almost 70% had 'diffuse disease' [313,314,317]. An Indian study of 161 patients achieved a histological diagnosis in 91% [316].

### Contraindications

These are no different from those listed for fine-needle biopsy.

### Mortality

Deaths resulting from trephine biopsy have rarely been

reported, a figure of about 0.5% having been obtained from a review of published data on drill biopsy for diffuse disease [300,316]. It has generally been supposed that morbidity and mortality is less when the drill is used to sample more localized and superficial disease processes.

## **Open and thoracoscopic lung biopsy**

### **Open lung biopsy**

Open lung biopsy is carried out under general anaesthesia through a thoracotomy. Rather than carry out a full posterolateral incision of the type used for pneumonectomy or lobectomy, most surgeons carry out a so-called 'limited thoracotomy', making their incision in the fourth or fifth intercostal space anteriorly. Other prefer to make a small incision anteriorly in the second or third intercostal space as advocated by some authors for mediastinotomy, finding that this approach allows access not only to all lobes but also to the hilum and anterior mediastinum [319,320]. The surgeon is able to inspect the lung and choose the site thought most likely to yield diagnostic information. It has been recommended that where disease is radiographically diffuse, a site of apparently 'average' involvement should be biopsied; and when disease is advanced, a macroscopically less involved site should be sampled. This approach avoids the submission of a piece of 'honeycombed' lung that on microscopic examination may show only end-stage fibrotic change, with no clues as to the original pathological process. The tip of the lingula and the middle lobe are if possible avoided, being considered less likely to be representative than other parts of the lungs and frequently showing inflammatory changes or fibrosis due to previous and unrelated inflammatory episodes. HRCT may help the physician decide which area of lung should be sampled.

Once a site has been chosen for biopsy, the anaesthetist gently inflates the lungs and the surgeon clamps and excises the portion of lung required and immediately places half to two-thirds of the sample in formalin fixative, thereby avoiding atelectasis [300]. As with any form of lung biopsy, whether percutaneous or open, the diagnostic yield is heavily influenced not only by the sampling techniques but also by the skill and care with which the tissue is subsequently handled and examined. In the author's view no open lung biopsy material should be submitted for laboratory examination without prior discussion with the histopathologist and microbiologist concerned, so that the specimen can be handled according to a protocol that may vary according to the clinical circumstances of each case. Without such discussion, the patient may be submitted to a potentially hazardous procedure with a suboptimal chance of the correct diagnosis being reached. In addition to haematoxylin and eosin, histological stains may include PAS, van Gieson and Prussian Blue; stains for organisms include Gram, auramine,

Ziehl-Nielsen, Gomori's methenamine silver, Giemsa, etc. according to circumstances.

The remaining piece of lung tissue may be submitted unfixed for further microbiological studies, including immunofluorescent tests where appropriate, one portion being ground up and cultured under aerobic and anaerobic conditions for bacteria, mycobacteria and fungi. Another portion may be placed under 4% glutaraldehyde for later electron microscopic studies and a further piece stored at  $-60^{\circ}\text{C}$  for any examination that may be considered helpful later, such as further immunofluorescent testing and viral studies [300].

The surgical procedure for open lung biopsy is relatively minor and the patient may be able to leave hospital within 3–4 days if the underlying condition permits. The 30-day mortality rate in a large series of over 500 cases was 0.2%, with no deaths if extensive carcinoma is excluded [300]. The complication rate from a review of several large series was 7% and mainly resulted from inadequate postoperative intercostal tube drainage. A high diagnostic yield in excess of 90% is usually claimed [134,300,321].

### **Video-assisted thoracoscopic lung biopsy**

This is a thoracic surgical procedure that is an acceptable alternative to open lung biopsy, having the principal advantage of being less invasive [17]. It is carried out in operating theatre conditions, under general anaesthesia and with single-lung ventilation, allowing the lung under thoracoscopic examination to be collapsed so that it can be displaced for a good view. The patient must therefore have sufficient pulmonary reserve to maintain adequate oxygenation with single-lung ventilation and the procedure cannot be carried out on sick hypoxic patients in respiratory failure without significant mortality, as indeed is also the case for conventional open lung biopsy [17]. Three ports of entry are commonly used: one for the thoracoscope, which carries the video camera attachment; one for a linear stapler device, which allows a large sample of lung to be secured for biopsy; and a third to allow instrumentation to remove the specimen. The procedure may not be possible in the presence of pleural adhesions. When compared with open lung biopsy, video-assisted thoracoscopic lung biopsy has been shown to provide specimens of equivalent volume, to have equal diagnostic accuracy, to be as rapid and to have no additional complications, the duration of pleural drainage and hospital stay both being reduced [322–324], although at greater cost [325]. Prior to the availability of video-assisted thoracic surgery and linear staplers, thoracoscopically guided lung biopsy was carried out with the conventional thoracoscope, the biopsy being obtained with forceps and the site being sealed with electrocautery [326], a technique generally regarded as being more likely to result in air leak.

### Is a lung biopsy necessary?

Patients are considered for lung biopsy when they are found to have a chest radiographic abnormality that demands an accurate diagnosis which cannot be reached by other less invasive means. The radiographic shadowing may be diffuse, such as occurs in sarcoidosis or cryptogenic fibrosing alveolitis, or localized, as in the case of peripheral mass shadows situated beyond bronchoscopic vision.

#### Diffuse disease

Lung biopsy is only indicated if the result of the investigation is likely to alter the subsequent management of the patient to his or her benefit. Accurate diagnosis need not improve survival to be regarded as beneficial; thus histological evidence of lymphangitis carcinomatosa may, by removing doubt, place the management of an individual case on a firm footing and allow adequate palliative measures to be taken with confidence.

Not infrequently in diffuse disease, the diagnosis can be made beyond reasonable doubt without recourse to lung biopsy. Such is the case in a patient with the syndrome of erythema nodosum and bilateral hilar lymphadenopathy who develops a diffuse pulmonary infiltrate in the absence of crackles or finger clubbing. The likelihood of sarcoidosis in this clinical context is so high that histological proof may be considered superfluous. Similarly, a patient with a clear occupational exposure to asbestos dust who develops clubbing and crackles with chest radiographic and physiological changes consistent with asbestosis may require no further diagnostic confirmation. Likewise, the diagnosis is sufficiently evident when exposure to some recognized cause of extrinsic allergic alveolitis, such as a budgerigar, is associated with typical features, including breathlessness, upper zone crackles and mid-inspiratory squawks, physiological evidence of lung restriction, reduced gas transfer, the usual radiographic features and the finding of allergen-specific precipitins in the serum. Chronic eosinophilic pneumonia may also present with sufficiently typical features to allow a non-invasive diagnosis to be made [327].

Lung biopsy becomes necessary in diffuse disease when there is doubt about the diagnosis and when the physician is reluctant to commit the patient to empirical treatment, which may itself be associated with morbidity, without a firmer knowledge of the underlying pathology and the likelihood of a response. Such may be the case in those patients in whom the probable diagnosis is sarcoidosis who may have some degree of effort intolerance, absent digital clubbing, no crackles, a variable degree of restrictive or obstructive impairment of ventilatory capacity and reduced gas transfer factor, diffuse pulmonary radiographic shadowing, with or without hilar lym-

phadenopathy, and no history of erythema nodosum. In such a situation the physician may feel that although the clinical probability of sarcoidosis is high, the diagnosis should be histologically confirmed prior to treatment with corticosteroids.

In cryptogenic fibrosing alveolitis, the decision about whether to biopsy is likely to be influenced by various factors, including the patient's age and general state of frailty. There will be reluctance to submit an elderly and breathless patient, whose life expectancy is short, to an unpleasant invasive procedure when the diagnosis is firmly supported by a typical history, physical signs and chest radiographic, lung function and HRCT findings, especially as the likelihood of response cannot be predicted accurately from histology so that corticosteroids will be tried anyway. However, there is no doubt that corticosteroid or other immunosuppressive treatment can be used with greater conviction in the light of a firm histological diagnosis and therefore this is more likely to be sought in the younger patient, who in the event of failure of treatment and progression of disease may become a candidate for a lung transplant.

Rare conditions that may be associated with diffuse pulmonary shadowing, such as Langerhans' cell histiocytosis, alveolar proteinosis and the pulmonary vasculitides, may well go undiagnosed without histology, leading to appropriate treatment being omitted or at best given on an empirical basis with no very clear idea of the likely prognosis.

A further important clinical situation encountered with ever-increasing frequency is that of the patient who is immunocompromised either as a result of AIDS or as a consequence of receiving immunosuppressive therapy for a variety of conditions, such as tissue transplantation, leukaemia or lymphoma (see Chapter 52). When strenuous therapeutic efforts are being pursued, it becomes important to know whether diffuse pulmonary shadowing is a consequence of opportunistic infection or, in the case of neoplastic disease, whether it may be accounted for by a recurrence of the disease itself or by an adverse effect of a cytotoxic drug. Patients with AIDS often present with perplexing pulmonary manifestations of their underlying disease. Although most diffuse pulmonary infiltrates in this group may be diagnosed by fiberoptic bronchoscopy with lavage, brushings and transbronchial biopsy, about 10% may undergo open lung biopsy in the following circumstances: (i) if the bronchoscopy is non-diagnostic, especially if the patient's condition is deteriorating clinically or radiographically; or (ii) if the patient is failing to respond to treatment despite bronchoscopy that has been diagnostic, provided that the patient is not in respiratory failure or being mechanically ventilated (both of which carry a high mortality and contraindicate open lung biopsy) [328,329]. The operative mortality has been reported to be less than 8% in these circumstances [318].

Others have also found a high diagnostic yield with low morbidity for open lung biopsy in patients with HIV infection and AIDS in whom bronchoscopy was non-diagnostic, also finding that the results significantly affected management [330].

It is not uncommon for extensive bilateral radiographic 'honeycombing' to be encountered for the first time in an elderly patient who may or may not have been treated on an empirical basis over many years without a histological diagnosis ever having been established. The probability of useful information being derived from an invasive procedure in such a case is slim since the histology is likely to be that of end-stage, 'burnt-out', fibrotic disease, perhaps with no clue as to the original pathological process.

Therefore, in all cases that show diffuse pulmonary radiographic shadowing a decision has to be made about whether the patient is best served by empirical treatment based on clinical probability or whether some form of invasive lung biopsy should be used to make the diagnosis firm.

#### **Localized disease (including coin lesions)**

The often solitary peripheral pulmonary lesion (coin lesion or solitary pulmonary nodule) provides another common diagnostic dilemma in which curiosity and enthusiasm should once again be restrained by the prime consideration as to whether the result of a biopsy will influence management. The question that should always be asked is 'What am I going to do if the result of the biopsy is non-diagnostic?' If the answer is 'Ask a surgeon to take it out', then why biopsy in the first place?

The immediate consideration is whether the lesion is a malignant neoplasm rather than a benign tumour or some form of inflammatory disease. Unless there is good evidence to the contrary, such as old chest radiographs that show an identical appearance, then the lesion is best assumed malignant until proved otherwise. A North American study of 40 such patients (mean age 65 years) with solitary pulmonary nodules (defined as rounded lung opacities 3 cm or less in diameter) found that 53% were malignant, over 90% being surgically resectable [331]. CT with contrast may be helpful in such lesions, as malignant tumours can be relied upon to enhance by 20 Hounsfield units, the sensitivity of this test at this level of enhancement approaching 100% [332]; this finding should therefore encourage surgical removal where feasible. Unfortunately a non-enhancing lesion cannot be relied upon to be benign, the specificity of the test being about 78% [332]. Although the published results of various methods of percutaneous biopsy usually claim high positive diagnostic yields, it must be realized that even in the most expert hands false-negative results may occur in patients with neoplastic disease unless sufficient tissue is obtained to enable the pathologist to diagnose a specific

benign process; thus if a decision is taken to withhold surgical excision on the basis of a negative percutaneous or transbronchial biopsy, a variable number of patients with potentially treatable disease may be denied a chance of cure and therefore follow-up in such cases should be very careful.

One approach to the patient with a peripheral mass lesion, in whom non-invasive tests have provided no support for a benign process, who has no evidence of metastatic disease (including CT of the thorax and abdomen) and who is otherwise considered fit for resective surgery, is to advise thoracotomy directly, without first having to submit to a percutaneous biopsy procedure with its additional risks, including that of converting a curable tumour into an incurable one as a result of needle track seeding of neoplastic cells to the chest wall or pleura [280–283,292]. This approach would appear the most prudent for the patient aged 45 years or over with a lesion 3 cm or more in diameter [333]. Occasional exceptions to this rule may have to be made: if it is decided that thoracotomy would for various reasons carry a high risk for an individual patient and the surgeon will only accept that risk if the diagnosis is firm; or if a radiotherapist for various reasons feels constrained not to treat without histological proof of tumour. It must be clear in such situations that the surgeon or radiotherapist will not be inclined to treat anyway, even if the biopsy procedure is negative, since in this case the procedure will have been unnecessary.

The other approach is one of observation, which is reasonable in a young non-smoker with no previous chest radiographs and a well-defined lesion less than 2 cm in diameter. Such lesions are likely to be benign and may be followed up with serial films unless they are found to enhance on CT. In other patients, an old chest radiograph showing that a nodular opacity has remained unchanged for 2 years is helpful as the lesion is likely to be benign. Benign lesions characteristically have a doubling time that exceeds 400 days [334]. It is a useful rule of thumb that a mass has doubled in volume when its diameter has increased by 25%, so that a lesion is likely to be benign if its diameter is increasing by less than 25% every 18 months. Certain patterns of central calcification have also been associated with a benign process but eccentric areas of calcification do not rule out malignancy [334,335].

#### **Which type of lung biopsy procedure?**

Once it has been decided that tissue is required in order to manage a patient optimally, it then becomes necessary to decide which of the various procedures available should be used: transbronchial, fine-needle aspiration, cutting needle, drill, open or thoracoscopic lung biopsy (Fig. 8.11). It has to be accepted that there is a lack of consensus in this regard and that the results of some published series show



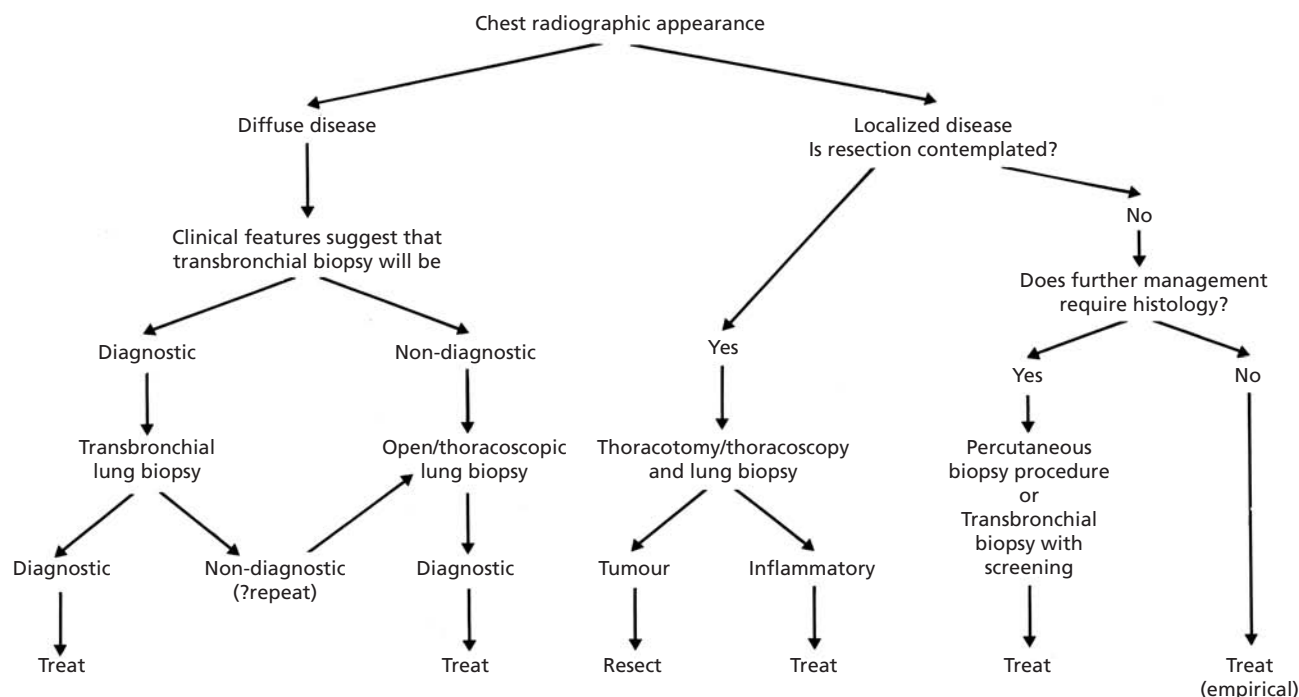


Fig. 8.11 Decision tree for lung biopsy.

a high degree of sensitivity for a particular test that may not necessarily be reproduced in another centre. Nevertheless, some observations of a general nature can be fairly made. Invariably the choice of biopsy procedure is influenced by the likely diagnosis and whether the disease is diffuse or localized.

### Diffuse disease

Some diffuse histopathological processes are so characteristic as to allow a diagnosis to be made from only a small piece of tissue. Thus in the case of diffuse disease in which sarcoidosis is considered probable, transbronchial lung biopsy is the technique of choice and is likely to produce a positive yield [336]. Percutaneous needle biopsies are less favoured in diffuse disease for various reasons. Fine-needle aspiration has been developed primarily for harvesting clumps of cells from solid lesions and can give no idea of lung architecture. Cutting-needle biopsies are also better suited to sampling solid, relatively superficial lesions and although lung tissue can be obtained in diffuse disease it may be torn or distorted (especially with non-automated methods); furthermore, the morbidity of the procedure exceeds that of transbronchial lung biopsy [300], which is preferred in diffuse disease with highly pathognomonic histology. Diffuse disease other than sarcoidosis in which transbronchial biopsy may produce a good yield includes lymphangitis carcinomatosa, *P. carinii* pneumonia (although BAL alone is usually adequate),

eosinophilic granuloma, alveolar proteinosis and pulmonary haemosiderosis. The mortality figures for transbronchial lung biopsy are likely to be skewed by its use in iller patients than tend to be subjected to cutting-needle biopsy and it is generally held that the passage of cutting biopsy needles through aerated lung exposes the patient to greater hazard than transbronchial lung biopsy [307]. Although trephine biopsy delivers a more representative core of tissue than transbronchial lung biopsy, it also carries a higher morbidity than transbronchial biopsy when used to sample diffuse disease. Despite producing good results in well-practiced hands, it is no longer widely used and for peripheral lesions where histology, rather than cytology, is required has been overtaken by automated cutting-needle biopsy using fluoroscopic, CT or ultrasound control.

Open or thoracoscopic lung biopsy is appropriate when investigating diffuse disease in which either transbronchial biopsy has failed to establish the diagnosis or the clinical features suggest from the outset that a larger piece of tissue might be required. This is often the case with disease in which the histological features are more variable, such as cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis), in difficult cases of suspected extrinsic allergic alveolitis, and in the pulmonary angitis and granulomatoses.

Open lung biopsy has the twin disadvantages of requiring general anaesthesia and being painful. Although the mortality of the procedure is reportedly greater than that for transbronchial lung biopsy and other closed procedures [300], such reports are likely to be distorted by the

surgical convention of using '30-day mortality' figures and by bias resulting from iller patients being submitted to the open procedure than is the case with closed procedures such as transbronchial biopsy. Open lung biopsy has the advantage of being almost entirely free from the hazard of massive and uncontrollable intrapulmonary haemorrhage, which may rarely complicate all closed lung biopsies. Nowadays, video-assisted thoracoscopic lung biopsy is increasingly favoured because large samples of lung tissue may be satisfactorily obtained with reduced morbidity.

### Localized disease

When disease is localized and peripheral, surgical exploration using an open procedure is usually indicated for both diagnosis and treatment as discussed above. If for some reason this approach is not possible, then the choice of biopsy technique depends to a large extent on individual preference and experience. The choice lies between fine-needle aspiration biopsy, cutting-needle biopsy, drill biopsy and transbronchial lung biopsy/needle aspiration under fluoroscopic control. All these procedures have been described in the preceding sections. It is again stressed that the practical procedure of obtaining the specimen, although clearly of crucial importance, is only one step towards a diagnosis; small specimens, such as the clumps of cells obtained with a fine needle, require expert cytopathological handling with a good level of cooperation between clinician and pathologist.

### Biopsy of the pleura

The pleura is usually biopsied as a closed procedure; less frequently biopsy may be carried out under direct vision at thoracoscopy or as an open procedure at thoracotomy.

### Needle biopsy

This is usually carried out with an Abrams punch [337] (Fig. 8.12), which is advanced through a small incision in the skin and intercostal muscle, with gentle but sustained pressure, using a clockwise–anticlockwise rotatory movement until 'give' is felt, according to the technique described in Chapter 43. This procedure is more easily

carried out in the presence of a pleural effusion, which provides the operator with the welcome reassurance that a good site was chosen. Sometimes needle biopsy may be attempted in the expectation of finding a pleural effusion only to meet the resistance of a grossly thickened pleura. It is generally possible to penetrate such pleural thickening using a rotatory movement to the point of give, without damaging underlying lung, as the tip of the Abrams biopsy punch is relatively blunt. Once this point has been reached it is easy to withdraw the needle slightly with firm pressure on the side of the open biopsy notch so that a pleural sample can be ensnared and removed, usually yielding neoplastic tissue. Some operators may prefer to use a Cope needle [338] or a disposable modified Vim-type cutting needle [339] (Tru-cut, see Fig. 8.9) in this situation, although the sharp tip of the latter may be more likely to puncture underlying lung.

### Complications

The commonest complication is a shallow pneumothorax, usually resulting from the ingress of some air through the biopsy needle or, less commonly, as a result of injury to the underlying lung [340]. Other complications of inappropriately directed needles include haemothorax, which may be massive if an intercostal artery is damaged [341]. Cases of intercostal artery aneurysm and arteriovenous fistula have also been described [341,342], as have injuries to other viscera including the spleen, pancreas and diaphragm. As with any thoracic paracentesis, it is possible for infection to be introduced causing empyema; in the case of malignant effusions, neoplastic cells may be seeded along the needle track [343].

### Diagnostic yield

In patients who are subsequently shown to have a neoplastic cause for a pleural effusion, a positive yield from pleural biopsy is found in 40–70% of cases, the usual diagnostic yield being about 50%. The chance of a positive result is increased by multiple biopsies, pleural fluid cytology and, if results are initially negative, later repeated attempts at pleural biopsy [344–349]. Such positive biopsies usually indicate secondary pleural involvement by tumour. Mesotheliomas may occasionally be diagnosed on needle



Fig. 8.12 Abrams pleural punch.

biopsy material, although this is not easy on a small sample and subsequent postmortem material may show metastatic adenocarcinoma or some other tumour.

When a pleural effusion is due to tuberculosis, the needle biopsy may show consistent granulomatous inflammatory changes or result in isolation of tubercle bacilli in 50–88% of cases, although by no means all cases show caseation, Langhans' giant cells and acid-fast bacilli [344–346,350]. The pleural biopsy in rheumatoid disease may show characteristic changes but more often than not the findings are non-specific [351].

### Simple (conventional) thorascopic biopsy

The principal use of the thoracoscope in the early part of the twentieth century was to allow the operator to divide pleural adhesions, by cutting or electrocautery, so that an artificial pneumothorax could be satisfactorily induced in the era before the antibiotic therapy of tuberculosis. Despite its invention by a physician, thoracoscopy was abandoned by chest physicians in English-speaking countries as effective antituberculous drugs were developed. However, the necessary skills were preserved by thoracic surgeons and also by respiratory physicians on mainland Europe and thoracoscopy began to be adopted increasingly by these groups as an investigative procedure, at first mainly in cases of undiagnosed pleural effusion [352]. Ordinarily, this problem is tackled first with pleural aspiration and closed-needle biopsy of the pleura, as described above, and it is in the 25–30% of patients in whom the diagnosis remains elusive that thoracoscopy may be undertaken in order to identify the local cause while avoiding the need for thoracotomy [353].

In recent years, thoracoscopy has undergone a revival as a result of improvements in the design of the conventional instruments used by both physicians and surgeons and also with the invention of the videothoracoscope. With its miniaturized video camera and fibreoptics, this device has enabled the thoracic contents to be displayed with great clarity on a video screen, thereby enabling the operator and assistant to carry out complex intrathoracic surgery through three small ports without recourse to conventional thoracotomy (see Fig. 44.15). This video-assisted thorascopic surgery has been referred to in the sections on lung biopsy (see p. 179) and remains firmly within the province of the thoracic surgeon, whereas simple or conventional thoracoscopy may be carried out under local anaesthesia and in an endoscopy suite and is being increasingly taken up by physicians.

### Technique

Thoracoscopy may be carried out, with the help of an assistant, under local anaesthesia using 10–20 mL of 1%

lidocaine. Premedication with atropine is usual and sedation with an agent that also produces amnesia, such as midazolam, is considered helpful. Intravenous access is set up, supplemental oxygen given and pulse oximetry recorded. The patient may be positioned in the lateral decubitus position with the healthy side down, the upper arm being cradled in abduction by a support. The dorsal decubitus position may also be used. Any pleural fluid first has to be completely drained in 250-mL aliquots, an equivalent amount of air being allowed to enter the pleural cavity under negative pressure following each aspiration so that the lung falls well away from the chest wall in order to allow full inspection of the pleural cavity. Such drainage can be achieved with a 2–3 mm diameter trocar with combined tap and both sharp and blunt obturators for easy passage and the removal of debris [354]. It is safest to check radiographically that the lung has fallen away from the chest wall before proceeding to the next stage and it may be convenient to carry out the drainage and collapse procedure the day before thoracoscopy.

Next, using blunt dissection, the drainage trocar is removed and replaced with a 5–7 mm thorascopic trocar and cannula in order to allow passage of the thoracoscope itself. This is usually in the mid-axillary line in the sixth or seventh intercostal space when pleural effusions are being investigated. Any pleural fluid remaining in dependent zones can then be aspirated by a small plastic tube introduced through this cannula, enabling the thoracoscope to be passed with good vision. An artificial pneumothorax may be similarly induced in cases where no pleural fluid is present, although care has to be taken not to damage the lung and attempts may be foiled by the presence of pleural adhesions [354].

Whereas the earlier Stortz rigid thorascopes were 11 mm in diameter, modern instruments are much smaller and have excellent optics. Thus a 4–7 mm diameter thoracoscope may be easily introduced into the pleural cavity through a small thorascopic cannula. Angled-vision thorascopes are essential in order to view the pleural cavity as fully as possible, in the fashion of a submarine periscope. 'View-ahead' instruments are also used to enable biopsies to be taken through a single port of entry. Sometimes it may be desirable to fashion a further port of entry using a second 5-mm trocar, the entry position being chosen by depressing an appropriate-looking intercostal space while viewing the inside of the chest wall through the thoracoscope. A second entry point may be useful in obtaining a biopsy from a point that is relatively inaccessible to the thoracoscope, acute angulation of which tends to produce pain by pressing up against the adjacent ribs. This second port may then be used to introduce a 5-mm forceps, which is guided under direct vision from the thoracoscope. The second port may occasionally also be useful as a channel for the introduction of an electro-

cautery loop, which can be used to divide pleural adhesions where these are hindering progress in some way.

Pleural biopsies may be taken with either optical forceps, using a single port, or larger forceps, using a second port of entry as described above. Care is taken to avoid the intercostal vessels when performing the biopsy, especially where the pleura is thin. Most lesions are found on the parietal pleura and multiple biopsies may be taken. In the unusual case where only visceral pleural lesions are found, one or two biopsies may be taken and any air leak or bleeding minimized by use of electrocautery forceps or YAG laser, if available [354]. Intercostal bleeding may be similarly dealt with or may be tamponaded with an epinephrine-soaked sponge through the second port. Insertion of a chest drain with suction to bring the lung rapidly up against the chest wall has also been found to be effective [354].

### Yield

Thoracoscopy is a useful method for diagnosing pleural malignancy that has been missed on pleural fluid cytology and closed-needle pleural biopsy. In a series of 161 patients with pleural effusions, 69% of 35 patients with two or more non-diagnostic pleural aspirations and 60% of another 41 patients with negative closed-needle biopsies were found to have pleural malignancy at thoracoscopy [355]. The procedure was sensitive for diagnosing malignancy, finding it in 95% of cases when this disease was present, with 100% specificity (i.e. no false positives for malignancy) [355]. In a series of 173 patients with pleural effusion due to malignant mesothelioma, a diagnosis was made thoracoscopically in 98% [356].

Thoracoscopy is also a reliable method for diagnosing pleural tuberculosis, although usually this is unnecessary as the yield from closed-needle biopsy is high (see above) [357]. Occasionally rheumatoid pleural effusions present diagnostic difficulties, in which case thoracoscopy may be performed; characteristic granular parietal pleural changes have been described, this material also showing characteristic histology [358]. Thoracoscopic mediastinal biopsy may provide a histological diagnosis in 86% of patients with mediastinal masses [359].

### Thoracoscopic talc pleurodesis

The thoracoscope may also be used therapeutically in malignant pleural effusions in order to obtain a pleurodesis by carrying out talc poudrage, 4.5g of pulverized sterile talc being insufflated under direct vision using a talc atomizer. A 28–30 French gauge intercostal tube, with side-holes cut along its length, can then be passed through the seventh intercostal space in the mid-axillary line and directed along the costovertebral gutter towards the lung

apex under thoracoscopic control, being kept in for a few days until drainage is complete [354,360]. Talc insufflation has been shown to be superior to both tetracycline and bleomycin in reducing the natural tendency for a malignant effusion to reaccumulate [361].

### Complications

Thoracoscopy itself appears to carry little risk, induction of a pneumothorax being well tolerated [362]. Air leaks from lung and bleeding from damaged intercostal vessels are both potential complications. The principal contraindication is the presence of dense pleural adhesions.

### Transtacheal aspiration

Transtacheal aspiration is a technique designed to obtain secretions from the lower respiratory tract of patients with suspected pulmonary infection in such a way as to avoid contamination of the sample with oropharyngeal organisms [363]. Having been in vogue in the 1970s, its application has diminished more recently as it is an unpleasant procedure for the patient and one not without morbidity and even mortality [364]. Another reason for its diminished use is that the ideal patient is infrequently encountered in modern hospital practice. Such a patient has suspected pneumonia with consistent radiographic findings, has no past history of chronic or recurrent lower respiratory tract infection, has escaped prior treatment with an antibiotic, is well enough to be cooperative and is yet unable to raise sputum. It is accepted practice for clinicians to rely on the initial empirical use of antibiotics designed to cover the likely organisms while awaiting the result of sputum Gram stain and culture, despite the recognized deficiencies of these tests. Although past enthusiasts found wider applications for its use, transtacheal aspiration is now seldom carried out and most physicians would only consider it in patients with pneumonia of moderate severity in whom sputum was not produced, or when it failed to yield pathogens in a patient whose initial response to antibiotics had been poor.

### Technique

The various steps involved are explained to the patient, who is reassured and then placed in a supine position with two pillows under the shoulders and one under the head so that the chin can be lifted, hyperextending the neck somewhat. The neck is cleaned with iodine or an equivalent antiseptic and towels applied, full sterile procedure being followed throughout. The shallow flat depression of the cricothyroid membrane is palpated with the gloved forefinger between the thyroid and cricoid cartilages of the larynx. A little 1% lidocaine is applied to the skin in this

area but should probably not be introduced into the trachea as it may have bacteriostatic properties and also induces premature coughing. The patient is instructed not to swallow or cough and a 14-gauge needle containing an indwelling, thin (17 or 18 gauge), 20-cm polyethylene catheter (e.g. central venous pressure line) connected to a 20-mL syringe is introduced percutaneously into the trachea in the midline. Correct entry can be checked by withdrawing air into the syringe. The needle is angled in a caudal direction and the catheter quickly passed 8–12 cm into the trachea so that the tip is unlikely to be coughed upwards into the oropharynx. The needle is then quickly withdrawn from the skin in order to avoid the risk of laceration and the catheter remains *in situ*. Suction is then applied to the catheter in the hope of retrieving secretions. Should this not prove possible, 2–5 mL of non-bacteriostatic sterile saline may be injected through the cannula to induce coughing. Suction is again applied in this case and the retrieval of 0.5–2 mL of saline/secretions is considered a satisfactory specimen. Once such a sample has been obtained, the catheter is withdrawn and pressure applied manually to the puncture site for about 5 min, the patient being encouraged not to cough during this period. Air is ejected from the sampling syringe, which is then capped and taken directly to the laboratory where, following prior discussion with the microbiologist, Gram staining is carried out and aerobic and anaerobic cultures are set up, along with any other special staining or culture techniques that might be thought necessary according to the clinical circumstances. A small adhesive dressing is applied to the puncture site and the patient is asked to place a finger over this dressing and to press gently during coughing for the rest of the day.

## Yield

It is difficult to determine the accuracy of transtracheal aspiration as a technique for detecting the bacterial causes of lower respiratory tract infection because in order to do so comparison has to be made with another specimen source, the validity of which is beyond question. One study found that transtracheal aspiration yielded the same pathogen as that retrieved from blood culture in all of 23 patients with pneumonia accompanied by bacteraemia [365]; 488 patients in the same series were considered on clinical criteria to have bacterial pneumonia. The transtracheal aspirates were negative in 48 of these cases, giving a 'false-negative' result of 12.5%. It is of note that 44 of these negative isolates were obtained from patients who had received prior antibiotic treatment, leaving only four negatives in untreated patients; thus the false-negative rate in patients who had not received prior antibiotic treatment was only 1% [365].

Positive bacterial cultures may be obtained from the transtracheal aspirates of patients without clinical evi-

dence of pneumonia. Thus potential pathogens have been recovered from a combined group of 55 subjects (comprising normal volunteers and asthmatic subjects) in 13% of cases, presumably as a result of the colonization of the trachea and lower respiratory tract by bacteria [366]. Positive yields are also obtained in a high proportion of patients with chronic bronchitis or bronchiectasis [365,367].

## Complications

The complication rate of transtracheal aspiration in reported series is low, being approximately 0.5% for subcutaneous emphysema extending beyond the front of the neck, 0.2% for haemorrhage other than blood-streaking of the sputum, and 0.2% for paratracheal infection [368]. The physician whose experience with the technique is limited will realize that these low complication rates were recorded in units that developed a special interest in transtracheal aspiration and that this alone would be likely to enhance the safety of the test. As with other invasive procedures, fatalities have been recorded; such deaths have resulted from haemorrhage and from cardiac arrest following the aspiration of gastric contents, vomiting having been induced by vigorous coughing as a result of the procedure [364,369]. Unfortunately, serious complications are more likely to occur in those iller patients who may be most likely to benefit from any positive diagnostic information provided by the test.

Complications may be avoided by ensuring that the person carrying out the procedure is either well versed with the protocol or supervised by someone who is. The patient should be in a state in which cooperation is possible. Bleeding is avoided if the patient is not uraemic, the platelet count is not less than  $50 \times 10^9/\text{L}$  and the prothrombin and activated partial thromboplastin times are both normal. A low platelet count may be corrected by replacement, 6–12 packs being infused for a count of less than  $50 \times 10^9/\text{L}$ . Bleeding is also avoided by the application of gentle pressure by the operator to the cricothyroid membrane for about 5 min after the puncture. Blood-streaking in the sputum is to be expected and patients should be reassured about this. Serious hypoxia is guarded against by ensuring that the  $\text{PaO}_2$  is at least 9 kPa (about 70 mmHg) on supplemental oxygen prior to the procedure and by continuing to administer oxygen during the procedure while monitoring oxygen saturation [370]. Subcutaneous emphysema is seldom an inconvenience but may become alarming to the patient if it becomes extensive. It can be prevented if the patient applies gentle digital pressure to the puncture site during any coughing that might occur for the rest of the day. Infection of the puncture site is seldom a problem, probably because of the concurrent use of antibiotics for the chest infection, but has been reported [371,372].

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# DRUGS IN LUNG DISEASE

DOUGLAS SEATON

This chapter is intended not as an exhaustive compendium of every drug that might conceivably be used in the management of respiratory illness but rather as a practical guide to certain groups of drugs worthy of consideration in this context. The first three sections cover antimicrobial agents used in bacterial, fungal and viral infection, including some drugs relevant to human immunodeficiency virus (HIV)-associated infections; further sections deal with bronchodilators and other drugs used in the treatment of airflow limitation, corticosteroids, respiratory stimulants and immunosuppressant/cytotoxic drugs. Antituberculous agents are discussed in Chapter 19. Readers who require a full account of individual agents are referred to standard texts on pharmacology and therapeutics and to the manufacturers' summaries of product characteristics.

## Antimicrobial agents for use against bacteria and bacteria-like organisms

### Penicillins

The penicillins are  $\beta$ -lactam antibiotics, so-called because they all contain a  $\beta$ -lactam ring in their molecular structure (Fig. 9.1). The different properties of individual members of the group (which also includes the cephalosporins, carbapenems and monobactams) mainly arise as a result of variations in the structure of their side-chain, one example of which has been the development of a subgroup of antistaphylococcal penicillins resistant to attack by  $\beta$ -lactamases.

#### *Mode of action*

All penicillins (in common with other  $\beta$ -lactam antibiotics) are bactericidal, attaching to so-called penicillin-binding proteins and interfering with bacterial cell wall synthesis, resulting in its disruption [1]. Many strains of bacteria, such as *Staphylococcus aureus*, produce  $\beta$ -lactamase enzymes that hydrolyse the penicillin molecule by disruption

of its  $\beta$ -lactam ring; many penicillins are susceptible to these  $\beta$ -lactamase producers, against which they are ineffective. Penicillins have no activity against organisms that lack a cell wall, such as *Mycoplasma pneumoniae*, and against other 'atypicals', such as *Chlamydia psittaci*, *Coxiella burnetii* and *Legionella* spp.

#### *Distribution and excretion*

Penicillins are widely distributed in body fluids. They cross the placenta but there is no evidence of adverse effects on the fetus. Most of these drugs are excreted in active form by the kidneys, a small fraction of broad-spectrum penicillins being excreted in bile. In the case of the ureidopenicillins this biliary excretion approaches 30%.

#### *Hypersensitivity reactions of penicillin and other $\beta$ -lactams*

The most serious adverse effects arise as a result of type I, immediate, anaphylactic, IgE-mediated hypersensitivity reactions, characterized by a combination of urticaria, angio-oedema, wheeze and hypotension and which may rarely result in collapse and death within minutes [2]. These reactions are more likely to occur following parenteral administration, but this may relate to dose rather than route [3]. Patients with no prior history of an allergic reaction may be affected, although a history of such a previous reaction increases the chance of a further attack four- to six-fold [4]. The incidence of these serious reactions has been estimated to be low, about 0.05%, and that of fatal ones much lower still, about 0.0002% [5,6]. Whereas 'immediate' reactions typically occur within a few minutes of taking an oral dose, other types of reaction may be more indolent, following different immunological pathways and sometimes taking 1–3 weeks to develop. Most penicillin reactions are in fact mild, taking the form of a late-onset (non-IgE-mediated) maculopapular erythematous rash in 2–3% of courses. Such rashes are more common following the use of semisynthetic penicillins, especially the aminopenicillins ampicillin or amoxicillin

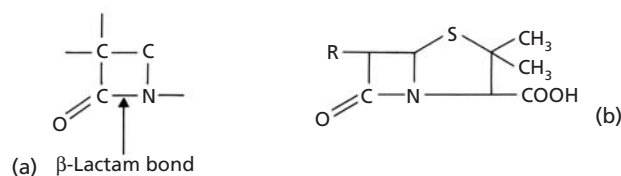


Fig. 9.1 The  $\beta$ -lactam ring (a) and penicillin molecule (b). R indicates the site for side-chain substitutions.

(amoxycillin), occurring in approximately 5–10% of courses [3].

Unfortunately patients often have only vague recollections of past 'reactions' to antimicrobial agents, including penicillins. Many of these incidents may not have been allergic at all, despite which anxieties about their true nature often serve to block the further use of penicillins for the rest of the patient's life [7]. Sometimes this can be sorted out by an accurate history or reference to old records but doubts often remain. The place of formal testing to refute or confirm a suspected penicillin allergy, while an attractive concept, is unfortunately somewhat controversial [8]. There are various protein-bound derivatives of penicillins that, given the right circumstances, may cause allergic reactions following the administration of the drug in question. The most plentiful of these are formed by the opening of the  $\beta$ -lactam ring to form a penicilloyl derivative known as the 'major determinant'. However, penicillins may also undergo degradation by other mechanisms, producing a number of different protein-bound moieties also capable of exciting allergic reactions. These tend to be produced in smaller quantities and are therefore known as 'minor determinants'. To add to the complexity of the problem, the molecular side-chains of semisynthetic penicillins such as amoxycillin and ampicillin may also incite allergic reactions [3]. Skin-prick testing against major and minor determinants can be carried out with positive and negative controls by personnel properly trained in both the techniques and how to deal with reactions. A skin-test preparation containing the major (penicilloyl) determinant is commercially available but those containing minor determinants are not, so that one approach has been to prepare a solution of benzylpenicillin, at a dilution of 10 000 units/mL, as a less satisfactory surrogate for a minor determinant mixture [3]. If these tests are read as negative they may be repeated intradermally. Such intradermal testing has been reported to produce systemic reactions that are usually mild in about 1% of cases [9]. Using this approach, the positive test rate in patients previously thought to have possible allergy ranged between 7 and 35% for the most part, the positive test rate in control subjects being about 2% [3]. Many workers in this field take the view that it is safe to treat patients with  $\beta$ -lactams once they have undergone such studies with negative results and that when subsequent

reactions do occur in such patients they are almost invariably mild, no cases of anaphylaxis having been reported in the USA in such a situation [3]. On the other hand, a positive test indicates a significant chance of an immediate reaction if an antimicrobial of this class is used. A radioallergosorbent test (RAST) to detect IgE antibodies specific for penicillin has also been proposed as a guide in an outpatient setting [7], but again cannot be relied upon to predict outcome because the commercially available preparations are derived from the penicilloyl major determinant and do not test for the minor determinants [8], which may account for 10–25% of skin-test positive reactions [3].

Other serious systemic reactions are uncommon [10]. Non-IgE-type reactions include the following:

- 1 immune complex-mediated serum sickness reactions and drug fever;
- 2 blood dyscrasias, including reversible IgG- and/or IgM-mediated haemolytic anaemia that may result from the coating of red cells with antibody (positive Coombs test);
- 3 leucopenia, thrombocytopenia and reversible interstitial nephritis may be caused by similar mechanisms, all of these being conventionally treated with high doses of corticosteroids;
- 4 encephalopathy with convulsions may be a consequence of excessive dosage but can occur following normal doses in the presence of renal failure, especially in the elderly [11];
- 5 various rashes may occur, usually maculopapular erythematous reactions as already mentioned, but occasionally more serious reactions, such as exfoliative dermatitis or Stevens–Johnson syndrome, are described.

Avoidance of hypersensitivity reactions is best and most simply achieved by using an antibiotic of a different class whenever the suspicion of  $\beta$ -lactam allergy exists. Such avoidance should be complete when it is suspected from the history that a previous episode was an immediate IgE-mediated reaction or if the patient had one of the more serious skin reactions. Allergy testing may be considered in the outpatient setting but skin and RAST testing have no predictive value where the history is suggestive of a previous non-IgE-mediated allergic reaction. When the history of a previous reaction is less clear and if there is a pressing need, an alternative approach if a  $\beta$ -lactam is felt to be strongly indicated is to introduce one in hospital using gradual dose escalation under controlled conditions and with careful initial monitoring [3,8].

Cross-sensitivity occurs between different types of  $\beta$ -lactam antibiotic, indicating that these side-effects are often related to the basic double-ring structure of the  $\beta$ -lactam molecule. Cross-sensitivity between penicillins and cephalosporins is well known, although its frequency may have been overestimated in the past as a result of the contamination of early cephalosporin preparations with



small amounts of penicillin [3]. Such cross-reactions may also occur with the carbapenems (imipenem and possibly also meropenem), although current evidence indicates that the monobactam aztreonam, whose ring structure is monocyclic rather than bicyclic, may be safely administered to penicillin-allergic patients.

The management of hypersensitivity reactions should be by drug withdrawal. Mild cases may be controlled by this measure alone or by the oral administration of an antihistamine. More uncomfortable reactions may require systemic corticosteroid therapy. Anaphylaxis should be managed by lying the patient flat and by giving epinephrine (adrenaline) 0.5–1 mg i.m. (0.5–1 mL of epinephrine injection 1:1000), repeated every 15 min according to response. This may be supplemented by a slow (1-min) intravenous dose of an antihistamine such as chlorphenamine (chlorpheniramine) 10–20 mg. Systemic corticosteroids should also be commenced to prevent later deterioration. Wheeze may be treated with inhaled or parenteral bronchodilators according to severity.

### Narrow-spectrum short-acting penicillins

#### *Benzylpenicillin*

This so-called 'natural' penicillin is also known as penicillin G and was originally produced by the fungus *Penicillium notatum* and now by *P. chrysogenum*, a high-yield mutant mould. It has a relatively narrow spectrum and is short-acting.

#### *Susceptible organisms*

Important respiratory pathogens that are usually sensitive include *Streptococcus pneumoniae* and most anaerobes, including the clostridia, but with the notable exception of *Bacteroides fragilis* for which metronidazole may be added. Resistant *Strep. pneumoniae* have now been isolated in many parts of the world, particularly Spain, Iceland, some eastern European countries and North America. Resistance in this situation is not due to  $\beta$ -lactamase production but to changes in the penicillin-binding proteins of the pneumococcus so that these have a reduced affinity for the penicillin molecule [12]. Fortunately the resistance is relative (defined in terms of minimum inhibitory concentration, MIC) and there is evidence to suggest that in severe pneumococcal pneumonia the infection can still be overcome by therapeutic doses, with no increased mortality [13]. The problem of penicillin resistance is discussed in this context in Chapter 13. Other less common or rare organisms that are sensitive include microaerophilic streptococci such as *Strep. milleri*, *Strep. pyogenes*, *Pasteurella multocida*, *Actinomyces israelii*, *Corynebacterium diphtheriae* and *Bacillus anthracis*. Almost all strains of *Staph. aureus* are resistant as a result of their production of

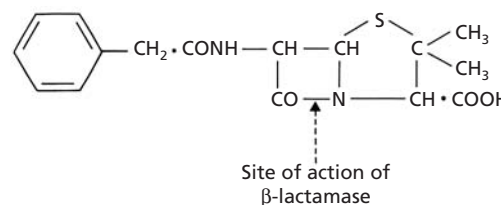


Fig. 9.2 Structure of benzylpenicillin showing site of action of  $\beta$ -lactamase.

$\beta$ -lactamase (penicillinase), a group of enzymes that break open the  $\beta$ -lactam ring of the penicillin molecule (Fig. 9.2), thereby converting it to microbiologically inactive penicilloate. In a survey carried out as long ago as 1983, 80% of the hospital and community isolates of *Staph. aureus* were resistant to penicillin [14] and sensitive strains are now regarded by microbiologists as collector's items. Many other bacterial genera, species and strains produce  $\beta$ -lactamases, notably *Pseudomonas aeruginosa*, some *Proteus* spp., the anaerobe *Bacteroides fragilis*, most strains of *Moraxella catarrhalis* and increasing numbers of strains of *Haemophilus influenzae*.

#### *Administration and dose*

Benzylpenicillin is unstable in gastric acid and the drug should therefore be given either by intramuscular or intravenous injection. A dose of 600 mg (1 megaunit) i.m. or i.v. 6-hourly is sufficient for the majority of infections, although higher doses and prolonged administration may be required for more severe infections, such as anaerobic pneumonia and lung abscess. Peak blood levels are achieved within 15–30 min of intramuscular injection and as the urinary excretion of benzylpenicillin is brisk it is sometimes necessary to give very high doses in order to achieve the desired therapeutic effect. Such high dosing is made possible by the drug's relative lack of toxicity.

Benzylpenicillin was available as both a sodium and a potassium salt. Either one could be dispensed unless benzylpenicillin sodium or benzylpenicillin potassium was specifically prescribed. Only the sodium salt is now generally available in the UK, although both are obtainable in the USA. The choice is usually inconsequential but may be a consideration if the patient is in cardiac or renal failure, since 1 g of the former preparation contains 2.8 mmol of sodium and 1 g of the latter contains 2.7 mmol of potassium.

It is inadvisable to mix benzylpenicillin with other antibiotics in a syringe or in infusion fluid as incompatibilities may occur.

#### *Principal uses in respiratory medicine*

The main indication for benzylpenicillin in respiratory medicine is pneumococcal pneumonia and it may be used



as primary treatment in community-acquired pneumonia in young previously healthy patients (see Chapter 13). Its role in the management of empyema and lung abscess due to anaerobic infection is dealt with in Chapters 14 and 15.

### *Phenoxymethylpenicillin (penicillin V)*

Like benzylpenicillin, phenoxymethylpenicillin is a 'natural' penicillin produced when *P. notatum* and related moulds are fermented with phenoxyacetic acid. It is generally dispensed as the potassium salt in either tablet or oral suspension form, being relatively stable in gastric acid. Its antibacterial spectrum and distribution are rather similar to benzylpenicillin (see above), but it should not be used in serious infections because its absorption is unpredictable and incomplete [15]. Its principal respiratory use has been as a follow-up treatment in pneumococcal pneumonia once the infection is responding satisfactorily to initial treatment with parenteral benzylpenicillin, although commonly ampicillin or amoxicillin (which are less protein-bound) are now used in its place. It is also used to treat upper respiratory tract infections in children and in streptococcal sore throat. This drug may also be used long term at a dose of 250 mg daily as prophylaxis against pneumococcal infection in patients with asplenia or dysfunctional spleens [16] (see Chapter 13).

The adult dose is 250–500 mg every 4–6 h at least 30 min before food. The principal side-effects and their management are similar to those of benzylpenicillin. Tolerance is usually good but nausea and diarrhoea may occur. Colitis and hepatotoxicity have also been described but are uncommon [17,18].

### **Narrow-spectrum long-acting penicillins**

Certain poorly soluble salts of benzylpenicillin have been developed that have a prolonged effect when given as an intramuscular depot injection, resulting in the slow release of benzylpenicillin. Procaine benzylpenicillin (procaine penicillin; USA, penicillin G procaine) in a single large dose may inhibit susceptible bacteria for 24–36 h. Benzathine benzylpenicillin (benzathine penicillin; USA, penicillin G benzathine) is even less soluble and a single 900-mg dose may produce low concentrations of benzylpenicillin for 4 weeks [19]. It is no longer available in the UK.

The mode of action, antibacterial spectrum, excretion and side-effects are as for benzylpenicillin. In addition, procaine benzylpenicillin may produce side-effects as a result of its procaine component and should not be given to patients with a history of sensitivity to these types of local anaesthetics. Accidental intravenous administration may produce auditory disturbances, feelings of impending mortality, convulsions, tachycardia and hypertension.

None of these preparations have a role in the conventional treatment of severe acute respiratory infection. The longer-acting preparations have been used in situations of limited antibiotic availability or where compliance with oral therapy is unlikely to be fulfilled, but their use cannot be regarded as ideal.

### **Wider-spectrum penicillins: aminopenicillins**

Modifications to the basic penicillin structure by the substitution of various side-chains has resulted in the production of semisynthetic antimicrobial agents with a wider spectrum of activity than benzylpenicillin. The first of these was ampicillin, which has the particular attraction in respiratory medicine of being effective against *H. influenzae* as well as *Strep. pneumoniae*. The only other important member of this group is the ampicillin analogue amoxicillin, which is produced by the insertion of a hydroxyl group in the benzyl side-chain of ampicillin. Another analogue, ciclacillin (cyclacillin), although better absorbed than ampicillin, is also rapidly cleared and has inferior antibacterial activity [20] and is not considered further; neither are the ampicillin esters or 'prodrugs', talampicillin, pivampicillin and bacampicillin. These have no antibacterial activity of their own but are hydrolysed during their absorption to liberate ampicillin. They are more rapidly absorbed than ampicillin and may produce diarrhoea less frequently but tend to produce gastric upsets and probably have no clear advantage over ampicillin itself [21]. Ciclacillin, bacampicillin and talampicillin are no longer available in the UK. All the aminopenicillins are susceptible to  $\beta$ -lactamases.

### *Ampicillin and amoxicillin*

#### *Susceptible organisms*

These antibiotics are slightly less effective than benzylpenicillin against Gram-positive cocci, such as *Strep. pneumoniae*, but possess a broader spectrum of activity. As with benzylpenicillin, they are almost always ineffective against methicillin-sensitive *Staph. aureus* but their activity against some Gram-negative organisms such as *H. influenzae* is of clear importance in respiratory medicine. Although the majority of isolates of *H. influenzae* are still sensitive to the aminopenicillins, the incidence of resistant  $\beta$ -lactamase-producing strains of *H. influenzae* in the UK and elsewhere unfortunately continues to rise [22]. Resistance rates of 8–15% are not uncommon in this country, with much higher rates in Spain, so that it is advisable to know the sensitivity rates in one's own locality [23,24]. The susceptibility of other Gram-negative organisms is much less dependable. About 80% of *Moraxella catarrhalis* isolates are  $\beta$ -lactamase producers and are therefore usually resistant [25], as are most of the Enterobacteri-

aceae (including increasing numbers of *Escherichia coli* isolates) and other Gram-negative pathogens such as *Pseudomonas* spp.

#### *Administration and dose*

Both ampicillin and amoxicillin are acid-stable and may therefore be taken orally. The absorption of ampicillin is inhibited by food so it should not be taken after meals, whereas the absorption of amoxicillin is twice as good and is unaffected by food [26]. Thus an orally administered dose of 500 mg ampicillin produces peak serum levels at 2 h, the half-life in serum being 1 h, whereas the peak serum level for a similar dose of amoxicillin is twice as high. Although the half-lives of both preparations are comparable, detectable amounts of amoxicillin may be present for up to 8 h.

Distribution in body fluids is similar to that of the penicillin group as a whole, although there is good evidence to suggest that the sputum penetrance of amoxicillin is superior to that of ampicillin (see Chapter 28). As with other penicillins, the major route of excretion is in the urine and this may be blocked by probenecid. The dose of ampicillin or amoxicillin may require modification in severe renal failure [27].

The conventional oral dose is 250–500 mg, depending on severity, every 6 h for ampicillin and every 8 h for amoxicillin. The high oral dosage of amoxicillin (3 g twice daily) that is sometimes used in bronchiectasis has been discussed in Chapter 28. When parenteral therapy is required, 0.5–1 g 6-hourly by intravenous bolus injection is acceptable for either preparation.

#### *Adverse effects*

Hypersensitivity reactions may occur with ampicillin and amoxicillin as for any member of the penicillin group and the principles of management are as described above. The range of further side-effects is similar for both antibiotics. Cutaneous rashes are much more frequent than with narrow-spectrum penicillins, occurring in about 7% of patients [3,28], and are the most common adverse effect. As these rashes are usually delayed and are macular or maculopapular rather than urticarial, they may be due to impurities and not an indication of true allergy to the penicillin nucleus or side-chains themselves [29,30]. Subsequent treatment with another penicillin or even with the same antibiotic may be undertaken without further trouble being inevitable, provided that a proper indication exists. However, an urticarial rash invariably implies true penicillin allergy and further dosage could be dangerous (see p. 193). Amoxicillin and ampicillin are particularly likely to cause rashes in patients with infectious mononucleosis, cytomegalovirus infection and acute lymphocytic leukaemia [31].

Oral candidiasis is common, as is the case with many broad-spectrum antibiotics; nausea, vomiting and diarrhoea may occur particularly with higher dosages. Pseudomembranous colitis caused by *Clostridium difficile* has been described but is unusual [32,33]; it is often self-limiting and need not necessarily require treatment with metronidazole or vancomycin.

#### *Principal uses in respiratory medicine*

The principal respiratory indications for these drugs are the management of infective exacerbations of chronic bronchitis, for which they remain a standard first-line agent (see Chapter 23), community-acquired pneumonia (see Chapter 13), bronchiectasis (see Chapter 28) and sinusitis (see Chapter 12).

#### *Amoxicillin–clavulanate (co-amoxiclav)*

Clavulanic acid is a naturally occurring penicillin compound found in cultures of *Streptomyces clavuligerus* [34]. It has negligible antibacterial activity of its own but is a  $\beta$ -lactamase inhibitor, binding to and irreversibly inhibiting many mainly plasmid-encoded  $\beta$ -lactamases produced by a variety of Gram-negative and Gram-positive bacteria. The potassium salt of clavulanic acid has therefore been combined in proprietary form with amoxicillin in order to extend the spectrum of the latter against certain  $\beta$ -lactamase-producing organisms that would ordinarily hydrolyse the  $\beta$ -lactam ring of the penicillin molecule to produce microbiologically inactive penicilloate.

Other examples of  $\beta$ -lactam/ $\beta$ -lactamase combinations are ampicillin–sulbactam (sultamicillin), which is available in the USA and other countries but not in the UK, and two extended-spectrum penicillins, ticarcillin–clavulanic acid and piperacillin–tazobactam (see p. 199).

#### *Susceptible organisms*

Co-amoxiclav may possess activity against amoxicillin-resistant strains of *H. influenzae*, *Moraxella catarrhalis*, *Staph. aureus*, *Klebsiella aerogenes* and *E. coli*. Unfortunately, it has no activity against the chromosomal  $\beta$ -lactamases produced by *Ps. aeruginosa*, *Enterobacter* and *Serratia* species, which are therefore resistant to it. This drug is likely to be effective in respiratory tract infections caused by organisms known to be resistant to amoxicillin alone, such as certain strains of *H. influenzae* and *Moraxella catarrhalis* [35]. In clinical practice, it may be used empirically as a second-line agent in patients with community-acquired exacerbations of chronic obstructive pulmonary disease (COPD) who have not responded to a first-line antimicrobial such as amoxicillin alone, or in patients who are iller and in whom broader cover from the onset seems more prudent. The combination also has useful activity

against anaerobes, including *Bacteroides fragilis*, although clinical trials are lacking in this difficult area (see Chapter 13). The drug is also useful in the upper respiratory tract for treating sinusitis. Data are poor for its use in serious staphylococcal infections, for which good alternatives already exist; more potent drug combinations also exist for treating serious respiratory infections thought to be caused by the Enterobacteriaceae, *E. coli* and *Klebsiella aerogenes* (see Chapter 13).

#### Administration and dose

The dose, expressed as amoxicillin, is 250–500 mg 8-hourly; at each dose level, the accompanying dose of clavulanate is the same (125 mg). On a point of economics, it is currently cheaper for an institution to dispense a lower-dose combination (250/125 mg) and an additional 250-mg dose of amoxicillin than to use the more expensive 500/125 mg preparation. For severe infection co-amoxiclav may be given parenterally (not available in USA) by infusion or slow intravenous injection of 1.2 g (1 g amoxicillin, 200 mg clavulanic acid) every 6–8 h.

#### Adverse effects

Side-effects are similar to those encountered with amoxicillin and the same precautions have to be applied to its use in patients with serious renal insufficiency. There have been some reports of cholestatic jaundice occurring in association with co-amoxiclav and it is suspected that this may be due to the clavulanate constituent [36]. This problem may be more relevant in elderly patients who receive prolonged courses.

#### Antistaphylococcal penicillins: methicillin, cloxacillin, flucloxacillin, oxacillin, dicloxacillin and nafcillin

Methicillin was the first of this group of semisynthetic penicillins, which contain acyl side-chain modifications that protect their molecular structure from hydrolysis by

staphylococcal  $\beta$ -lactamases. This structural modification gives these antibiotics bactericidal activity against *Staph. aureus* but renders them ineffective against Gram-negative bacteria, including *H. influenzae*, and Gram-positive cocci, including *Strep. pneumoniae*, against which benzylpenicillin is up to 20 times more effective [37]; thus the only indication for their use is the treatment of staphylococcal infection. The increasing numbers of isolates of methicillin-resistant *Staph. aureus* (MRSA) have gained their biological advantage not as a result of  $\beta$ -lactamase production but by acquisition of a low-affinity penicillin-binding protein, rendering them resistant to the antistaphylococcal penicillins as a group.

Three antistaphylococcal penicillins used to be available in the UK: methicillin, cloxacillin and flucloxacillin. There have been concerns that penicillin-related interstitial nephritis is more common with methicillin and this antibiotic is no longer marketed in the UK. Oxacillin, dicloxacillin and nafcillin are available in the USA but not in the UK; flucloxacillin is unavailable in the USA. Their properties are summarized in Table 9.1.

Methicillin is acid-labile and can therefore only be given parenterally. Its use is therefore limited to the treatment of severe penicillin-resistant staphylococcal infections. Methicillin is rapidly excreted by the kidneys, like benzylpenicillin, and some dosage reduction may need to be made in severe renal failure [27]. This is not the case with other members of the group such as flucloxacillin, which although excreted by the kidneys also undergoes significant metabolism in the liver. The serum concentration and half-life of all members of the group may be increased by probenecid.

Parenteral administration of this group of drugs is generally preferable in systemic staphylococcal infection and mandatory in bacteraemia (Table 9.2). Where oral administration is contemplated then flucloxacillin (UK) or dicloxacillin (USA) are the best absorbed. Cloxacillin, nafcillin and particularly oxacillin are all less well absorbed by comparison with flucloxacillin and dicloxacillin. Absorption of all five drugs is further reduced by food in

**Table 9.1** Properties of antistaphylococcal penicillins. (After Wise [37].)

	Antistaphylococcal activity (MIC mg/L)*	Protein binding (%)	Route of administration	Percentage absorbed by mouth†
Methicillin	2.5	40	i.v., i.m.	N/A
Cloxacillin	0.25	94	oral, i.m., i.v.	20–40
Dicloxacillin	0.25	96	oral, i.m., i.v.	60
Oxacillin	0.50	94	oral, i.m., i.v.	20
Flucloxacillin	0.25	95	oral, i.m., i.v.	55
Nafcillin	0.50	87	oral, i.m., i.v.	'Poor'

\* The mode MIC (minimum inhibitory concentration) for  $\beta$ -lactamase-producing strains.

† As measured by urinary recovery.

N/A, not applicable.

**Table 9.2** Administration of antistaphylococcal penicillins.

Methicillin†	1–2 g i.v. 4–6-hourly (parenteral only)
Cloxacillin	500 mg to 1 g i.v. 6-hourly 500 mg to 1 g orally* 6-hourly
Flucloxacillin*	500 mg to 2 g i.v. 6-hourly 250–500 mg orally 6-hourly
Nafcillin†	500 mg to 2 g i.v. 6-hourly (oral absorption unreliable)
Oxacillin†	500 mg to 1 g i.v. or orally 6-hourly
Dicloxacillin†	250 mg to 1 g 6-hourly (oral only)

\*Not available in USA.

†Not available in UK.

the gut and they should preferably be taken 1 h before meals.

Flucloxacillin is commonly used in the UK as it has a similar antistaphylococcal activity to cloxacillin while achieving better absorption and higher blood levels [38,39]. Cholestatic jaundice has occasionally been reported with the use of flucloxacillin and hepatotoxic reactions have also occurred with other members of this group [39]. This problem appears to be more likely in older patients who receive the drug for longer than 2 weeks [40].

#### Extended-spectrum (antipseudomonal) penicillins: carboxypenicillins and ureidopenicillins

A number of semisynthetic penicillins have been developed for their bactericidal activity against *Ps. aeruginosa*, an organism resistant to all other penicillins so far described. Two of the antipseudomonal penicillins belong to the carboxypenicillin group: ticarcillin and carbenicillin [41]. Three remaining antibiotics belong to the ureidopenicillin group: azlocillin, piperacillin and mezlocillin [42]. Although all have therapeutic antipseudomonal activity, dose for dose piperacillin is the most potent agent, followed by azlocillin. Mezlocillin and ticarcillin are of approximately equal antipseudomonal potency and carbenicillin is the least effective, so that higher doses are required with an increased likelihood of side-effects. Carbenicillin also carries a high sodium load and may, as a result of a high, non-reabsorbable renal anion load produce hypokalaemia; it is no longer commercially available in the UK and neither is mezlocillin. Piperacillin is described below as an example.

#### Piperacillin

##### Susceptible organisms and main indications

Whereas azlocillin is 8–11 times more potent than carbenicillin as an antipseudomonal agent, piperacillin possesses even greater *in vitro* potency [42,43] and has been shown to

be effective in serious bacterial infections. The only clear indication for its use is the knowledge or suspicion that such serious infection is due to *Pseudomonas* spp. or other Gram-negative enteric bacilli, such as *E. coli*, *Klebsiella* and *Proteus* spp. These types of organisms are often responsible for severe hospital-acquired pneumonia (see Chapter 13). It is common practice when treating a severe pseudomonal or other Gram-negative enteric bacillary infection to use an aminoglycoside such as gentamicin as well as an antipseudomonal penicillin, as resistance to the penicillin may emerge if it is used singly [44], whereas together they act synergistically. It is worth noting that piperacillin's spectrum of activity covers other organisms and that it is as effective as ampicillin against Gram-positive cocci [43] and is also active against *H. influenzae*. It is susceptible to  $\beta$ -lactamases produced by *Staph. aureus*. The extended-spectrum penicillins also have good activity against anaerobic mouth flora, a property that may be useful for mixed pneumonic infections in which aspiration may have occurred. Many of these properties are shared by azlocillin and mezlocillin and to a lesser extent by ticarcillin and carbenicillin.

##### Administration and dose

Piperacillin, in common with all other antipseudomonal penicillins, has to be given intravenously so that adequate blood levels can be achieved. The drug is moderately protein-bound (20–40%) and its distribution is similar to that of other penicillins. It is rapidly excreted by the kidneys and has a plasma half-life of about 1 h. This is prolonged in renal insufficiency or if probenecid is used concurrently. These properties are shared to varying degrees by the other extended-spectrum penicillins. The side-effects are those of any penicillin (see pp. 193–195). Piperacillin has a much lower sodium content (about 1.7 mEq/g) than carbenicillin, reducing the risk of congestive heart failure in susceptible individuals. The risk of hypokalaemia due to a high anion load on the distal tubules is also diminished.

The usual dose is 12–18 g infused intravenously in four divided doses daily, each over 20–40 min. The extended-spectrum penicillins should never be mixed with an aminoglycoside in the same infusion or syringe as the penicillin binds chemically to the other antibiotic [45].

##### Piperacillin–tazobactam and ticarcillin–clavulanate

Piperacillin has been combined with tazobactam, a  $\beta$ -lactamase inhibitor like both clavulanic acid and sulbactam, and is now available as a parenteral preparation piperacillin–tazobactam (Tazocin) [46] for use with an aminoglycoside in serious infections, including hospital-acquired pneumonia and those associated with neutropenia. There appears to be no enhancement of its

antipseudomonal activity but the combination has activity against *Staph. aureus* and its activity against some Gram-negative enteric bacilli and *H. influenzae* is enhanced. The usual dose is 4.5 g (piperacillin 4.0 g, tazobactam 0.5 g) every 8 h.

The bacterial spectrum covered by piperacillin-tazobactam is similar to that achieved by another combination of extended-spectrum penicillin and  $\beta$ -lactamase inhibitor, ticarcillin-clavulanate (Timentin) [47], which may also be combined with an aminoglycoside to treat the same range of serious infections. The usual dose is 3.2 g (ticarcillin 3 g, clavulanic acid 200 mg) every 6–8 h.

Temocillin is a more recent parenteral penicillin that has increased resistance to the  $\beta$ -lactamases produced by many Gram-negative organisms, including *H. influenzae* and *Moraxella catarrhalis*. However, it must be stressed that it has no useful activity against *Ps. aeruginosa* and little or no activity against staphylococci, streptococci and anaerobes [48]. These are clearly major drawbacks in the treatment of serious lower respiratory tract infection, in which initial treatment is usually empirical and designed to cover a wide spectrum of core organisms (see Chapter 13). It therefore has no obvious role in respiratory medicine.

### Cephalosporins

This seemingly ever-enlarging group of antibiotics has some general points in common with the penicillins. Cephalosporins were also developed from the product of a mould (originally known as *Cephalosporium acremonium*). Like penicillins, cephalosporins are bactericidal and also have their effect by attaching to penicillin-binding proteins on the bacterial cell wall, which is then disrupted. Their chemical nucleus is somewhat similar to that of penicillin, including the presence of a  $\beta$ -lactam ring (Fig. 9.3). This ring, essential for the stability of the cephalosporin molecule, may be attacked by  $\beta$ -lactamases produced by a range of organisms, both Gram-positive, such as *Staph. aureus*, and Gram-negative, such as the Enterobacteriaceae. Just as different penicillins have been synthesized by side-arm substitutions so have the cephalosporins, although in the latter case there are not one but two substitution points, one of which (R' in the C-3

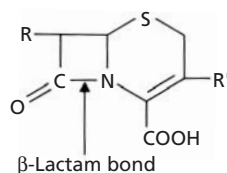


Fig. 9.3 Structure of the cephalosporin nucleus showing  $\beta$ -lactam bond. R and R' represent substitution points.

position) affects pharmacokinetics and the other (R) antibacterial activity (Fig. 9.3). Innumerable modifications have been made to the molecular structure of these 'designer drugs', so that their individual antibacterial properties result from varying degrees of  $\beta$ -lactamase stability, cell membrane penetrance and penicillin-binding protein affinity. With some exceptions they are excreted unchanged in the urine (at a rate that may be slowed by probenecid) and dosage modification may be required in renal insufficiency.

### Adverse effects

As a group, cephalosporin toxicity is low, a further point of similarity with the penicillins. Anaphylactic reactions are very rare but some subjects who are allergic to penicillins also show hypersensitivity to cephalosporins [3]; thus substitution of the second class of drug for the first may not be entirely hazard-free, although the risk is low [49]. Allergy to  $\beta$ -lactams in general has been discussed in the section on penicillin. Rashes may occur as with penicillins [50]. Nausea, vomiting and diarrhoea may also occur, sometimes with *Clostridium difficile*-associated colitis, as with other broad-spectrum antibiotics, particularly penicillins and clindamycin [51,52]. Diarrhoea is probably more likely in those preparations that are poorly absorbed or that are excreted to a significant degree in bile. Minor disturbances of liver function may be observed [50].

The potential for nephrotoxicity is low but does exist [53], particularly with one of the earliest members of the group, cefaloridine (cephaloridine), which has been withdrawn from general availability in the UK and USA. Although cefalotin (cephalothin) has been implicated in acute tubular necrosis, particularly in the elderly, it is still obtainable in the USA. In renal insufficiency, dose modification is generally needed, although with cefotaxime, which is metabolized, this is only necessary in severe impairment (glomerular filtration rate <10 mL/min). As with the penicillins, interstitial nephritis may rarely occur as an allergic reaction to cephalosporins.

High or prolonged dosage of some cephalosporins has been associated with a haemorrhagic tendency [54,55] due to interference with vitamin K-dependent clotting factors or platelet function but this is unusual, particularly with the cephalosporins currently available in the UK (Table 9.3). It is associated only with those drugs that have an N-methylthiotetrazole (MTT) substitution at the C-3 position indicated by R' (Fig. 9.3). Included among these is cefamandole. Patients may occasionally develop positive direct antiglobulin (Coombs) reactions but haemolytic anaemia is rare as is neutropenia [56,57].

A disulfiram reaction to alcohol may also occur with cefamandole and with other cephalosporins with the MTT

**Table 9.3** Classification of cephalosporins by generation (see text for details).

First generation	Second generation	Third generation
Cefradine*,†	Cefuroxime†,*	Ceftazidime*
Cefalexin†	Cefamandole*,	Cefotaxime*
Cefadroxil†	Cefaclor†	Ceftizoxime*
Cefazolin*	Cefoxitin*,**	Ceftriaxone*
Cefalothin*,‡	Cefonicid*,‡	Cefodizime*
Cefapirin*,‡	Cefprozil†,‡	Cefpirome*,‡‡,§
Cefaloridine†,‡,§	Loracarbef†,‡,¶	Cefpodoxime†
	Cefotetan*,‡,**,	Ceftibuten†
	Cefmetazole*,‡,**,	Cefixime†
	Ceforanide*,‡,§,	Cefdinir†,‡,§
		Cefsulodin*,‡,§
		Cefoperazone*,‡,
		Cefpiramide*,‡,§
		Cefepime*,‡‡,‡
		Cefmenoxime*,‡,§,
		Latamoxef*,‡,§,   ,†† (moxalactam)

\* = Parenteral,  
† = Oral,  
‡ = Not generally available UK,  
§ = Not generally available USA,  
|| = Investigational drug,  
¶ = Carbacephem antibiotic,  
\*\* = Cephamycin antibiotic,  
†† = Oxycephem antibiotic,  
‡‡ = '4th generation',  
§§ = Anti-pseudomonal,  
||| = MTT group (see text).

group at R' on the cephalosporin ring structure (Table 9.3). These MTT reactions were particularly noted with latamoxef (moxalactam, USA), this drug having been withdrawn from general availability.

**Classification and spectrum of activity**

There are currently 17 cephalosporins listed in the *British National Formulary* [58], allowing for one cephamycin antibiotic (cefoxitin) sufficiently closely related chemically to permit its inclusion in the group (Table 9.3). Only one of this number is currently unavailable in the USA (cefodizime), and the USP lists seven that are unavailable in the UK: cephapirin, cefonicid, cefprozil, loracarbef (a carbacephem), cefotetan, cefmetazole, cefoperazone and cefepime. Current European Union legislation is attempting to standardize the spelling of many drugs, including that of the cephalosporins so that they all begin with the letters 'cef'. The remaining parts of the generic names are seemingly designed to test the physician's memory, as indeed are the various merits and demerits of this profuse group of drugs.

One well-established, if somewhat arbitrary, method of cephalosporin classification is according to the antimicro-

bial spectrum, each antibiotic, whether oral or parenteral, being assigned to one of three 'generations' as befits its antibacterial activity [59] (Table 9.3). As with the penicillins, the cephalosporins are all ineffective in the treatment of respiratory infection due to organisms causing so-called 'atypical pneumonia', such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *C. psittaci*, *Coxiella burnetii* and *Legionella* spp. Cephalosporins in general are inactive against enterococci, although these cause respiratory infection extremely rarely [60]. Only certain members of the third generation are active against *Ps. aeruginosa*.

**First-generation cephalosporins**

This group includes cefradine (cephradine) (parenteral/oral), cefalexin (cephalexin) (oral), cefazolin (cephazolin) (parenteral) and cefadroxil (oral). The first-generation cephalosporins have a relatively narrow spectrum, with excellent activity on Gram-positive cocci. They therefore tend to be effective against the pneumococcus and methicillin-sensitive *Staph. aureus*. They are active against many anaerobes but (as with benzylpenicillin) *Bacteroides fragilis* is resistant. Their drawback for many community-

acquired lower respiratory tract infections in patients with pre-existing lung disease is a relatively poor level of activity against *H. influenzae* and *Moraxella catarrhalis*. They have no activity against *Ps. aeruginosa* and are unreliable for treating infections where other aerobic Gram-negative enteric bacilli might be anticipated, such as in hospital-acquired pneumonia (see Chapter 13).

Individual drug points:

- 1 Cefazolin: 8-hourly dosing, whereas cefradine requires 6-hourly.
- 2 Cefalexin, cefradine and cefadroxil all well absorbed.
- 3 Cefadroxil: twice-daily dosing, although its half-life is not long.

### Second-generation cephalosporins

This group includes cefaclor (oral), cefuroxime (parenteral/oral as ester), cefamandole (cephamandole) (parenteral) and cefoxitin (parenteral). Cefoxitin is actually a cephamycin produced by a species of *Streptomyces* but is chemically similar to the cephalosporins and is therefore included in the group. This group has more variable activity than the first-generation drugs against Gram-positive cocci but improved activity against Gram-negative bacteria (including *H. influenzae* and *Moraxella catarrhalis*), with the notable exception of *Ps. aeruginosa*, against which all members of this group are ineffective.

Individual drug points:

- 1 Cefuroxime is more active than first-generation drugs against the pneumococcus but less so against *Staph. aureus*. It is active against *H. influenzae*, *Moraxella catarrhalis* and other Gram-negative bacilli. The oral prodrug (cefuroxime axetil) [61] is taken twice daily but, in common with comparable agents, its absorption characteristics result in diarrhoea in up to 4% of recipients, with occasional *Clostridium difficile* infection.
- 2 Cefamandole is active against Gram-positive cocci but is less reliable than cefuroxime against Gram-negative bacilli.
- 3 Cefaclor has problems with resistant strains of  $\beta$ -lactamase-producing *H. influenzae* and *Moraxella catarrhalis*.
- 4 Cefoxitin has better activity against *Bacteroides fragilis* and some Gram-negative bacilli but this is offset by reduced activity against both Gram-positive cocci and *H. influenzae* compared with other group members.

### Third-generation cephalosporins

This group includes ceftazidime (parenteral), cefotaxime (parenteral), ceftriaxone (parenteral), ceftipime (parenteral), cefpodoxime (oral), ceftibuten (oral), cefixime (oral) and ceftizoxime (parenteral and no longer generally available in the UK). This extended-spectrum group is

more diverse, with increased stability against  $\beta$ -lactamases than drugs of the other two generations [37]. Third-generation cephalosporins are noted for a high level of activity against Gram-negative enteric bacilli, e.g. *Enterobacter* spp., *E. coli*, *Serratia marcescens*, *Klebsiella* and *Proteus* spp.; some members are active against *Ps. aeruginosa* (Table 9.3). Coverage may therefore extend to those organisms that frequently cause serious hospital-acquired and intensive care unit-linked pneumonia. These antipseudomonal drugs are also effective against *H. influenzae* and *Moraxella catarrhalis* and have a good degree of activity against the pneumococcus, but are weaker than the first-generation cephalosporins against methicillin-sensitive *Staph. aureus*. Many strains of *Bacteroides fragilis* are resistant. The oral third-generation cephalosporins tend to be less active against Gram-positive organisms as a trade-off for their increased Gram-negative activity.

Individual drug points:

- 1 Ceftazidime and ceftipime are also antipseudomonal; of these ceftipime is more effective than ceftazidime against both streptococci and staphylococci but is not such a powerful antipseudomonal.
- 2 Cefotaxime, ceftriaxone and ceftizoxime all have similar antibacterial activity. However, ceftriaxone, being highly protein-bound and with a long half-life, may be given by once-daily injection, a factor of potential economic importance. It is excreted in both urine and bile so that its dose needs modifying only if renal and hepatic insufficiency coexist; it also has a propensity to form a biliary precipitate ('biliary sludge') and symptoms of cholecystitis if used at prolonged or high dose [62].
- 3 Ceftizoxime is excreted unchanged in the urine so dose adjustment is needed in renal insufficiency and it is no longer generally available in the UK.
- 4 Cefixime and ceftibuten are oral agents, sharing the general characteristics of the group but with pharmacokinetics permitting once-daily dosage. Only 20% of cefixime is recoverable in the urine [63], a fact that reflects relatively poor absorption and that might increase the likelihood of diarrhoea [64]. Ceftibuten has borderline *in vitro* activity against *Strep. pneumoniae* but may compensate for this clinically as a result of good pharmacokinetics [65].
- 5 Cefpodoxime proxetil is an oral prodrug that is esterified to release cefpodoxime. It requires twice-daily dosage and is highly active against *H. influenzae* and *Moraxella catarrhalis* [65]. It is effective against *Strep. pneumoniae* and has moderate activity against *Staph. aureus*, whereas cefixime and ceftibuten do not.

### Summary of principal uses of cephalosporins in respiratory medicine

Although oral cephalosporins are seldom the drugs of first choice in respiratory infections, they have nevertheless



been very widely prescribed in North America and in out-of-hospital general practice in the UK, a tendency that may be reinforced by the arrival of a number of newer oral third-generation members [65]. As a group, they are relatively expensive and it is debatable whether the benefits that these oral agents have conferred are commensurate with their cost.

Community-acquired pneumonia is most commonly caused by *Strep. pneumoniae*. Although cephalosporins of any generation may be effective against this organism, they are less so than benzylpenicillin and have not been shown to be better in clinical practice (as opposed to *in vitro* testing) than amoxicillin or ampicillin, both of which are cheaper. Cefuroxime may be used in a patient ill enough to require parenteral treatment for pneumonia (see Chapter 13), particularly when there is concern about the possibility of resistant *H. influenzae* or *Moraxella catarrhalis*, such as in older patients or those with chronic lung disease. Although cephalosporins may be variably active against methicillin-sensitive *Staph. aureus* infection, an antistaphylococcal penicillin is the drug of first choice in this situation [66]. Third-generation cephalosporins need not be used routinely for community-acquired pneumonia, for which empirical treatment on the basis of probability with more narrowly targeted antimicrobials is more appropriate (see Chapter 13).

There is no convincing evidence to indicate that cephalosporins have a major role in the management of acute purulent exacerbations of COPD. The first-generation oral cephalosporins, cefradine, cefalexin and cefadroxil are unsuitable oral treatment for exacerbations of chronic bronchitis because although active against *Strep. pneumoniae* they are inactive against *H. influenzae* and *Moraxella catarrhalis* [67,68]. Resistance to second-generation cefaclor may also occur with some strains of *H. influenzae* and with *Moraxella catarrhalis*. Evidence is lacking to suggest that cefaclor is clinically any more effective than ampicillin or amoxicillin in this situation. When an exacerbation is associated with sputum isolates of amoxicillin-resistant *H. influenzae* and if this drug is failing, then the second-generation oral cephalosporin cefuroxime axetil may be indicated, alternatives being co-amoxiclav, one of the newer macrolides such as clarithromycin, or a fluoroquinolone such as ciprofloxacin. The third-generation oral cephalosporins generally lose their Gram-positive efficacy as a price for improved Gram-negative cover and there are no reliable trials to demonstrate that they are clinically superior to earlier compounds [69]. They are also expensive and their only clear advantage over older agents is reduced dose frequency.

The use of the antipseudomonal parenteral third-generation cephalosporins should be restricted to situations where infection with *Ps. aeruginosa* is suspected or confirmed [70]. These drugs lend themselves to the treat-

ment of severe hospital-acquired pneumonia (see Chapter 13), in which Gram-negative bacteraemia is often suspected, and also exacerbations of lower respiratory tract infection in which *Ps. aeruginosa* is known to be a colonist, e.g. in cystic fibrosis and bronchiectasis. The combination of an appropriate third-generation cephalosporin such as ceftazidime with an aminoglycoside gives a broad degree of cover for pathogens such as *Ps. aeruginosa*, *Klebsiella aerogenes* and other Enterobacteriaceae [71]. There is probably little to choose between such a regimen and those containing an extended-spectrum antipseudomonal penicillin (see p. 199) and an aminoglycoside or a carbapenem such as imipenem/cilastin or meropenem (see p. 204) with an aminoglycoside. Both regimens might need the support of an antistaphylococcal penicillin according to clinical circumstances. Needless to say, reasonable efforts should be made to determine the nature of the causative organism and treatment may be modified in the light of laboratory findings.

Those third-generation members with no antipseudomonal activity may have a place in the treatment of somewhat less severe ward-based cases of hospital-acquired pneumonia in which Gram-negative infections are thought to be likely, cefotaxime or ceftriaxone being reasonable choices in this situation (see Chapter 13).

One of the ever-present dangers of the overuse of third-generation cephalosporins is the induction of increasing numbers of chromosomally mediated extended-spectrum  $\beta$ -lactamases by enteric Gram-negative bacilli [12]. The genes encoding these  $\beta$ -lactamases may be disseminated among other Gram-negative bacilli, resulting in a steadily increasing pool of organisms that are resistant to many antimicrobial agents [12].

For dosages of the cephalosporins the reader is referred to the *British National Formulary* or to product data sheets [58].

### Other $\beta$ -lactam antibiotics

Apart from the penicillins and cephalosporins, there are two other classes of  $\beta$ -lactam antibiotic, the monobactams and carbapenems.

#### Monobactams

##### *Aztreonam*

Aztreonam is a parenteral antibiotic that is the only currently available member of the monobactam group, so-called because the  $\beta$ -lactam ring is single rather than bicyclic as is the case with the other  $\beta$ -lactam antibiotics. It has a narrow spectrum, being active against Gram-negative bacteria including most Enterobacteriaceae, *Ps. aeruginosa* and *H. influenzae* but having no significant activity against Gram-positive organisms or anaerobes.

This is because it attaches selectively only to those penicillin-binding proteins found on Gram-negative aerobic organisms. Although it has been used in patients with serious lower respiratory tract infections, it should not be used alone on an empirical basis if there is a possibility of a mixed infection with involvement of aerobic Gram-positive or anaerobic organisms. It can apparently be used with impunity in patients who are hypersensitive to penicillins and other  $\beta$ -lactams (see p. 193) [72].

## Carbapenems

### *Imipenem–cilastatin and meropenem*

Imipenem was the first member of the carbapenem class of  $\beta$ -lactams. It is given intravenously by infusion in combination with cilastatin, a renal dipeptidase inhibitor that prevents renal metabolism, increasing urinary excretion of the active drug and inhibiting its transformation into a nephrotoxic metabolite. This drug has a very broad spectrum of activity, encompassing most Gram-negative and Gram-positive aerobic and anaerobic bacteria including most species that produce  $\beta$ -lactamases [73,74]. It is ineffective against MRSA.

Meropenem is the second member of the carbapenem class of  $\beta$ -lactams and has a spectrum of activity very similar to imipenem. It does not require combination with cilastatin and may be given by intravenous bolus injection rather than infusion.

### *Adverse effects*

Imipenem–cilastatin may cause phlebitis at the injection site. Other adverse effects are similar to those described under penicillin. As with any  $\beta$ -lactam, excessive dosage may produce seizures, and dose modification in the presence of renal impairment (glomerular filtration rate  $<50$  mL/min) is advisable. Meropenem appears to be less liable to cause seizures.

### *Principal uses in respiratory medicine*

Both these carbapenems may be used in patients with serious hospital-acquired pneumonias and in febrile neutropenic patients, who are likely to be bacteraemic. Although they may be used as monotherapy, particularly in febrile neutropenic patients [74], resistant strains of *Ps. aeruginosa* may emerge, as with other single-agent treatments; thus these drugs are often combined with an aminoglycoside, particularly when used to treat more chronic sepsis such as in cystic fibrosis. Both drugs are probably as effective as the more conventional extended-spectrum penicillins or third-generation anti-

pseudomonal cephalosporin/aminoglycoside combinations [75]. Although similarly priced, they are both costly and should be considered when problems with resistance to less expensive regimens are encountered.

## Macrolides

This group includes erythromycin, clarithromycin, azithromycin, roxithromycin, dirithromycin and others.

### *Erythromycin*

Erythromycin was originally obtained from the mould *Streptomyces erythreus* and was for many years the only antibiotic of any clinical importance belonging to the macrolide group.

### *Mode of action*

Erythromycin is primarily bacteriostatic, although in high concentration it may be bactericidal to small numbers of rapidly dividing bacteria [76]. It has its effect by reversibly binding to bacterial ribosomes, with the result that RNA-dependent protein synthesis is inhibited.

### *Spectrum of activity against respiratory pathogens*

The range of activity of erythromycin overlaps the spectrum of some penicillins so that it may be substituted for penicillin, ampicillin or amoxicillin in patients who are thought to be allergic to these drugs. Although it usually has good *in vitro* activity against *Strep. pneumoniae*, there have been increasing concerns about the emergence of pneumococci resistant to erythromycin [77–79]. Such patterns of drug resistance may be geographically based, depending on the degree of local use [80]. The activity of erythromycin and other macrolides is unaffected by the presence of  $\beta$ -lactamases. There are theoretical concerns about the effectiveness of macrolides, which are predominantly concentrated intracellularly, on bacteraemic pneumococcal infection [81]. Erythromycin usually remains active against *Strep. pyogenes* (syn.  $\beta$ -haemolytic or group A streptococcus) but is less so against methicillin-sensitive *Staph. aureus* and resistant forms of this organism may emerge during treatment [82,83]. The emergence of resistance to erythromycin during treatment may occur via various mechanisms and is more likely to develop during a prolonged course of treatment (e.g. for endocarditis) than with a standard course, such as is used in respiratory disease [84]. Erythromycin is the drug of choice in the treatment of *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia* spp. infections. It may be effective in treating infection caused by *Moraxella catarrhalis* and *Coxiella burnetii* but has only moderate activity against

anaerobic infection. Many strains of *H. influenzae* are now resistant [85]. It has no significant activity against the Gram-negative Enterobacteriaceae, including *E. coli*, *Proteus*, *Klebsiella*, *Serratia*, *Citrobacter* and *Yersinia* spp. Erythromycin has been used in pertussis prophylaxis and treatment before it reaches the paroxysmal stage of whooping cough (see Chapter 12) and is also effective against *Corynebacterium diphtheriae*.

#### *Administration, distribution and excretion*

Erythromycin base is inactivated by gastric acid and is therefore available in enteric-coated formulations as a stearate salt or in esterified form in order to allow its passage through the stomach intact. Erythromycin stearate dissociates in the duodenum, being hydrolysed and absorbed as erythromycin base in the upper small bowel. Conversely, erythromycin estolate is absorbed from the small bowel intact before undergoing hydrolysis to release the base. An ethylsuccinate ester also exists that may be taken in liquid form. Oral absorption is usually adequate [86] but varies between individuals [87], and in serious infection parenteral treatment is recommended, at least initially. The intramuscular route is painful and therefore avoided.

The half-life of erythromycin is approximately 1.5h, during which time it diffuses well into most tissues and into sputum [86,88]. It crosses the placenta but can be used safely in pregnancy. Less than 15% of a given dose is excreted unchanged in the urine and dosage reduction is not therefore usually necessary in renal failure [89]. Some of the drug is concentrated in the liver, some excreted in bile and the remainder degraded.

#### *Dosage*

The oral dose of erythromycin is 250–500 mg every 6 h; the intravenous dose is 0.5–1 g every 6 h [77]. Pharmacokinetic data suggest that this regimen is more appropriate than twice-daily dosing.

#### *Adverse effects*

Erythromycin is one of the safest antibiotics available. Oral or parenteral administration may produce dose-related nausea and occasional epigastric discomfort, vomiting or diarrhoea. These effects may occur in 20–30% of patients taking erythromycin 500 mg four times daily and are less frequent with the newer, more expensive macrolides [90]. Intravenous use may be bedevilled by local thrombophlebitis, which can be reduced or avoided by diluting the drug in 250 mL normal saline and infusing it over 1 h rather than by giving it as bolus injections [91].

Cholestatic jaundice is the most important side-effect. It is non-fatal and reversible within days or weeks of drug withdrawal. It occurs infrequently but when it does usually follows the use of erythromycin in adults for periods exceeding 10 days [92,93]. The risk of jaundice is said to be increased in pregnancy, in which condition the estolate should be avoided [94].

Other side-effects are even more unusual and include allergic reactions, pseudomembranous colitis (as with other broad-spectrum antibiotics) [95] and transient sensorineural deafness, particularly if erythromycin is used in high dosage in elderly patients with renal insufficiency [96]. This toxic effect may be augmented by concurrent cimetidine therapy [97].

Drug interactions may occur as a result of the propensity of erythromycin to inhibit hepatic metabolism (cytochrome P450 enzymes). This may cause toxic accumulation of various drugs, including theophyllines, midazolam, digoxin, disopyramide and carbamazepine, and the potentiation of warfarin and glucocorticoids [90,98,99]. For the same reason, erythromycin should not be given with terfenadine or astemizole, the accumulation of which may rarely lead to ventricular dysrhythmias [90]; indeed, intravenous erythromycin itself has rarely been associated with torsades de pointes [100]. Cyclosporin levels may also be increased.

#### *Principal uses in respiratory medicine*

Erythromycin or another macrolide may be used in the treatment of community-acquired pneumonia, both when there is a history suggestive of penicillin allergy and when a decision is taken to cover infection caused by intracellular organisms such as *Legionella pneumophila* and *Chlamydia* spp. or the pathogen *Mycoplasma pneumoniae* (see Chapter 13) [77]. It has been used to treat acute bronchitis and acute infective exacerbations of chronic bronchitis, although resistant strains of *H. influenzae* are increasingly encountered, against which clarithromycin and azithromycin are better equipped. It may also be used for upper respiratory tract infection as an alternative to penicillin.

#### *Clarithromycin*

Clarithromycin is an erythromycin derivative with a 14-membered ring. The antimicrobial activity of clarithromycin is enhanced by an active 14-hydroxy metabolite [101]. Clarithromycin has the same mode of action but better pharmacokinetics than erythromycin. It is more acid-stable than its parent drug and is rapidly absorbed with good serum and tissue levels, its longer half-life (5–7 h) permitting twice-daily dosing. The lower total dosage results in a reduced incidence of gastrointestinal side-effects.

*Spectrum of activity against respiratory pathogens*

This is broadly similar to erythromycin except that clarithromycin and its metabolite together have enhanced activity against *H. influenzae* and *Moraxella catarrhalis*. It also has slightly improved *in vitro* activity against *Legionella* and *Chlamydia* spp. It is effective against *Mycoplasma pneumoniae* and may also be used in combination with other drugs to treat *Mycobacterium avium-intracellulare* infection, against which it is four times more active than azithromycin *in vitro*. Those streptococci and staphylococci resistant to erythromycin are also resistant to the newer macrolides.

*Administration, distribution and excretion*

Clarithromycin is available in tablet form, as a suspension and as a reconstitutable powder for intravenous infusion. It is well absorbed with or without food. Hepatic metabolism produces the pharmacologically active 14-hydroxy-clarithromycin mentioned above. Significant amounts of both clarithromycin and its active metabolite are excreted unchanged in the urine, so that dose adjustment may be needed in severe renal failure but not in liver disease. Adequate serum and tissue levels are achieved.

*Dosage*

The usual oral dose of clarithromycin is 250 mg twice daily, giving a peak blood level equivalent to 500 mg erythromycin [102]. The intravenous dose is 500 mg twice daily.

*Adverse effects*

These are broadly similar to erythromycin except that gastrointestinal symptoms are less common [102]. Thrombophlebitis also occurs with intravenous clarithromycin. Drug interactions are also similar (cytochrome P450). Clarithromycin may reduce concentrations of zidovudine. In the respiratory context, both theophyllines and warfarin are commonly potentiated, as is rifabutin so that uveitis or a polyarthralgia syndrome may occur with this drug.

*Principal uses in respiratory medicine*

These are similar to erythromycin. The drug is used in community-acquired pneumonia, particularly where there is a history of penicillin allergy, and may also be effective in acute bronchitis and sinusitis. Clarithromycin is more likely to deal with *H. influenzae* in exacerbations of chronic bronchitis. The newer macrolides have been the most important advance in the treatment of opportunistic mycobacterial disease since rifampicin. Clarithromycin is

the cornerstone in regimens used to treat infections caused by organisms of the *Mycobacterium avium-intracellulare* complex, including the disseminated bacteraemic form of this infection that occurs in patients with AIDS [103–105]. In treating this infection in immunocompetent patients (see Chapter 20), clarithromycin may be given at a dose of 500 mg twice daily for 18–24 months or more in combination with rifampicin (or rifabutin) and ethambutol, sometimes with a fourth drug such as ciprofloxacin or clofazimine. An aminoglycoside such as amikacin or streptomycin is sometimes used as a fourth drug for part of the course [106]. Ethionamide or cycloserine have been used occasionally but tend to be avoided because of their toxicity [106]. One study has shown that the three-drug combination of clarithromycin, rifabutin and ethambutol is more effective at clearing *Mycobacterium avium* complex bacteraemia and prolonging survival in patients with AIDS than a four-drug regimen comprising rifampicin, ethambutol, clofazimine and ciprofloxacin [107]. Clarithromycin is also active against *Mycobacterium kansasii* and although the standard regimen for these infections comprises rifampicin, ethambutol and isoniazid, clarithromycin may be useful in resistant cases [106].

*Azithromycin*

Azithromycin is the first member of a group of macrolides known as azalides (because of the insertion of a nitrogen atom in the macrolide nucleus) and is an acid-stable semi-synthetic erythromycin derivative with a 15-membered ring. The drug achieves very low serum levels in comparison with other macrolides but is rapidly and highly concentrated intracellularly, particularly in neutrophils and macrophages, and it has been suggested that these cells may help to transport the drug to sites of infection [108]. Azithromycin has a long terminal serum elimination half-life of about 57 h, high tissue concentrations persisting for up to 5 days following a single oral dose, suggesting that significant bacterial activity in tissues persists for this length of time after a short course [109].

*Spectrum of activity against respiratory pathogens*

This is broadly similar to erythromycin except that azithromycin has greater *in vitro* activity against *H. influenzae* and *Moraxella catarrhalis* than both erythromycin and clarithromycin [65,108]. Activity against *Strep. pneumoniae* is similar to other macrolides. It is active against *Legionella* and *Chlamydia* spp., as well as *Mycoplasma pneumoniae*. It is less active *in vitro* than clarithromycin against *Mycobacterium avium-intracellulare* [110]. Those streptococci and staphylococci resistant to erythromycin are also resistant to the newer macrolides.

### Administration, distribution and excretion

Azithromycin is available as 250mg capsules, 500mg tablets and as an oral suspension. Absorption is reduced by food. Serum concentrations are low but concentrations in lung and sputum are high. Some hepatic metabolism takes place but most of the drug is excreted unchanged in the gut, presumably via the biliary tract. There is a small amount of renal excretion but dose modification is not required in patients whose creatinine clearance exceeds 40mL/min. Data are currently unavailable for severe renal failure.

### Dosage

The recommended oral dose of azithromycin in respiratory infections is 500mg once daily for 3 days. The dose should be taken *between* meals (1h before or 2h after) as the presence of food or antacids in the stomach reduces absorption significantly [111]. This is probably as effective as an alternative regimen that uses 500mg on day 1 and 250mg on days 2–5 [108]. Compliance is likely to be greater in such short once-daily regimens [112]. There is as yet no intravenous formulation.

### Adverse effects

These are broadly similar to erythromycin except that gastrointestinal symptoms are less common [108]. Headaches and dizziness occasionally occur. Azithromycin appears to have no affinity for the hepatic cytochrome (P450) enzymes responsible for some of the drug-enhancing effects common to both erythromycin and clarithromycin. It may therefore be used without increasing the levels of theophylline, warfarin, glucocorticoids and carbamazepine [110]. There also appears to be no interaction with terfenadine [108]. Cyclosporin levels may be increased.

### Principal uses in respiratory medicine

These are similar to clarithromycin. Azithromycin is the macrolide with the greatest *in vitro* activity against *H. influenzae* and *Moraxella catarrhalis*. This drug has also been used in regimens used to treat *Mycobacterium avium-intracellulare* [103,104], including the disseminated form of this infection that occurs in patients with AIDS [106], although it has less *in vitro* activity against these organisms than clarithromycin. A dose of 500mg once daily has been used in the treatment of *Mycobacterium avium* complex (see Chapter 20) in combination with other drugs as outlined for clarithromycin [106]. Low blood, as opposed to intracellular, levels are a theoretical concern in the treatment of patients with community-acquired pneumonia who may be bacteraemic.

### Other macrolides

Roxithromycin and dirithromycin are both structural modifications of erythromycin and there are others worldwide. The spectrum of activity of roxithromycin is similar to that of erythromycin but its pharmacokinetics and tolerance are improved, permitting a dose regimen of 300mg daily as single or two divided doses [65]. Excretion is hepatobiliary and dose modification is needed in hepatic but not renal failure. The pharmacokinetics of dirithromycin permits a dose regimen of 500mg once daily. They both have relatively poor activity against *H. influenzae* and dirithromycin is ineffective against *Legionella* spp. [65]. Neither drug is available in the UK.

### Trimethoprim

Trimethoprim, a synthetic broad-spectrum antimicrobial, is a diaminopyrimidine of similar structure to the antimalarial compound pyrimethamine. It was originally developed to potentiate the effect of sulphonamides and was at first only available in combined form with sulfamethoxazole (sulphamethoxazole) as co-trimoxazole. Ten years later, following doubts about the *in vivo* validity of *in vitro* synergism between these drugs and because of concern about the side-effects of the sulphonamide component of co-trimoxazole, trimethoprim was made available as a single agent that is now recognized to have potent antibacterial properties when used alone.

### Mode of action

Trimethoprim has a slow bactericidal action by causing inhibition of the enzyme dihydrofolate reductase, which is necessary in bacterial amino acid synthesis for the conversion of folate to folinic acid. Although this enzyme is also possessed by humans, trimethoprim has up to 100 000 times more inhibitory action against the bacterial form than against the human enzyme, so that normal folate metabolism is not usually significantly upset (see Adverse effects). Sulphonamides also act on the same metabolic pathway but one step earlier (Fig. 9.4).

### Spectrum of activity against respiratory pathogens

Trimethoprim has a wide range of activity *in vitro* against most Gram-positive cocci and Gram-negative bacilli. Amongst the common respiratory pathogens, *Strep. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis* are still usually sensitive but becoming less so. However, *Ps. aeruginosa* is inherently resistant and the drug has no useful activity against anaerobes. Resistance can also develop during treatment by a variety of mechanisms, as is the case with other antimicrobial agents and the number of isolates of resistant *H. influenzae* had increased from

0.2% in 1977 to 1.4% in 1981 according to a British survey [113,114]. It is not clear whether the release of trimethoprim from its sulphonamide partner has increased this likelihood.

#### Administration, distribution and excretion

It is usual to prescribe trimethoprim orally and 100 mg or 200 mg tablets are available as is a liquid suspension. A parenteral preparation is available in the UK but not the USA.

The drug is well absorbed when taken by mouth and is widely distributed. It is highly lipid soluble and therefore tends to achieve better tissue concentrations than sulfamethoxazole, so that when taken in compound form the blood levels of trimethoprim are lower than those of the sulphonamide. By the same token, trimethoprim achieves higher levels in pleural fluid and bronchial secretions than in the blood. Provided that renal function is normal, about 70% of a given dose of trimethoprim is excreted in the urine within 24 h. The majority of this is in active form, about 8% being conjugated and inactive. Some trimethoprim is excreted in bile. The plasma half-life is about 10 h but is prolonged in renal insufficiency, in which case dose modification or omission may be necessary.

#### Dosage

The usual dose is 200 mg 12-hourly by mouth. If the creatinine clearance is 15–30 mL/min, the dose should be reduced to 50 mg 12-hourly; if the creatinine clearance falls below this level, trimethoprim should not be given.

#### Adverse effects

About 6% of patients experience some nausea, taste disturbance, abdominal discomfort, vomiting or diarrhoea, and about 4% develop rashes [115]. The likelihood of these relatively minor problems occurring is increased at higher doses or if the course of treatment is prolonged. Although there is a theoretical risk of the development of folate deficiency, since the drug is much more active against bac-

terial rather than host dihydrofolate reductase it seems that this problem only occurs in patients who are relatively folate depleted before treatment; nevertheless, if prolonged treatment is required, regular blood counts are advisable. If clinical evidence of folate deficiency does develop, it can be corrected with folinic acid without countering the drug's antibacterial action [116]. There is no evidence of teratogenicity but alternative antimicrobial agents are advised in pregnancy [117].

It is believed that most of the side-effects arising from the use of co-trimoxazole have been from the sulphonamide component; however, for further possible trimethoprim-related adverse effects, including hyperkalaemia, the reader is referred to the following section on co-trimoxazole.

#### Principal uses in respiratory medicine

Trimethoprim is still sometimes used in the treatment of acute purulent exacerbations of chronic bronchitis, usually as a second-line agent in cases that have either failed to respond to a first-line drug (e.g. amoxicillin) and/or when *in vitro* sensitivities indicate that trimethoprim is the more appropriate antimicrobial. Published work has indicated that trimethoprim alone is as effective in this respect as co-trimoxazole and that it produces fewer side-effects [118]. This apparent efficacy is in keeping with the drug's activity against the common pathogens of chronic bronchitis, namely *Strep. pneumoniae* and *H. influenzae*. The clinical efficacy of trimethoprim alone for treating pneumonia is unproven.

Another use of trimethoprim has been in combination with dapsone (see below) as an alternative to high-dose oral co-trimoxazole in the treatment of mild to moderate *Pneumocystis carinii* pneumonia.

#### Co-trimoxazole and *Pneumocystis carinii* pneumonia

Trimethoprim was originally available only in combined form with the sulphonamide sulfamethoxazole, as the two compounds together were shown to greatly potentiate

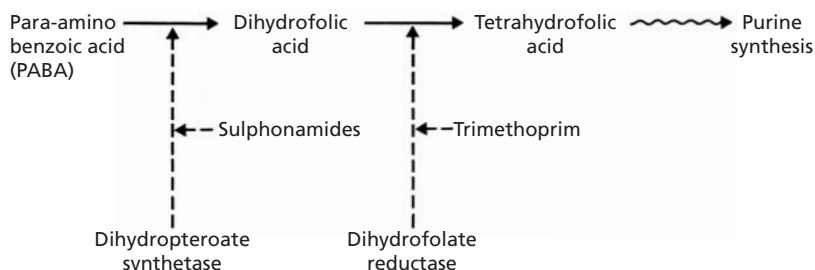


Fig. 9.4 Sites of action of sulphonamides and trimethoprim.

each other's *in vitro* antibacterial activity. There are now considerable doubts about whether this laboratory observation translates into improved clinical potency *in vivo*, at least in the treatment of acute exacerbations of chronic bronchitis [118]. This drug combination remains the first-choice treatment in immunocompromised patients with *Pneumocystis carinii* infection (see also section on pentamidine and Chapter 52).

#### Mode of action

The mode of action of trimethoprim has been outlined above. Sulfamethoxazole acts on the same metabolic pathway, but one step earlier, by inhibiting the bacterial enzyme dihydropteroate synthetase (Fig. 9.4), which is necessary for the conversion of *p*-aminobenzoic acid to dihydrofolic acid. This enzyme does not occur in humans, who therefore require dietary folate. The optimal *in vitro* concentration ratio of sulfamethoxazole to trimethoprim was found to be 20:1, this being the ratio of their MICs for most organisms. However, because of the greater diffusibility of trimethoprim, which is dispersed in body water more widely than sulfamethoxazole, the available preparations of co-trimoxazole have been formulated in a 20:4 (5:1) ratio that has been found to reproduce the 20:1 ratio most closely in plasma.

Sulphonamides are principally bacteriostatic while trimethoprim may act bactericidally, and the rationale for the compound preparation was that this bactericidal effect was more likely to occur with the combined form.

#### Spectrum of activity against respiratory pathogens

The spectrum of activity of co-trimoxazole is similar to that of trimethoprim except that the susceptibilities of both Gram-positive and Gram-negative organisms to co-trimoxazole *in vitro* are greater than to trimethoprim alone. Like trimethoprim, co-trimoxazole has no useful activity against *Ps. aeruginosa* and the majority of anaerobes. The combination has also been shown to be active against the fungal organism *Pneumocystis carinii* and against the actinomycetes *Nocardia* spp. (see p. 210).

#### Administration, distribution and excretion

Co-trimoxazole may be administered by mouth or intravenously. The pharmacokinetics of trimethoprim have already been summarized. Sulfamethoxazole, although selected as a sulphonamide with pharmacokinetic behaviour most closely resembling that of trimethoprim, is well absorbed orally but less well distributed in total body water. Like trimethoprim it is excreted in urine, 70% being recoverable as metabolite and 30% unchanged. It too accu-

mulates in renal insufficiency, in the presence of which the dose may need to be reduced (see below).

#### Dosage

The usual dose for exacerbations of chronic bronchitis was 160 mg trimethoprim and 800 mg sulfamethoxazole (expressed as 960 mg co-trimoxazole) every 12 h. These amounts were given as two 'single-strength' (80/400) tablets or in one 'double-strength' (160/800) tablet of co-trimoxazole, the duration of a course being about 1 week. However, co-trimoxazole is no longer recommended for this purpose by the UK Committee on Safety of Medicines unless a good reason can be demonstrated (see p. 210).

Much higher levels of co-trimoxazole are required to treat *Pneumocystis carinii* pneumonia (PCP), the daily dose being 20 mg/kg of trimethoprim and 100 mg/kg of sulfamethoxazole. It is usual to administer the co-trimoxazole as three or four divided doses and to treat for 2 weeks in the case of non-AIDS-associated PCP and 3 weeks in the presence of HIV infection, provided that the therapy is tolerated (see Chapter 52). A course of co-trimoxazole is conventionally given intravenously at first at this 120 mg/kg daily dose until clinical improvement occurs, after which the course is completed orally as the drug combination is well absorbed. Milder cases may be treated orally from the outset [119]. Dosage reductions should be made in renal failure as above. A full dose can be given if the estimated creatinine clearance (ECC; see Eqn 9.1, p. 215) is greater than 30 mL/min, the dose being halved when the ECC is 15–30 mL/min and omitted completely when the ECC is less than 15 mL/min. The necessity for 3-week courses has been questioned and it may well be possible to conclude treatment after 2 weeks in the face of adverse effects if the patient has apparently responded and provided that secondary prophylaxis is started at the conclusion of the course [120].

Prophylaxis using a once-daily or three times weekly (Monday/Wednesday/Friday) oral dose of co-trimoxazole 960 mg or a once-daily dose of 480 mg is commonly used in immunosuppressed patients to reduce the chance of PCP becoming established [119,121]. All have been shown to be effective and the lower doses are better tolerated [122]. In HIV infection such intervention is recommended:

- 1 when the CD4 (T-helper) lymphocyte count falls below  $0.2 \times 10^9/L$ ;
- 2 if the ratio of CD4 to total lymphocytes is less than 1:5;
- 3 where there is oral thrush or an unexplained fever;
- 4 where there is an AIDS defining diagnosis such as Kaposi's sarcoma, cerebral toxoplasmosis or cryptococcal meningitis;
- 5 in a patient who has recovered from a previous episode of PCP [119].



### Adverse effects

The incidence of side-effects from standard dosage was found to be 8% in a survey of 30 000 patients [123]. These are usually minor when the preparation is used at this original dosage and it is generally supposed that the sulphonamide component is responsible for more mischief than the trimethoprim [124], although hyperkalaemia is one possible exception. Co-trimoxazole produces nausea and other mild gastrointestinal symptoms in 3–4% of recipients. Cutaneous rashes occur in a similar percentage. Serious cutaneous eruptions such as erythema multiforme (Stevens–Johnson syndrome) are fortunately rare [125]. Interference with folate metabolism may produce megaloblastic anaemia in patients who are already bordering on folate deficiency, such as pregnant women, alcoholics and epileptics taking phenytoin. Both components of co-trimoxazole are potentially toxic to bone marrow, and bone marrow aplasia, leucopenia and thrombocytopenia have been described. Fatalities due to these blood dyscrasias have rarely been attributed to co-trimoxazole. Other unusual side-effects include acute interstitial nephritis, crystaluria (which may occur in situations of low urine flow, with metabolites of co-trimoxazole precipitating in the renal tubules) and cholestatic jaundice [126].

Side-effects are very much more commonly encountered with the high doses of co-trimoxazole required for the treatment of PCP, where over 30% of patients may need to discontinue treatment before the course is completed [127–129]. Hyperkalaemia may occur in about 20–50% of patients with AIDS when they are being treated with high-dose trimethoprim in combination with sulfamethoxazole or dapsone [129]. This is probably due to the mild potassium-sparing diuretic effect of the trimethoprim molecule, which is structurally related to both amiloride and triamterene, this effect only becoming clinically evident when the drug is used at high dosage [130].

Drug interactions, with potentiation of the effects of warfarin, oral hypoglycaemics, rifampicin and phenytoin, may occur as a result of competition for protein-binding sites.

### Principal uses in respiratory medicine

Co-trimoxazole has been used in similar fashion to trimethoprim, as a treatment for patients with acute infective exacerbations of chronic bronchitis [131]. Despite the *in vitro* superiority of co-trimoxazole, no clinical trial has ever convincingly demonstrated its superiority in this respect over trimethoprim alone [115]. This may in part be due to the rather poor tissue penetration of sulfamethoxazole, so that although the plasma ratio may be optimal the ratios in lung tissue are not, with the result that the *in vitro*

situation is therefore not reproduced. A further theoretical reason for the combined preparation, over and above that of synergy, was to diminish the development of resistant strains. However, this may not be borne out in practice, since countries such as Finland, where trimethoprim has been available as a single agent for many years, do not appear to have a higher proportion of resistant strains than those countries where separation of the two drugs was made relatively recently [132]. In the UK, the Committee on Safety of Medicines has ruled that co-trimoxazole, while remaining the treatment of choice in PCP and being indicated in toxoplasmosis and nocardiosis, should only be used in acute exacerbations of chronic bronchitis 'when there is bacteriological evidence of sensitivity to co-trimoxazole, and good reason to prefer this combination of drugs to a single antibiotic' [133].

Co-trimoxazole is the agent of choice in the treatment of PCP, the most common treatable pneumonic infection in AIDS, corticosteroid treatment being started at the same time in the hypoxic patient provided that the diagnosis is secure. Second-line agents for the iller patient who fails to respond or cannot tolerate the drug include pentamidine or trimetrexate/folinic acid with dapsone, if the patient can take oral therapy. Second-line agents for treatment of mild to moderate cases of PCP include dapsone/trimethoprim and clindamycin/primaquine.

Co-trimoxazole is also used prophylactically to prevent PCP in immunosuppressed patients, such as those with HIV infection (see above), and in those receiving immunosuppressant treatment for a variety of conditions, such as acute lymphocytic leukaemia or following organ transplantation in order to prevent rejection [121]. For an account of the clinical management of PCP the reader is referred to Chapter 52.

### Tetracyclines

Tetracyclines were the second 'broad-spectrum' antibiotics to become available, chloramphenicol being the first. Their usefulness in respiratory medicine has declined with the gradual emergence of resistant strains among common pathogens such as *Strep. pneumoniae*, and with growing concern about their safety in patients, often the elderly, who have relative renal insufficiency. They retain a high degree of activity against organisms responsible for 'atypical pneumonia'. Each member of the group has a basic structure of four fused benzene rings (Fig. 9.5), various side-chain substitutions accounting for their different pharmacokinetic properties [134]. There are six generic compounds listed in the *British National Formulary*: tetracycline, oxytetracycline, demeclocycline, lymecycline, minocycline and doxycycline [58]. Research has produced two new developmental synthetic glycyclines that are more active against those strains of *Strep. pneumoniae* and *H. influenzae* that have become resistant to

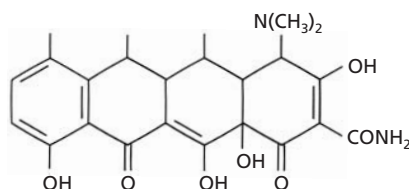


Fig. 9.5 Tetracycline nucleus.

existing tetracyclines but it remains to be seen whether these drugs go into commercial production [69]. The tetracyclines are primarily bacteriostatic antimicrobial agents that have their action by inhibiting microbial protein synthesis.

The tetracyclines may be grouped in terms of their duration of action. The early compounds tetracycline and oxytetracycline have elimination half-lives of 7–10 h and require 6-hourly administration. The newer (and more expensive) tetracyclines have longer half-lives of 17–22 h, so that doxycycline can be given once daily. The other tetracyclines fall at various points between these extremes.

#### *Spectrum of activity against respiratory pathogens*

The spectrum of activity of all the tetracyclines is rather similar and although some of the more recent members may have greater *in vitro* activity [135], the significance of this in clinical practice is unclear. Although retaining activity over a very wide range of microorganisms, significant resistance continues to be reported among common respiratory pathogens. By 1975, 13% of *Strep. pneumoniae* were found to be resistant across the country [136]. Almost one-quarter of pneumococcal isolates were resistant at one hospital in Liverpool 30 years ago [137] and wide geographical differences in susceptibility have been noted. An even higher resistance rate for *Strep. pyogenes* has been found (36%) [136], and tetracyclines are therefore unlikely to be effective in streptococcal pharyngitis. They are active against *H. influenzae*, although resistant strains of this organism also occur. Doxycycline has been used to treat *Legionella* pneumonia [138], although there is more experience with macrolides. Tetracyclines are effective against *Mycoplasma pneumoniae*, *Chlamydia* spp. and *Coxiella burnetii* as well as rare causes of respiratory infection such as *Francisella tularensis*, *Brucella* spp. (with an aminoglycoside), *Ps. pseudomallei*, *Yersinia pestis* and the causes of rickettsial and leptospiral pneumonias (see Chapter 13).

#### *Administration, distribution and excretion*

Tetracyclines are usually administered orally but, with the exception of minocycline and doxycycline, absorption

may be inhibited by food so that they should be taken before meals. Absorption is also reduced by milk, calcium, aluminium, bismuth, magnesium and zinc salts, antacids, and oral iron, sucralfate and quinapril, so that tetracyclines should not be taken within 2 h of these substances.

Tetracyclines are distributed widely in body fluids in much the same way as penicillins and reach appreciable concentrations in sputum, pleural fluid and paranasal sinuses. Oral administration is satisfactory for most clinical application and an intravenous preparation of tetracycline is no longer available in the UK. Oxytetracycline, minocycline and doxycycline preparations for intravenous use may be obtained in the USA. Intramuscular injection of tetracyclines is painful.

The main excretion route for most tetracyclines is via the kidneys, so that accumulation may occur in renal failure. Such accumulation does not occur with doxycycline, which is excreted in the bowel in these circumstances and can be used in renal insufficiency [139].

#### *Dosage*

The usual dose of short-acting tetracycline is 1 g daily in four divided doses. The longer-acting tetracyclines may be given in smaller doses, that of doxycycline being 100 mg once daily and minocycline 100 mg twice daily.

#### *Adverse effects and interactions*

The commonest side-effects are minor and related to gastrointestinal tract irritation, with nausea, abdominal discomfort and vomiting. Non-specific diarrhoea may occur and is rarely accompanied by staphylococcal enterocolitis or pseudomembranous colitis. Monilial infection of mucosal surfaces is common as with other broad-spectrum antibiotics. Allergic reactions are rare but photosensitivity may occur especially with demeclocycline (demethylchlortetracycline). Minocycline may cause a greyish-black skin pigmentation.

Tetracyclines may be deposited in growing bone and in new tooth enamel, producing brown discoloration [140,141]; for this reason they should be avoided in children under the age of 12 years and in pregnant and nursing women, as they also cross the placenta and are secreted in breast milk.

Tetracyclines may exacerbate systemic lupus erythematosus and should be avoided in this condition [142].

Hepatotoxicity is rare but has been produced with fatal consequences when large (more than 2 g daily) doses have been given parenterally or when the drug has accumulated as a result of renal insufficiency [143]. Minocycline may have the least potential for worsening liver damage but even with this drug rare idiosyncratic reactions leading to liver failure have been described [144].

Pre-existing renal insufficiency may be worsened by

tetracycline [145,146], although doxycycline does not accumulate in renal failure and is apparently safe in this respect. These effects are related to the degree of pre-existing renal failure, the dose used and the duration of therapy. Demeclocycline may produce nephrogenic diabetes insipidus and this property has been applied to clinical advantage in the management of inappropriate antidiuretic hormone (ADH) secretion.

Reversible dizziness and vertigo may occur with minocycline [147]. Benign intracranial hypertension is reported with its long-term use and eosinophilic pulmonary infiltrates have been reported, although these are rare [148,149].

The efficacy of oral contraceptives may be reduced during and for 7 days after a course of tetracycline. Warfarin may be potentiated and blood levels of cyclosporin are increased.

#### *Principal uses in respiratory medicine*

The use of tetracyclines declined in respiratory medicine once these drugs were no longer considered to be first-choice antimicrobial agents in exacerbations of chronic bronchitis. However, they are still extensively used worldwide for this purpose, sometimes on the grounds of cost, although resistant *Strep. pneumoniae* are more likely to be encountered than with amoxicillin or trimethoprim; 3–23% of pneumococcal isolates are resistant as are 1–6% of isolates of *H. influenzae*, while *Moraxella catarrhalis* is usually susceptible. They remain active in chlamydial and mycoplasma pneumonias and in Q fever [150]. In practice, however, the organisms responsible for these infections are frequently covered by erythromycin or a newer macrolide and these drugs also have the added advantage of being the antimicrobials of choice in *Legionella* pneumonia and of retaining a good degree of activity against *Strep. pneumoniae* and *H. influenzae*, particularly in the case of the newer macrolide compounds.

Demeclocycline is sometimes used in the treatment of inappropriate ADH secretion, while doxycycline is relatively safe in renal failure. Minocycline is probably the safest tetracycline to use in hepatic insufficiency but care should nevertheless be exercised (see above).

Tetracycline is commonly used as a local intrapleural irritant (1g tetracycline hydrochloride in 50mL 0.9% saline made up to 60mL in a syringe with 10mL 10% lidocaine) to produce a chemical pleurodesis in the management of malignant pleural effusions, although it is claimed that talc (which may be injected with water as a slurry) is more likely to be effective.

### **Aminoglycosides**

Aminoglycosides occupy an important position in the

treatment of serious infection, particularly in Gram-negative sepsis. Gentamicin is the most widely used member of the group, which also contains tobramycin, netilmicin, amikacin and kanamycin. Streptomycin and neomycin are also aminoglycosides; the former, the original member of the group, is now mainly used as a second-line antituberculous drug and the latter as a minimally absorbed oral preparation for bowel sterilization, it being too toxic for parenteral use. All aminoglycosides are chemically related by the possession of an aminocyclitol ring. Those whose generic names contain the root ‘-mycin’ owe their original synthesis to a species of *Streptomyces*, whereas those containing ‘-micin’ such as gentamicin have been derived from *Micromonospora* spp.

#### *Mode of action*

Aminoglycosides are bactericidal, causing the inhibition of microbial protein synthesis by binding intracellularly to RNA subunits, thereby interfering with normal ribosomal activity. Bacteria may become resistant to them by various mechanisms including the production of enzymes that alter the drug’s structure. Microbial resistance to gentamicin is becoming an increasing problem in some countries.

#### *Spectrum of activity against respiratory pathogens*

The principal area of activity of the aminoglycosides is against aerobic (or facultatively anaerobic) Gram-negative bacilli, including the Enterobacteriaceae *E. coli* and *Klebsiella*, *Proteus*, *Serratia*, *Yersinia* and *Citrobacter* spp. Gentamicin, tobramycin, amikacin and netilmicin are also active against *Ps. aeruginosa*. Kanamycin is not and its usefulness is therefore severely limited. Streptomycin is not used in the treatment of Gram-negative sepsis because of the rapid emergence of microbial resistance. None of the aminoglycosides are effective against anaerobic infection, which should be treated with penicillin or metronidazole if this is thought to be a possibility.

Aminoglycosides also have useful activity against methicillin-sensitive *Staph. aureus*, although they are not a first-line drug for known infection by this organism, which is susceptible to effective and less toxic alternatives. However, aminoglycosides may play an important supportive role in the treatment of serious *Staph. aureus* infection.

Aminoglycosides have only weak activity against *Strep. pneumoniae*, *Strep. pyogenes* and *H. influenzae*, which need separate antimicrobial cover according to clinical circumstances when gentamicin is being used empirically in the treatment of severe bacteriologically undiagnosed infection. Despite their inactivity against streptococci when used alone, their combination with a  $\beta$ -lactam antibiotic may increase the susceptibility of these organisms, this

being the basis for their synergistic use with penicillins in streptococcal and staphylococcal endocarditis. Such combined use with  $\beta$ -lactams may also produce synergism for Gram-negative organisms, as well as broadening cover and reducing the frequency with which resistant organisms emerge.

*Distribution, administration and excretion*

Aminoglycosides are widely distributed in body fluids but achieve levels in bronchial secretions only one-fifth as high as those in plasma [151], an observation that has led some clinicians to administer the drugs by intratracheal instillation or nebulization (see below) in serious persistent Gram-negative infection, such as may occur in patients with cystic fibrosis infected by *Ps. aeruginosa* [152–154]. Intracellular concentrations of aminoglycoside are low following parenteral administration, with the notable exception of the proximal renal tubular cells which are susceptible to toxic damage.

Gentamicin, tobramycin, amikacin and netilmicin may all be given either intramuscularly or intravenously. Absorption after intramuscular injection is rapid, provided that tissue perfusion is normal, peak plasma concentrations being reached in about 60 min. Intravenous injection may be direct, via a cannula over about 3 min, or alternatively by infusion over 20–30 min. If aminoglycosides are infused they should not be mixed in the same solution with  $\beta$ -lactam antibiotics because they bind and inactivate each other [155]; furthermore, infusions lasting more than 30 min are inadvisable in terms of the achievement of optimum drug levels. The peak level may be assayed 60 min after the onset of an intravenous injection or infusion, as this allows sufficient time for diffusion from the vascular space into extravascular fluid compartments [156]. The bactericidal effect is heavily concentration dependent, so that peak concentrations have been shown to correlate with clinical and bacteriological response [157]; indeed in serious sepsis, the peak aminoglycoside level should be about eight times the MIC of the target pathogen or pathogens [158]. The effectiveness of such transient high peak concentrations is the reason for current recommendations regarding once-daily dosing with aminoglycosides (see p. 214) and contrasts with  $\beta$ -lactams, where the length of time that the antibiotic spends above the MIC for the target organism, rather than peak concentration, governs clinical success. The trough concentrations of aminoglycoside are largely irrelevant with regard to clinical effect but have to be watched closely to avoid toxicity.

The pharmacokinetics of parenterally administered aminoglycosides are somewhat complex but for practical purposes they undergo no metabolism and are excreted in the urine unchanged, the principal phase of excretion

being governed by the glomerular filtration rate, which results in a half-life of about 2 h in a subject with normal renal function. A much smaller proportion of the drug is eliminated more slowly over the space of a week or more, possibly as a result of slow intracellular losses [159]. Perhaps in part as a consequence of their pharmacokinetics, aminoglycosides may demonstrate a 'postantibiotic effect', i.e. bacterial growth of susceptible organisms remains suppressed after only a short exposure. The combination with  $\beta$ -lactam antibiotics may increase the postantibiotic effect.

One study showed that the levels of aminoglycoside in bronchoalveolar lavage fluid following the topical administration of 80 mg tobramycin by jet nebulizer exceeded the MIC for most pathogenic organisms despite very low or undetectable tobramycin levels in the blood [160].

*Adverse effects*

The aminoglycosides need to be administered cautiously as their therapeutic and toxic plasma levels are close, i.e. they have a low therapeutic index. Their two principal side-effects are renal tubular necrosis and ototoxicity.

*Renal toxicity.* Treatment with aminoglycosides is a relatively common cause of acute renal failure due to tubular necrosis [161]. These drugs are reabsorbed in the proximal renal tubules so that their concentration in the renal cortex may exceed their plasma concentration 10–50 fold. Tissue levels of aminoglycoside tend to creep up gradually during a prolonged course, even though the serum levels may remain within a given band. Any consequent renal cortical damage may be guarded against provided that reasonable precautions are taken:

- 1 measurement of serum aminoglycoside levels, which should be kept within the target range for the given drug;
- 2 monitoring of the plasma creatinine/urea;
- 3 avoidance, where possible, of drugs that may enhance the nephrotoxicity of aminoglycosides (Table 9.4) or, where such avoidance is not possible, the administration of such drugs as far apart from the aminoglycoside dose as the clock allows;

**Table 9.4** Drugs that may enhance the nephrotoxicity of aminoglycosides.

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Furosemide (frusemide) and other loop diuretics
Parenteral cefalotin (cephalothin) and other cephalosporins
Clindamycin
Vancomycin
Capreomycin
Amphotericin B
Cisplatin

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4 use of once-daily dosage regimens in certain given circumstances (see below).

Nephrotoxicity is more likely to occur with prolonged courses, in the elderly, in the presence of hypotension or in subjects with pre-existing renal insufficiency [162]. When such renal insufficiency is present, aminoglycosides may be continued if they are considered essential and if no suitable non-nephrotoxic alternative antimicrobial is available. The usual practice is to increase the length of time between doses and this is discussed more fully below. Renal insufficiency is usually reversible if the drug is stopped, although recovery may be slow.

*Ototoxicity.* Although of less critical importance, ototoxicity may nevertheless result in significant impairment of hearing and/or balance. It may occur in the absence of nephrotoxicity. Hearing loss is due to cochlear damage and may be potentiated if loop diuretics, particularly etacrynic (ethacrynic) acid, are used concurrently. Vestibular effects include feelings of dizziness, vertigo, nausea and vomiting. Disturbances of balance resulting in gross ataxia may sometimes be produced and may only become evident when the patient has recovered sufficiently to get out of bed. These effects may be worse when visual compensation is reduced, such as in the dark or on face-washing over a basin. Vestibular damage is due to destruction of the hair cells in the inner ear [163]. Ototoxicity may be irreversible, although patients may learn to compensate for their unsteadiness to some extent. It may arise despite seemingly satisfactory serum concentrations. It is likely to occur only with prolonged administration [164] (e.g. infective endocarditis) and is therefore not commonly seen in respiratory medical practice. The chances of these adverse effects are minimized by careful attention to serum levels but it may be as well to warn patients of the risks if a prolonged course of treatment is considered necessary [165].

*Other side-effects.* The aminoglycosides are mild neuromuscular blockers and may therefore potentiate the effect of anaesthetic relaxants such as succinylcholine. They should not be used in patients with myasthenia gravis unless there is no alternative, and then only if facilities for mechanical ventilation are available. Prolonged aminoglycoside administration may cause hypomagnesaemia. Aminoglycosides cross the placenta and if used in pregnancy may result in fetal eighth cranial nerve damage. Allergic reactions are rare.

#### *Choice of aminoglycoside*

Various claims have been made with regard to greater antimicrobial activity or diminished likelihood of toxicity with this or that agent, but there are no substantial differences in terms of clinical efficacy or nephrotoxicity

between gentamicin, tobramycin, netilmicin and amikacin. Kamamycin suffers from the fundamental drawback of lack of efficacy against *Ps. aeruginosa*. The deficiencies of streptomycin and neomycin as Gram-negative antimicrobial agents have been mentioned above. The choice between the remaining four aminoglycosides may therefore be reasonably made on the grounds of the *in vitro* sensitivities and cost of treatment.

#### *Principal uses in respiratory medicine*

Aminoglycosides are often used in combination with a  $\beta$ -lactam antibiotic for the treatment of serious hospital-acquired pneumonia (see Chapter 13) and the treatment of patients with chronic bronchial infection by susceptible organisms occurring in association with cystic fibrosis (see Chapter 30) or other forms of bronchiectasis. Streptomycin and amikacin are occasionally used as supportive agents in resistant forms of tuberculous and non-tuberculous (opportunistic) mycobacterial disease (see Chapters 19 & 20).

#### *Gentamicin*

Gentamicin is the aminoglycoside of first choice for Gram-negative bacillary infection, largely because its patent expired a long time ago and is therefore presently cheaper than the other drugs of the same class. It can be given intravenously or intramuscularly. Bolus dosage or intermittent infusion are more likely to produce therapeutic levels than continuous infusion, which should be avoided [151].

#### *Divided or extended dosage regimens*

A loading dose of 2 mg/kg may be given initially, irrespective of renal function, in order to achieve an adequate plasma level [166]. Thereafter it has been common practice to administer a total daily dose of up to 5 mg/kg in two or three divided doses, provided that the patient's renal function is normal. Peak and trough serum levels may be checked after the second or third maintenance dose and, provided that these are satisfactory, renal function is monitored with twice-weekly creatinine levels. In the presence of impaired renal function, the total daily dose may be manipulated downwards in order to achieve satisfactory blood levels by adjusting the time interval between doses according to the patient's estimated creatinine clearance (ECC) using the equation:

$$\text{ECC} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 1.23}{(\text{serum creatinine } [\mu\text{mol/L}])} \quad [9.1]$$

The ECC is multiplied by a correction factor of 0.85 for women. When the ECC is found to be reduced, the time interval between doses may be varied as follows [166]:

ECC, 80–90 mL/min: every 12 h  
 ECC, 50–80 mL/min: every 12–24 h  
 ECC, 10–50 mL/min: every 24–48 h  
 ECC, < 10 mL/min: every 48–72 h

Repeated calculations of the ECC may need to be made in a patient whose plasma creatinine is changing. Supplemental doses need to be given to patients on haemodialysis and further adjustments are needed in renal failure patients on continuous haemofiltration [167]. Alternative schedules exist that scale down the dose but continue administration every 8 or 12 h [156,168]. There are no studies comparing one regimen with another and either method may be used, although there are theoretical reasons for choosing the former since larger individual doses achieve higher peak levels with greater bactericidal effect.

#### *Once-daily dosage regimens*

Work in experimental animals and observations in patients suggest that once-daily dosing may be less likely to cause nephrotoxicity and ototoxicity, without the loss of bactericidal effect. This premise has received support from reports showing equal clinical efficacy with reduced nephrotoxicity in adults with severe infections who were treated with either a single daily dose or the equivalent dose given three times daily [169]. Similar conclusions were drawn in a group of 96 patients, in which elderly males predominated, when 4 mg/kg once daily was compared with 2 mg/kg 12-hourly [170]. However, in this study a correlation was found in the once-daily group between nephrotoxicity and an initial peak serum concentration exceeding 12 mg/L [170]. Although using different end-points, meta-analyses of the results of individual trials, which for the most part comprised relatively small numbers of patients with normal renal function and uncomplicated infections, have concluded that once-daily dosing appears to introduce no loss of efficacy in these groups and that overall it is neither more toxic nor less toxic to the kidneys than divided dosing [171,172].

It is conventional with once-daily regimens to infuse aminoglycoside intravenously in 100-mL diluent over 1 h rather than give it as a slow intravenous injection, in order to avoid any theoretical risk of neuromuscular blockade (see p. 214) [173]. This method of administration is acceptable in patients with uncomplicated lower respiratory tract infection in which susceptible organisms are suspected or have been demonstrated. Aminoglycosides have also been used successfully once daily in patients with cystic fibrosis, although there are few data concerning their efficacy and safety in this patient group [174]. There is also a relative paucity of data on once-daily aminoglycoside usage in patients with significant renal impairment, although most clinicians would find a substitute rather than use this class of drug at all in such circumstances without a pressing reason to the contrary.

#### *Blood levels with divided dose schedules*

A common convention with divided dose schedules is to check the peak serum level 1 h after a slow intravenous or intramuscular injection. The trough level should be estimated immediately before the next dose is due. Toxicity should be avoided if the peak level is kept below 10 mg/L and the trough level below 2 mg/L by manipulation of the length of time between doses (as above) and/or of the dose itself [166]. Dosage schedules and nomograms are intended for guidance only and should not be rigidly observed, as there is much pharmacokinetic variation in the handling of aminoglycosides between patients [175]. There is published work to suggest that patients with pneumonia due to Gram-negative bacilli do better if their peak serum levels of gentamicin (or tobramycin) exceed 7 mg/L, i.e. approach the toxic range [176]. High trough levels (>2 mg/L) are more important than high peaks with regard to the causation of toxic side-effects.

#### *Blood levels with once-daily dose schedules*

When once-daily dose schedules are used, each dose may be regarded as a loading dose. Peak serum levels are assumed to be high and need not be measured for clinical purposes. Similarly, trough levels at 24 h are low in the absence of significant renal impairment (ECC < 50 mL/min), so that measurement is also pointless. One approach is to use a fixed dose, such as 7 mg/kg (using ideal body weight if obese), of gentamicin or tobramycin and to determine whether the dose interval should be 24 h or longer by using a nomogram (Fig. 9.6), such as that validated at Hartford Hospital, Connecticut, using data from 2184 patients [177]. In such a case, the blood sample may be taken 6–14 h following the commencement of the infusion and the timing of the sample accurately recorded. Application of the nomogram tells the clinician whether to give the next dose in 24, 36 or 48 h or if the limits are

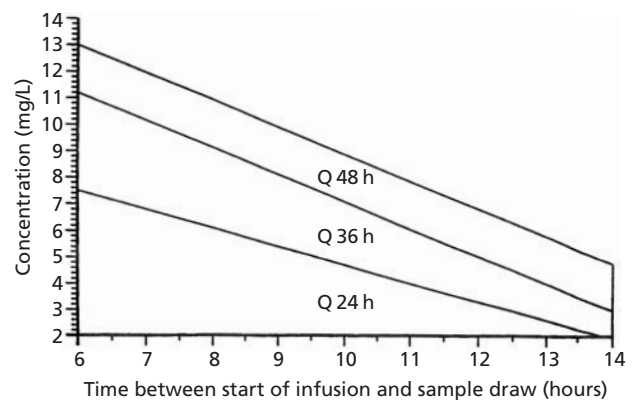


Fig. 9.6 Nomogram for once-daily gentamicin dosing. (Modified from Nicolau *et al.* [177] with permission.)

exceeded to ask for expert advice. Serum levels are thereafter monitored twice weekly, along with renal function using the plasma creatinine.

### *Tobramycin*

The routes of administration are as for gentamicin. Laboratory evidence exists to suggest that this aminoglycoside is more active than gentamicin against *Ps. aeruginosa* and less so against other Gram-negative bacteria such as *Serratia* spp. [178]. These *in vitro* findings do not appear to have produced any obvious differences between the two drugs in terms of clinical efficacy. It has been suggested that tobramycin is less likely to cause renal impairment and ototoxicity [179,180]. However, such claims have not been clearly translated into a measurable clinical advantage. A small study in patients with cystic fibrosis has suggested that 12-hourly intravenous dosing may be as effective and less toxic than conventional 8-hourly dosing [181].

The loading dose and usual dose range, as well as the peak and trough targets, are the same as those for gentamicin as outlined above [166], and the same induction and maintenance plans may also be used.

### *Netilmicin*

Netilmicin is very similar to gentamicin and tobramycin. The methods of administration, pharmacokinetics, dosage requirements and calculations are similar to those outlined for gentamicin. *In vitro* testing has shown it to be more active than gentamicin against some Gram-negative bacteria and less active for others such as *Ps. aeruginosa* [178] but these observations have not been translated into detectable clinical differences, nor indeed have claims, based on experimental work, that it is less toxic to the kidneys or ears [182]. The loading dose is the same as for gentamicin and tobramycin, as are the target peak and trough levels, a usual daily maintenance dose being 6 mg/kg [166].

### *Amikacin*

This compound, a derivative of kanamycin, is also available for intramuscular or intravenous use. At laboratory level it is less active than gentamicin, tobramycin and netilmicin against many of the Gram-negative bacillary organisms for which these drugs are used [178], but this can be compensated for by increasing the dose. However, amikacin has an important advantage over its three cousins in that it is unaffected by many of the aminoglycoside-inactivating enzymes to which gentamicin, tobramycin and netilmicin are susceptible. It is therefore at the very least a useful reserve drug when *in vitro* testing has shown resistance to these other drugs and some have advocated its routine use in place of gentamicin [183].

The dosage calculations require a loading dose of 7.5 mg/kg. Toxicity should be avoided by assaying peak and trough levels as outlined for gentamicin, peak levels being kept between 15 and 30 mg/L and the trough levels between 5 and 10 mg/L [166].

### *Nebulized aminoglycosides and other antimicrobial agents*

This method of administering antimicrobial agents [152] has mainly been used in patients with cystic fibrosis, whose lower respiratory tracts are known to be colonized by *Ps. aeruginosa*, the usual approach being to administer the drug on a regular basis to try to diminish the microbial load in order that the rate of decline in lung function might be reduced and to increase the time between exacerbations that might otherwise require hospital admission for parenteral therapy. A number of trials have been carried out, but because of their small size and varying methodology there has been lack of consensus and there are no good data on the optimal frequency of administration, e.g. continuous daily administration, short bursts, once, twice, three times daily, etc. Various antipseudomonal antimicrobial agents have been used in this manner, including colistin (a polymyxin), tobramycin, gentamicin, amikacin, carbenicillin, ticarcillin, azlocillin and ceftazidime, either alone or in combination [152,184]. Of the aminoglycosides, there is greatest experience with tobramycin [185,186]. A controlled trial using high-dose (600 mg three times daily) preservative-free tobramycin was shown to be effective in both controlling pseudomonal sputum load and improving forced expiratory volume in 1 s (FEV<sub>1</sub>) [187]. It is probable that lower doses may be effective and further studies are underway [185,186,188]. A meta-analysis of five controlled trials of nebulized antipseudomonal antimicrobial agents in cystic fibrosis claimed to show benefit in terms of reducing respiratory exacerbations and pseudomonal load and improving pulmonary function [184]. The disadvantages of this form of therapy are the inconvenience of administration, leading to reduced compliance, and its expense. Fears that this method of treatment might produce significant numbers of drug-resistant organisms do not appear to have been realized.

### **A polymyxin for respiratory use: colistin**

Colistin is a polymyxin that is not significantly absorbed from the gastrointestinal tract. Although available for intravenous use, its adverse effect profile has, up to now, limited its application by this route and its usually respiratory indication has been in nebulized form for the prophylactic control of *Ps. aeruginosa* infection between exacerbations in patients whose lower respiratory tracts are colonized by this organism, particularly those with cystic fibrosis [152]. The usual dose by this route is 1



megaunit (80 mg) twice daily after postural drainage has been performed, half this dose being recommended for patients who weigh less than 40 kg.

It has recently been suggested that reports of this drug's toxicity are exaggerated and claims have been made for its efficacy when used intravenously, either alone or in combination with a second antipseudomonal antibiotic, at a dose of 2 megaunits intravenously in 50 mL 0.9% saline over 30 min every 8 h in a trial of cystic fibrosis patients with *Ps. aeruginosa* infection [189].

The principal side-effects from its parenteral use are renal (acute renal failure) and neurological (perioral and peripheral paraesthesiae, vertigo, confusion, muscle weakness and respiratory impairment secondary to neuromuscular blockade), so that like aminoglycosides it is contraindicated in myasthenia gravis. The parenteral prescriber should monitor renal function with care and should also be alert for neurological symptoms. As with other antibiotics, wheezing may occasionally be produced when the more usual nebulized method of administration is used.

### Metronidazole in anaerobic infection

Metronidazole, a nitroimidazole, is one of the most important drugs currently available for the treatment of anaerobic infection and is also antiparasitic, being widely used for treating *Entamoeba* diarrhoea and giardiasis.

#### Mode of action

Metronidazole has a low molecular weight, which allows it to diffuse easily into bacteria. The drug, or one of its intermediate metabolites, appears to exert its bactericidal effect on anaerobic bacteria by interaction with DNA [190,191].

#### Spectrum of activity against respiratory pathogens

Metronidazole is highly active against virtually all Gram-negative anaerobic bacilli, including *Bacteroides fragilis*, which is commonly resistant to penicillin and one of the most frequently encountered pathogenic anaerobes [192,193]. It is also active against Gram-positive obligate anaerobic cocci and *Clostridium* spp. It has no useful activity against aerobic or microaerophilic organisms but resistant anaerobic organisms are unusual.

#### Administration, distribution and excretion

Metronidazole is well absorbed orally and diffuses readily throughout body water to the extent of penetrating not only pleural empyema fluid but also brain abscesses. Excellent blood levels can be achieved by this method of administration and there is no advantage in using

the expensive intravenous route if the drug can be swallowed. Absorption after rectal administration is reasonably good. Most of the drug is metabolized by the liver; about 15% of a dose being excreted unchanged in the urine, by which route the metabolic products are also removed. A small amount is excreted in the faeces. The serum half-life is approximately 8 h. This is unchanged in renal failure because of hepatic metabolism but may increase in liver disease, so that dose reduction in the presence of significant hepatic dysfunction may be necessary [194].

#### Dosage

The standard oral dose for anaerobic infection is 800 mg initially, then 400 mg 8-hourly. This gives comparable blood levels to the intravenous route for which a 15 mg/kg loading dose over 1 h followed by 7.5 mg/kg every 6–8 h is recommended [191]. The usual rectal dose is 1 g 8-hourly for 3 days, then 1 g 12-hourly. The duration of treatment depends upon the nature of the infection and its response. It may be necessary to treat a suppurative process such as an empyema for 2–4 weeks or even longer (see Chapter 14).

#### Adverse effects

Minor side-effects include the usual upper gastrointestinal disturbances that may be associated with many antibiotics, namely nausea, anorexia and vomiting. In addition, glossitis, a furred tongue and an unpleasant metallic taste may be recorded. The most serious side-effects are neurological and include ataxia, peripheral neuropathy, somnolence and seizures, so that the drug should be used cautiously in patients with a history of epilepsy. These are all rare but are potential risks if treatment is prolonged, if it involves high dosage or if there is associated liver disease. Other side-effects include reversible neutropenia and rarely pseudomembranous colitis, this being a somewhat paradoxical complication in a drug specifically used to treat this condition when caused by *Clostridium difficile* [195].

Drug interactions may result in the potentiation of warfarin via reduction of its hepatic metabolism. A disulfiram effect may occur with alcohol, which should therefore be avoided for the duration of metronidazole therapy.

There are no reports of teratogenicity but metronidazole crosses the placenta and common sense dictates that it should be avoided if possible during pregnancy, especially in the first trimester, as well as in nursing mothers unless a pressing need exists.

#### Principal uses in respiratory medicine

The main uses of metronidazole in respiratory medicine are in the treatment of aspiration pneumonitis (see Chapter 13) and other infections such as lung abscess or

empyema (see Chapters 14 & 15), in which anaerobic infection is likely. Such infection is often mixed and it is not recommended that metronidazole be used alone, as some anaerobic cocci and most microaerophilic streptococci (e.g. *Strep. milleri/intermedius*) are resistant. The addition of a second antimicrobial agent such as penicillin deals with these organisms. Thus the presence of microaerophilic streptococci or aerobes may cause treatment failures if metronidazole is used alone [196].

Other roles for metronidazole include the treatment of pseudomembranous colitis due to *Clostridium difficile* [195], in which its effect is comparable to that of vancomycin, and in thoracic complications of *Entamoeba histolytica* infection.

### Tinidazole

Tinidazole is a second nitroimidazole antimicrobial that is orally administered and that has a similar spectrum of activity and characteristics to metronidazole, except that it has a long half-life of 14 h, permitting a twice-daily dose of 500 mg–1 g after a loading dose of 2 g.

### Clindamycin

Clindamycin is the principal member of the lincosamide group of antibiotics, of which the parent compound lincomycin was derived from a soil *Streptomyces*. Lincomycin is not discussed further as it has been superseded by its derivative clindamycin, which has both greater antimicrobial activity and better absorption than the parent compound [197]. Clindamycin and related compounds act by binding to bacterial ribosomes and thus inhibiting protein synthesis. They are usually bacteriostatic but can act bactericidally.

#### Spectrum of activity against respiratory pathogens

The spectrum of clindamycin is, in some respects, similar to that of erythromycin, although it is not chemically related. It is active against *Strep. pneumoniae* and its good antistaphylococcal activity and penetrative properties are illustrated by its use in the treatment of osteomyelitis. However, it is inactive against *H. influenzae*, Gram-negative aerobes, *Mycoplasma pneumoniae* and the Legionellaceae. Clinically, it is most important for its effectiveness against Gram-positive and Gram-negative anaerobic bacteria, including *Bacteroides fragilis* [194], although a few resistant strains exist [192].

#### Administration, distribution and excretion

Clindamycin is well absorbed after oral administration, following which its serum half-life is about 3 h. A parenteral preparation for both intramuscular or intravenous

use also exists. It is well distributed to various tissues including lung and also penetrates the contents of abscesses, being actively transported into leucocytes [198–200]. The drug undergoes metabolism in the liver and is excreted into the gut via bile both unchanged and as metabolites and, to a lesser extent, in the urine. Dose modification may need to be made in the presence of significant hepatic or renal insufficiency.

#### Dosage

The oral dose range is 150–450 mg 6-hourly, a usual dose being 300 mg 6-hourly in the form of 150 mg capsules. An intravenous regimen of 600 mg 6-hourly or 800 mg 8-hourly is usual [201]. Dosage reduction may be necessary in hepatic or severe renal insufficiency.

#### Adverse effects

Diarrhoea occurring as a non-specific irritative effect may occur in about 20% of patients. It usually resolves promptly on withdrawal of the drug but should cause concern about the possibility of pseudomembranous (or antibiotic-associated) colitis, which is the most serious adverse effect of clindamycin. Pseudomembranous colitis may occur with virtually all antibiotics but is seen more frequently with clindamycin, which achieved notoriety as the first antibiotic to be linked with this complication, its reported incidence varying widely (according to diagnostic criteria) between less than 1% and 10% of cases [51,194,202]. The condition is characterized by the formation of yellow/white plaques or 'pseudomembranes' on the colonic mucosa and may be mild and self-limiting, although fatalities have occurred. It arises as a result of the production of cytotoxin by *Clostridium difficile*, an anaerobic organism that colonizes the bowel of about 3% of healthy adults. This organism is transmissible by the faecal–oral route and is resistant to many antibiotics including clindamycin but sensitive to vancomycin and metronidazole by mouth [51]. Treatment of antibiotic-associated diarrhoea is by prompt discontinuance of the antibiotic, hydration and the avoidance of antidiarrhoeal agents, which may result in toxic megacolon; metronidazole or vancomycin may be used if *C. difficile* and its toxin are demonstrated in the faeces. Some strains of *C. difficile* are non-toxicogenic.

Other adverse effects include skin rashes, which occur in 3–5% of cases; hepatic dysfunction, as indicated by a transient elevation of transaminase levels; and haematological abnormalities, indicated by neutropenia or thrombocytopenia. Anaphylactic reactions are rare.

#### Principal uses in respiratory medicine

The widespread use of clindamycin has been curtailed by

fears about its propensity to cause pseudomembranous colitis, so that its use is reserved for serious infections. Its main application in respiratory medicine is in the treatment of anaerobic infection, e.g. aspiration pneumonia/lung abscess, particularly when these have arisen in the community. Many physicians would use benzylpenicillin as the drug of first choice, possibly supplemented by metronidazole, before falling back on clindamycin if the patient fails to respond. Clindamycin has a clear role in such infection when the patient is known to be allergic to penicillin and some would use it as a drug of first choice in seriously ill patients. The use of clindamycin in these circumstances is supported by some trial work that has suggested its superiority to penicillin in anaerobic pulmonary infection [203,204].

Clindamycin has also been used as an oral therapy in combination with primaquine (see below) for AIDS patients with mild to moderate PCP as an alternative to co-trimoxazole.

## Glycopeptide antibiotics and MRSA

### Vancomycin

Vancomycin is a high molecular weight glycopeptide produced using a *Streptomyces* originally recovered from a Borneo jungle soil sample that was found to *vanquish* staphylococci, hence the name. It has its action by interfering with both cell wall and RNA synthesis. It has been available since the 1950s and is the original member of its class, the appearance of early samples earning them the sobriquet of 'Mississippi mud'. Teicoplanin is the most recent member of this class to become generally available. Were it not for the toxicity of vancomycin, it might well have been the drug of choice for serious staphylococcal infections; indeed the fact that its use has been limited by its toxicity is probably one reason why it remains effective. However, it has undergone a revival both with the emergence of staphylococci resistant to semisynthetic penicillins, especially MRSA, and with the recognition of antibiotic-associated pseudomembranous colitis caused by toxins from *Clostridium difficile* [51,205].

### Spectrum of activity against respiratory pathogens

Vancomycin is a relatively narrow spectrum agent that is bactericidal against Gram-positive cocci including *Staph. aureus* and *Staph. epidermidis*. MRSA are ordinarily sensitive but the emergence of vancomycin-resistant enterococci is a major concern because the plasmid-mediated transfer of enterococcal resistance to other genera such as staphylococci is a real possibility that could lead to untreatable systemic staphylococcal infection [12,83,206]. Indeed a few reports of *Staph. aureus* with reduced vancomycin susceptibility (MIC  $\geq 8\mu\text{g/mL}$ ) have recently

been documented in North America and Japan [207–209], these organisms having also been referred to as vancomycin-insensitive MRSA. As with *Staph. aureus*, so *Staph. epidermidis* and other coagulase-negative staphylococci are increasingly resistant to methicillin, which is relevant to general medical practice as they may colonize plastic catheters and cannulae and use them as stepping stones to infection of prosthetic and, uncommonly, native heart valves. Although these organisms are ordinarily sensitive to vancomycin, a resistant coagulase-negative *Staphylococcus* was first documented over 10 years ago [210]. Of other Gram-positive cocci, *Strep. pneumoniae* (including penicillin-resistant forms) and *Strep. pyogenes* are also sensitive to vancomycin. Streptococci of the viridans group and non-respiratory streptococci may require the addition of an aminoglycoside to achieve a bactericidal effect. Many anaerobic organisms, including *Clostridium difficile*, are sensitive. Vancomycin is ineffective against Gram-negative respiratory pathogens [211].

### Administration, distribution and excretion

There is no therapeutically significant absorption from the gut and oral administration is confined to the treatment of *Clostridium difficile*-associated colitis. Intramuscular injection is particularly painful and the intravenous route is therefore used for parenteral administration. Adequate levels have been found in pleural fluid following parenteral administration [212]. The drug is excreted largely unchanged by the kidneys and in the presence of normal renal function the plasma half-life is about 6 h.

### Dosage

A parenteral loading dose of 750 mg to 1 g (15 mg/kg) is recommended. An average dose thereafter would be 500 mg infused over 1 h every 6 h although, in view of its half-life, 1 g may be given 12-hourly over 100 min as an alternative. Particular care has to be paid to dosage because of the potential for serious side-effects, especially ototoxicity. Peak plasma levels should not exceed 30–40  $\mu\text{g/mL}$  and 60–80  $\mu\text{g/mL}$  is within the toxic range [211]. Maintenance dosage in renal insufficiency may be estimated from the formula:

$$\text{Vancomycin dose (mg) per 24 h} = 150 + (15 \times \text{creatinine clearance [mL/min]}) \quad [9.2]$$

Creatinine clearance may be estimated using Eqn 9.1 on p. 214. Alternatively vancomycin dose in patients with renal insufficiency may be predicted using a nomogram [213]. Blood levels of vancomycin may be monitored during parenteral treatment, although the value of this practice has been questioned [214]. Samples should be taken immediately before and 2 h after completion of the

infusion. In general, such assays may be made after the third or fourth dose and subsequently at least twice weekly. Typical target ranges are 5–10 µg/mL for the trough level and 20–30 µg/mL for the peak level, leaning towards the lower end of the range in patients with renal insufficiency. As with aminoglycosides, an alternative to reducing the dose is to increase the length of time between doses.

The oral dose for *Clostridium difficile* colitis is 125 mg 6-hourly for 7–10 days.

#### *Adverse effects*

The most serious side-effect is deafness due to eighth cranial nerve damage. This can be permanent and is sometimes preceded by tinnitus, which can be taken as an indication to discontinue the drug. Nephrotoxicity may also occur but is less common, having been a problem with earlier relatively impure preparations of 'Mississippi mud'. Both these side-effects may be avoided by careful dosing and observance of plasma levels (see above). It should be noted that patients who are in renal failure may attain toxic levels of vancomycin when the drug has been administered orally for the treatment of *Clostridium difficile* colitis [215]. The likelihood of ototoxicity and nephrotoxicity may be increased by concurrent aminoglycoside therapy which, if used, should be attended by a dosage limitation of vancomycin to 0.5 g every 8 h [216].

Other adverse effects include rashes, fever and local thrombophlebitis. Extravasation of the drug may cause local tissue necrosis. Alarming flushing of the face and trunk may occur ('red man syndrome') if intravenous doses are given rapidly, hence the recommendation for a slow infusion rate. This is caused by histamine release and has been associated with hypotension and collapse. Febrile reactions and reversible neutropenia are described.

#### *Principal uses in respiratory medicine*

Vancomycin is reserved for use in serious infections because of its potential toxicity. It is widely used in the treatment of MRSA infections and may also be used in patients with serious *Staph. aureus* infections who cannot take penicillin derivatives because of allergy.

Oral vancomycin is the drug of choice in ill patients with antibiotic-induced pseudomembranous colitis, metronidazole being an inexpensive preparation that may be used as an alternative in a less sick patient.

#### *Teicoplanin*

Teicoplanin is a more recent high molecular weight glycopeptide complex, produced by an *Actinomyces*. It is chemically similar to vancomycin but more lipophilic,

having good intracellular penetration. It has a similar spectrum of activity to vancomycin, has a less troublesome adverse effect profile but is more costly. Its pharmacokinetics permit once-daily intravenous injection. Unlike vancomycin, it may be given intramuscularly without excessive pain and absorption by this route is equivalent to intravenous injection. There is no oral formulation.

#### *Spectrum of activity against respiratory pathogens*

The antimicrobial activity of teicoplanin is broadly similar to that of vancomycin. It too has excellent activity against *Staph. aureus*, including MRSA. Its combination with an aminoglycoside may produce a synergistic effect against *Staph. aureus* and this is usual in endocarditis. There is some variability between teicoplanin and vancomycin with regard to coagulase-negative staphylococci and enterococci, some organisms of either class being resistant to one and sensitive to the other [217].

#### *Administration, distribution and excretion*

Peak serum concentrations occur 30 min after intravenous, and 4 h after intramuscular, injection. The drug is widely distributed and largely excreted unchanged by the kidneys. It has a long elimination half-life of about 1 week [217]. This is increased in renal insufficiency, necessitating either dose reduction or an increase in time between doses.

#### *Dosage*

Three loading doses of 400 mg (about 6 mg/kg) 12-hourly by intravenous bolus or 30-min infusion are recommended for severe infection, followed by 400 mg once daily either intravenously or intramuscularly. This is likely to achieve a desirable trough level of greater than 10 mg/L. It is not usually necessary to monitor blood levels of teicoplanin as this drug is less likely to be associated with significant adverse effects. Such monitoring may be required when treating endocarditis, in which case dose adjustment up to 800 mg in order to achieve trough levels of greater than 20 mg/L may be necessary.

#### *Adverse effects*

Side-effects include rashes, fever and local thrombophlebitis but these are uncommon. Ototoxicity and altered renal function are both unusual, occurring in 0.3 and 0.6% of patients respectively [217]. Impairment of renal function is seen less commonly when teicoplanin is administered with an aminoglycoside than when vancomycin is used in a similar combined fashion. Anaphylactoid reactions with histamine release ('red man syndrome', see above) appear to be rare. They may, but

need not necessarily, occur following substitution of teicoplanin for vancomycin. Leucopenia, thrombocytopenia and eosinophilia are described.

#### *Principal uses in respiratory medicine*

Teicoplanin has similar indications to vancomycin and experience with its use is increasing. Its once-daily dosage and relative freedom from adverse effects, particularly ototoxicity and nephrotoxicity, when administered with an aminoglycoside are relative advantages. It has therefore been advocated as a secondary agent that may be added to a  $\beta$ -lactam/aminoglycoside combination if fever fails to resolve in the neutropenic bacteraemic patient. Whether the emergence of staphylococcal resistance will be a greater problem for teicoplanin than vancomycin remains to be seen.

There is no oral preparation of teicoplanin and oral vancomycin remains the drug of choice in ill patients with antibiotic-induced pseudomembranous colitis (see above).

### **Pentamidine and *Pneumocystis carinii* pneumonia**

Pentamidine isethionate is an antiparasitic agent that has been used for over 50 years in the treatment of African trypanosomiasis (sleeping sickness) and leishmaniasis (kala-azar). It was found to be effective against *Pneumocystis carinii* in the 1950s, and PCP is the only respiratory application for this drug. Its use increased both as a result of the AIDS epidemic and the growth of immunosuppressant therapy in medicine. For an account of the clinical management of PCP the reader is referred to Chapter 52.

#### *Mode of action, administration and pharmacokinetics*

Pentamidine is a diamidine, the precise antimicrobial actions of which are incompletely understood, although the inhibition of folate metabolism, glycolysis and nucleic acid synthesis have been proposed as possible mechanisms [218,219].

Pentamidine is not absorbed following oral administration. It may be given intravenously (see Adverse effects), intramuscularly or, in certain circumstances, as a nebulized solution. Although well absorbed following intramuscular injection, plasma levels are low and it is thought that the drug is taken up by tissues. It may be partially metabolized by the liver and excretion, which is principally renal, is slow so that the drug may be detected in the urine for several weeks [220,221].

#### *Dosage*

When pentamidine has to be used in the treatment of PCP,

it is recommended that it should be given as a single intravenous dose of 3–4 mg/kg daily [219]. Caution is advised in administering pentamidine to patients with renal insufficiency because the drug is known to have nephrotoxic properties and it has a tendency to accumulate. If the creatinine clearance is 10–50 mL/min, the dosage interval should be prolonged to 36 h, and at a level of less than 10 mL/min to 48 h [222]. The usual course of treatment lasts for 14 days, although this may need to be prolonged to 3 weeks in patients with AIDS [223]. It was usual to give pentamidine by deep intramuscular injection but it is now customary to give the drug intravenously, provided that it is given by slow infusion in about 100 mL 5% dextrose over 60–120 min in order to reduce side-effects.

Aerosolized pentamidine may be given as PCP prophylaxis at a dose of 300 mg once a month or 150 mg every 2 weeks and is dispensed as a ready-to-use solution [224]. Prior treatment with a bronchodilator is advised (see Adverse effects). The type of jet nebulizer and the flow rate used may be important in achieving adequate lung deposition, as the optimal particle size for alveolar deposition is 1–2  $\mu$ m. Systems such as Respigard ii (Marquest), driven by air (or oxygen) at a flow rate of 6 L/min, have been validated for this purpose [225].

#### *Adverse effects*

Side-effects (Table 9.5) are a particular problem with parenteral pentamidine therapy and are experienced by almost 50% of patients receiving this form of therapy [226]. Immediate effects may take the form of severe hypotension, with associated sweating, dizziness, syncope and dyspnoea [227]. These reactions may occur in about 5% of patients after intramuscular injection and in about 75% after *rapid* intravenous injection. Fatal reactions have been recorded in children. In addition, there may be associated nausea, vomiting and itching. Such effects may last for 30 min and do not require cessation of therapy but clearly the patient should be forewarned about them. The greater incidence of these effects with intravenous injection led to the recommendation that the intramuscular route should be used, although further evidence suggests that this recommendation may be inappropriate provided that the drug is infused over 1 h [227]. Intramuscular administration is painful and local abscess formation at the injection site is well described. The anterior aspect of the thigh is preferred in order to reduce the possibility of faecal contamination of an ulcerated gluteal injection site.

The most important limiting side-effect is nephrotoxicity [226]. This occurs in about one-quarter of patients receiving pentamidine and although usually mild and reversible it necessitates discontinuance of the drug as it has been implicated in reported fatalities. Alternate-day plasma creatinine estimations are advised during the

**Table 9.5** Adverse effects of parenteral pentamidine.

<i>Immediate</i>
Severe hypotension
Nausea and vomiting
Pruritis
<i>Later</i>
Nephrotoxicity
Pancreatitis
Hypoglycaemia
Diabetes mellitus
Hypocalcaemia
Marrow toxicity
Hepatotoxicity
Rashes
Local abscess formation

course of treatment. Careful consideration should be given before the concurrent addition of other potentially nephrotoxic drugs, such as aminoglycosides, foscarnet and amphotericin B, as rapidly progressive renal failure may follow [228].

Other adverse effects include hypoglycaemia [229], which occurs as a result of inappropriately high insulin levels, and is followed within days, in some cases, by diabetes mellitus. These effects result from the toxic effects of pentamidine on the  $\beta$  cells in the pancreatic islets [218], and requires blood glucose monitoring for early detection. Pancreatitis may also occur [230]. Hypocalcaemia has been described but is uncommon. Other electrolytic abnormalities include hyperkalaemia and hypomagnesaemia. Haematological abnormalities are unusual and include anaemia, neutropenia and thrombocytopenia [218]. Abnormal liver function may be reflected by raised transaminases [229]. QT interval prolongation may occur on the ECG and torsades de pointes or other dysrhythmias may arise. Cutaneous rashes may also occur.

Aerosolized pentamidine is free from systemic side-effects as little of it is absorbed. It has a propensity to induce wheezing in susceptible subjects and this may be countered by prior treatment with a nebulized bronchodilator [231,232]. The patient may complain of an unpleasant metallic taste as indeed may also be the case with parenteral administration.

#### *Principal uses in respiratory medicine*

The only therapeutic indication for pentamidine therapy in respiratory medicine is the treatment of PCP [220]. It is mainly used as second-line therapy in patients who are failing to respond to treatment with high-dose co-trimoxazole after 4–5 days or in those patients in whom co-trimoxazole has to be discontinued because of its own adverse

effects. Co-trimoxazole is generally considered more efficacious, both treatments having a high incidence of side-effects.

Aerosolized pentamidine has been used as a daily single dose for 3 weeks to treat patients with PCP in which the infection was classed as mild or moderate ( $PO_2 > 8$  kPa, 60 mmHg) but this approach has proved less effective than the conventional intravenous route [220]. This route of administration is more commonly used as a monthly prophylactic dose in patients who cannot tolerate prophylactic co-trimoxazole because of cutaneous allergy or other adverse effects.

### **Antimicrobial agents, other than co-trimoxazole and pentamidine, used for treating PCP**

#### *Trimetrexate/folinic acid*

Trimetrexate is a lipid-soluble antifolate and, like trimethoprim and methotrexate, is an inhibitor of dihydrofolate reductase although it is much more potent in this regard than trimethoprim. It was developed as a myelosuppressive agent and has its antiparasitic effect by preventing *Pneumocystis carinii* from synthesizing folate. Trimetrexate must be supplemented with calcium folinate (leucovorin) in order to prevent or reduce myelosuppression and mucosal ulceration, as well as hepatic and renal dysfunction. The microbe itself is unable to take up this supplement as it lacks a folate transport system [233]. Trimetrexate may be given by once-daily intravenous infusion at a dose of 45 mg/m<sup>2</sup> for 3 weeks, calcium folinate being given at a dose of 20 mg/m<sup>2</sup> 6-hourly orally or by slow intravenous injection (at a separate site) for 3 days longer. Nausea, rashes and a peripheral neuropathy may also occur. This drug has been found to be effective in the treatment of moderate to severe PCP ( $PO_2 < 8$  kPa, 60 mmHg), although less so than co-trimoxazole. It is as well or better tolerated [234]. Some experts have used trimetrexate alone or in combination with dapsone (see below) as a second-line treatment, in preference to the more toxic pentamidine, for patients who are intolerant of co-trimoxazole or in whom this drug has failed [220].

#### *Atovaquone*

Atovaquone is a member of a group of antiprotozoal agents (hydroxynaphthoquinones) and has been found to be effective in the treatment of PCP. It probably has its effect by inhibiting nucleic acid and ATP synthesis. It is administered orally and has a low bioavailability, its absorption being increased significantly if it is taken with food, especially if this is fatty. It is predominantly excreted unchanged in the faeces. The dose is 750 mg taken as three

250-mg tablets once daily with food. An oral suspension may provide better bioavailability. The principal side-effect that limits its use is diarrhoea, since absorption may be further impaired with subsequent treatment failure. Nausea and rashes may also occur. Atovaquone has been used as an effective secondary substitute for co-trimoxazole and combinations such as dapsone/trimethoprim and clindamycin/primaquine in the treatment of mild to moderate cases of PCP ( $PO_2 > 8$  kPa, 60 mmHg) when these agents cannot be tolerated [220].

#### **Dapsone/trimethoprim**

Dapsone is an orally administered antileprotic drug also used in malaria prophylaxis. It belongs to the sulphone group and may also be effective in the treatment of PCP when used in combination with other drugs. It has its effect by inhibiting folate metabolism. It is well absorbed from the gut and is mainly metabolized by the liver. Haematological side-effects include haemolytic anaemia, leucopenia and methaemoglobinemia. Drug rashes are common. Hepatic reactions and fever may also occur. Eosinophilic pneumonia has occurred. Dapsone has been found to have a high failure rate when used singly to treat PCP of mild to moderate severity ( $PO_2 > 8$  kPa, 60 mmHg) and this has led to its use in an orally administered regimen with trimethoprim (dapsone 100 mg daily as one dose, trimethoprim 20 mg/kg daily in two to four divided doses). There are some data suggesting that this combination appears to be of approximately equal efficacy to orally administered co-trimoxazole and clindamycin/primaquine but with fewer adverse effects [129,220].

#### **Clindamycin/primaquine**

The lincosamide antibiotic clindamycin has been described above and is best known in respiratory practice for its activity against anaerobes. Another respiratory use of clindamycin is for the treatment of mild to moderate PCP in conjunction with the antimalarial primaquine, the main side-effect of which is haemolysis in patients with glucose 6-phosphate dehydrogenase deficiency, which should be excluded before its use in those with coloured skins. One such regimen comprised clindamycin 600 mg three times daily orally and primaquine 30 mg base as a single daily dose [235].

### **Antibiotics used in tuberculosis and opportunistic mycobacterial disease**

The preferred antituberculous drugs are rifampicin, isoniazid, pyrazinamide and ethambutol. Less commonly used drugs include rifabutin, streptomycin, newer macrolides such as clarithromycin and azithromycin, quinolones such

as ciprofloxacin and ofloxacin, cycloserine, prothionamide (not marketed in the UK), capreomycin, kanamycin and amikacin.

The management of tuberculous and non-tuberculous (opportunistic) mycobacterial disease is described in Chapters 19 and 20 and is not discussed in detail here. The respiratory applications of the aminoglycosides (see above) are almost entirely non-tuberculous, although streptomycin and amikacin have a secondary role in tuberculous and opportunistic mycobacterial disease. Rifabutin, a newer rifamycin, is now licensed for use as prophylaxis against *Mycobacterium avium-intracellulare* complex infections in patients with a low CD4 count, as well as for the treatment of non-tuberculous mycobacterial disease and tuberculosis. A role is emerging for the newer macrolides (see above) in the management of non-tuberculous mycobacterial disease, particularly *M. avium-intracellulare* complex. A description of rifampicin with reference to its non-tuberculous applications in respiratory medicine follows.

#### **Rifampicin**

Rifampicin (USA, rifampin) is a semisynthetic derivative of one of the rifamycin antibiotics produced by a *Streptomyces*, being the most active of those so far investigated, although rifabutin (see below) shows better activity against the *M. avium-intracellulare* complex group of organisms. It is bactericidal by virtue of its inhibition of DNA-dependent RNA polymerase.

#### *Spectrum of activity against respiratory pathogens*

In addition to its antimycobacterial properties (see Chapters 19 & 20), rifampicin is active when used to treat a wide range of other bacteria including both coagulase-positive and coagulase-negative staphylococci, against which it is very effective. It also has the greatest *in vitro* potency of any known antibiotic against *Legionella pneumophila*; *Legionella micdadei* is also sensitive. It is effective against *H. influenzae* and also active against streptococci, but less so than penicillins and its activity against most Gram-negative aerobic bacilli tends to be lower than that of the aminoglycosides. It is active against the opportunist pathogen *Rhodococcus* (formerly *Corynebacterium*) *equi*, a variably acid-fast Gram-positive bacillus that may cause lung abscesses and progressively cavitating pneumonia in immunosuppressed patients, especially those with AIDS.

As is the case with mycobacteria, many large bacterial populations may contain mutant organisms that are resistant to rifampicin. It is therefore a general rule that rifampicin should never be given alone (except for short-term meningococcal prophylaxis among contacts) and



that it should be supported by another antibiotic to which the organisms in question are likely to be sensitive.

#### *Administration, distribution and excretion*

Rifampicin is very well absorbed from an empty stomach after oral administration and reaches effective concentrations in the lungs and other tissues, as well as in abscess cavities and pleural exudates. Hepatic metabolism occurs and both unchanged rifampicin and its metabolites are secreted in bile. Unmetabolized rifampicin is reabsorbed from the gut and the process repeated; the metabolites are excreted in the faeces. This excretion accounts for about two-thirds of a dose, the remainder being excreted in the urine where it can be usefully detected by qualitative assay or visually, by virtue of its orange-reddish colour, in order to check patient compliance. The plasma half-life is about 5 h [236], although a therapeutic level may be maintained for 12 h or more, partly due to the enterohepatic circulation referred to above. No dosage modification is necessary in renal failure because of clearance through the liver but it should be avoided or used with extra care in the presence of hepatic insufficiency. Rifampicin may also be given intravenously as a brilliant orange-coloured infusion, although this route probably offers no advantage, other than brightening up the ward, unless the patient is unable to take oral medication.

#### *Dosage*

The usual adult dosage of rifampicin in tuberculosis is 600 mg daily for patients who weigh 50 kg or more and 450 mg daily for those below this weight. These doses are well tolerated but whether they are ideal for other forms of infection is not known. The same single dose may be given by infusion over 2 h in a tuberculous patient who cannot swallow. If rifampicin is used parenterally with a macrolide to treat serious *Legionella* infection, it is conventional to administer the drug at a total dose of 600–1200 mg daily, split 12-hourly.

#### *Adverse effects and interactions*

These have been discussed in Chapter 19. The effect of rifampicin as an inducer of liver and intestinal microsomal enzymes is particularly important when it is used in asthmatic patients who require systemic corticosteroid therapy. These patients are likely to experience a significant deterioration in their asthma when rifampicin is started unless the dose of corticosteroid is increased [237]. Similar deterioration in the condition of patients with other disease controlled by corticosteroids may well occur. Similar reductions in the serum concentrations of many other drugs may occur if they are used concurrently, including diltiazem and other antidysrhythmic

agents, fluconazole and other antifungal antibiotics, phenytoin, warfarin, cyclosporin, azathioprine, theophylline, thyroxine, chlorpropamide and other sulphonylureas, atovaquone and oral contraceptives. It behoves the prescriber of rifampicin to check for potential interactions against any other drug that the patient might happen to be taking. The capacity of rifampicin to induce liver enzymes may produce adrenal crisis within 2 weeks of the onset of treatment by increasing the oxidation of endogenous cortisol in patients with pre-existing adrenal insufficiency, such as may occasionally occur in patients with tuberculosis [238]. As with isoniazid and pyrazinamide, hepatic reactions, which have rarely been fatal, may occur with rifampicin; thus it is recommended that liver function tests should be checked before commencement of therapy and if abnormal should be repeated during treatment, if the patient develops symptoms or signs of hepatitis or if they become generally unwell during the course, so that they may be withdrawn promptly if clinically significant hepatic abnormalities occur [239].

#### *Principal uses in respiratory medicine*

The place of rifampicin in respiratory diseases other than tuberculosis is not clear-cut. It is not a first-line drug in the management of serious staphylococcal infection, but reports of its successful use in combination with vancomycin to increase serum bactericidal activity in patients with MRSA endocarditis [240] suggest that its role in the management of MRSA infections may merit further investigation. If serious MRSA infection does not respond to vancomycin or teicoplanin alone, then the addition of an aminoglycoside such as gentamicin and rifampicin may be justifiable [240]. Caution should be exercised before assuming that such combinations will be beneficial, as some studies have indicated that antagonism between rifampicin and other antibiotics may occasionally occur [241,242]. When any such combination is used in clinical practice, its efficacy should ideally be tested in the laboratory by the measurement of serum bactericidal activity.

Rifampicin has also been proposed as a second antibiotic for use in combination with a macrolide in the treatment of severe cases of Legionnaires' disease [243] (see Chapter 13).

#### *Rifabutin*

Rifabutin is another bactericidal rifamycin that has become available more recently than rifampicin. It is administered orally and has broadly similar pharmacokinetics. It has no advantages over rifampicin in the treatment of tuberculosis, although rifampicin-resistant strains may sometimes be susceptible to rifabutin [244]. However, it does show greater activity than rifampicin against

organisms of the *M. avium-intracellulare* complex and is usually used at a dose of 300–600 mg daily as a single dose in combination with other drugs such as clarithromycin (see p. 205) and ethambutol. Higher doses of rifabutin have a propensity to produce uveitis and particular care has to be taken in this regard when it is used together with clarithromycin, fluconazole or ritonavir (and other HIV protease inhibitors). It may be used singly at a dose of 300 mg daily as prophylaxis against disseminated *M. avium-intracellulare* complex infection in patients with AIDS, when the CD4 T-lymphocyte count falls to  $<0.1 \times 10^6/L$ , and has been shown to significantly reduce the frequency of this important complication that contributes significantly to the morbidity and mortality of this group of patients [245].

### Sodium fusidate (fusidic acid)

Sodium fusidate is a salt of fusidic acid that was isolated from a strain of the fungus *Fusidium coccineum*. It is an antibiotic of relatively low toxicity and with a narrow band of activity, being most effective against *Staph. aureus* and *Staph. epidermidis*, including some strains resistant to penicillin derivatives such as methicillin. It is relatively ineffective against other common respiratory pathogens and staphylococcal infection is virtually the only indication for its use.

Its mode of action involves the inhibition of bacterial protein synthesis, with either bacteriostatic or bactericidal effects. Fusidic acid-resistant strains of *Staph. aureus* have been noted to emerge readily *in vitro* and the development of clinical resistance during treatment has also been reported [246]. This has led to a tendency for fusidate to be used with another agent such as an antistaphylococcal penicillin and, despite laboratory reports of antagonism with such combinations, this may produce satisfactory clinical results [247].

Fusidate is very well absorbed orally and there seems to be little point in using the parenteral route if the more natural route is available [248]. A topical ocular preparation has been proposed as a less toxic alternative to chloramphenicol [249]. The drug is well distributed and its metabolic products are secreted in bile, urinary secretion being minimal, so that dosage modification in renal failure is unnecessary [250]. When oral administration proves impossible, the drug may be given intravenously as diethanolamine fusidate. The dose of sodium fusidate is 500 mg 8-hourly, with up to 3 g daily in severe infection. The usual intravenous dose is 500 mg given by slow infusion three times daily.

Adverse effects include mild gastrointestinal tract disturbance, rashes and venospasm followed by thrombophlebitis, especially if infusion has been too rapid. Reversible abnormalities of liver function may occur, particularly with the parenteral route, as may clinical

jaundice which necessitates discontinuance of the drug [251].

Clinical confidence in the use of fusidate as a single antistaphylococcal agent is somewhat thin. However, it is frequently used in a supporting role, despite some laboratory reservations about a possible antagonistic effect against penicillins. It is not commercially available for use in the USA.

### Fluoroquinolones

Ciprofloxacin was the first of the fluoroquinolone antimicrobials to become available in the UK [252]. These drugs are related to, but considerably more potent than, the early antiseptic quinolone group of which nalidixic acid is a familiar member, this increased potency having been achieved by various modifications to the basic dual ring structure, including the addition of fluorine and piperazinyl substituents. Ofloxacin and its optical isomer levofloxacin are also available in the UK, as is grepafloxacin. Fluoroquinolones currently under development or not available in the UK include lomefloxacin (available in the USA), sparfloxacin (available in the USA), cinafloxacin and others. This group of drugs is bactericidal and has a broad spectrum, with excellent activity against Gram-negative bacteria, including *H. influenzae*, *Moraxella catarrhalis*, Enterobacteriaceae and *Pseudomonas* spp. They are effective against *Staph. aureus* but on the whole have more modest activity against streptococci, although this is likely to be improved with some of the more recent compounds such as levofloxacin, cinafloxacin and grepafloxacin. Their activity against anaerobes, including *Bacteroides fragilis*, is minimal. Temafloxacin was withdrawn worldwide by the manufacturer in 1992 soon after its launch because of a much higher rate of serious adverse reactions (hypoglycaemia, haemolytic anaemia, renal failure, coagulation defects, anaphylaxis and death) than had been seen with previous quinolones. One result of this is that all new drugs belonging to this class are subject to intense scrutiny and a long gestational period before their release.

### Ciprofloxacin

#### Mode of action

The mode of action of ciprofloxacin and other quinolones is primarily by inhibition of a bacterial enzyme, DNA gyrase, which is essential in the process of bacterial DNA replication and other cellular processes [253].

#### Spectrum of activity against respiratory pathogens

Ciprofloxacin has an unusually broad spectrum of activity, being effective *in vitro* against those Gram-negative

organisms associated with hospital-acquired pneumonia, including the Gram-negative enteric bacilli such as *Enterobacter* spp., *E. coli* and *Serratia*, *Klebsiella* and *Proteus* spp., as well as more highly resistant organisms such as *Ps. aeruginosa* and *Acinetobacter* spp. It is also highly effective against *H. influenzae* and *Moraxella catarrhalis* [254]. It is active against methicillin-sensitive *Staph. aureus* but less so against *Strep. pneumoniae*, the commonest causal organism in community-acquired pneumonia. Most strains of MRSA are resistant. It has no useful activity against anaerobes. 'Atypical' causes of pneumonia, such as *Mycoplasma pneumoniae*, *Legionella* spp. and *Chlamydia* spp., may be susceptible to ciprofloxacin and other 4-quinolones but data concerning clinical effectiveness in this area are unsurprisingly thin, with an absence of comparative trials with first-line drugs [255–257]. Ciprofloxacin may be active *in vitro* against *Mycobacterium tuberculosis* as well as some opportunistic mycobacteria including *M. kansasii* but its activity against the *M. avium-intracellulare* complex is poor.

As with all antimicrobial agents, the emergence of resistant organisms is likely to become an increasing problem [258,259]. It is not uncommon to isolate resistant strains of *Ps. aeruginosa* in patients whose lower respiratory tracts are colonized by these organisms when they have received repeated courses of treatment with ciprofloxacin for infective exacerbations. Resistance among Enterobacteriaceae has also been reported when this drug has been used prophylactically in neutropenic patients [253].

#### *Administration, distribution and excretion*

The absorption of ciprofloxacin after oral administration, although incomplete, is adequate to permit this route to be used effectively, peak serum levels being reached at 90 min with a half-life of about 4 h. Its absorption from the gut is much reduced by the simultaneous administration of cationic compounds, including aluminium- or magnesium-containing antacids, calcium and iron salts and enteral tube feeds [253]. The drug penetrates the lung well. Ciprofloxacin is excreted in the urine both unchanged and, to a small extent, as its metabolites. Dosage reduction in significant renal insufficiency (ECC <30 mL/min) may be achieved by once-daily administration. Ciprofloxacin may also be given by intravenous infusion.

#### *Dosage*

The usual oral dosage is 500–750 mg twice daily. It is probable that the higher dose should be used in treating pseudomonal infection by this route. The intravenous dose is 200–400 mg twice daily, infused over 30–60 min to minimize venous irritation.

#### *Adverse effects and interactions*

The most common side-effects are minor gastrointestinal tract upsets, serious adverse reactions being rare [260], although this statement is subject to review as experience with the drug increases. Antibiotic-related *Clostridium difficile* colitis is rare, possibly because of the drug's minimal disturbance of bowel anaerobes [261]. Central nervous system (CNS) effects may occur and include headache, dizziness, restlessness, sleep disturbance and tremors. The quinolone group of antibiotics have an epileptogenic potential, so that they should be used with caution in patients with a history of seizures, particularly if used in combination with theophylline. This potential may be enhanced by an interaction with non-steroidal anti-inflammatory drugs [262]. Hepatic reactions, Achilles tendonitis/rupture and photosensitivity are rare [261]. Ciprofloxacin inhibits cytochrome P450 and therefore the metabolism of theophylline, the plasma level of which may be substantially increased so that levels should be monitored; in this situation it is recommended that the usual dose of theophylline is halved [263]. Warfarin may be potentiated. Rashes in general are uncommon and vasculitis rare [264]. Its use in growing children is discouraged by the potential risk of damage to articular cartilage that has been observed in experimental animals following quinolone therapy [260], although its use may be justified in appropriate circumstances such as in exacerbations of *Ps. aeruginosa* infection in adolescent children with cystic fibrosis [261]. Arthralgia occasionally occurs in this situation [253]. Haemolytic anaemia, renal impairment, hypoglycaemia and anaphylaxis are all rare side-effects of quinolones but have been reported [265].

#### *Principal uses in respiratory medicine*

Ciprofloxacin and other quinolones currently under laboratory or clinical evaluation have a useful place in the management of difficult respiratory infections, particularly in hospital-acquired pneumonia where infection with Gram-negative enteric bacilli is likely. The empirical use of ciprofloxacin as a first-line agent for the treatment of community-acquired respiratory infections, both in hospital and in the community, remains inadvisable in view of the ready availability of safe narrower-spectrum alternatives that are more effective against *Strep. pneumoniae*. It is notable that pneumococcal bacteraemia has occurred in some patients during treatment with ciprofloxacin [266]. Ciprofloxacin may be an entirely appropriate second-line choice in patients with COPD whose infective exacerbations have failed to respond to a penicillin, in which case the problem may be resistant *H. influenzae* or *Moraxella catarrhalis*, both of which are susceptible to ciprofloxacin. Although the availability of oral antipseudomonal agents has obvious attractions, the clinical response to medica-

tion via this route in patients whose lower respiratory tracts are permanently colonized by large numbers of these organisms and who experience exacerbations may be disappointing. In this situation the higher oral dose of 750 mg twice daily should be used, which is generally considered to produce equivalent blood levels to 200 mg twice daily by the intravenous route. Ciprofloxacin is commonly used as an effective parenteral agent, usually in combination with an aminoglycoside, for treating infective exacerbations in patients with cystic fibrosis and in whom *Ps. aeruginosa* is known to be a major colonist; however, there are less costly alternatives and the prescriber should be guided by the sensitivities and clinical response.

### Other fluoroquinolones

Ofloxacin has a broadly similar antimicrobial spectrum to ciprofloxacin. Although its *in vitro* activity against *Ps. aeruginosa* is lower than that of ciprofloxacin, it is probably as effective in clinical practice for the indications described in the preceding section [267–269]. This may be a consequence of its superior kinetics as it has an oral bioavailability of about 90% compared with approximately 70% for ciprofloxacin. It is administered orally at a dose of 400 mg once or twice daily according to the severity of the infection. The intravenous dose is 200–400 mg twice daily. The adverse effects profile is similar to ciprofloxacin but there is no potentiation of theophylline with this drug [257].

Lomefloxacin (not available in the UK) is ineffective against the pneumococcus and less effective against *Pseudomonas* spp. but has been used as a second-line antibiotic in infective exacerbations of chronic bronchitis. Sparfloxacin (not available in the UK) has improved activity against aerobic Gram-positive cocci including the pneumococcus while retaining Gram-negative activity, with antipseudomonal activity intermediate between that of ciprofloxacin and ofloxacin [270]. As with ofloxacin, it does not appear to interfere with the metabolism of theophylline. It has a long plasma half-life, permitting once-daily dosing. It has been used for the oral treatment of lower respiratory tract infection, with a loading dose of 400 mg followed by a once-daily dose of 200 mg. Although only a small proportion of this drug is excreted in the urine, dose adjustment is required in severe renal failure (creatinine clearance <30 mL/min). Drug regulatory authorities in some countries where lomefloxacin and sparfloxacin have become available have found it necessary to issue guidance notes or restrictions on their usage because of an increased frequency of photosensitivity reactions with these two class members.

Grepafloxacin is one of a number of newer fluoroquinolones (including clinafloxacin and trovafloxacin) currently undergoing clinical assessment [271]. It is rapidly absorbed and is the most hydrophobic of the

fluoroquinolones, with good tissue penetration. It is mainly metabolized, only a small proportion being excreted unchanged in the urine. Its elimination half-life is about 12 h, allowing once-daily administration; 300–600 mg daily has been used in clinical trials. It has improved *in vitro* activity against *Strep. pneumoniae*, while retaining good activity against *H. influenzae* and *Moraxella catarrhalis* but with reduced antipseudomonal efficacy. It has recently been *withdrawn* from use because of rare reports of *torsades de pointes*.

Levofloxacin (available in the UK as oral and parenteral formulations) is an optical isomer of ofloxacin with excellent oral bioavailability and better Gram-positive cover than ciprofloxacin (including *in vitro* activity against MRSA) at the expense of significantly inferior Gram-negative cover.

Clinafloxacin (not available in the UK) is well absorbed and 50% is excreted unchanged in the urine. It has powerful *in vitro* activity against a wide range of respiratory pathogens. It is more effective than ciprofloxacin against *Strep. pneumoniae* and also seemingly has useful activity against methicillin-sensitive *Staph. aureus* and MRSA. It has a high degree of activity against Gram-negative organisms, including *Ps. aeruginosa*, and unlike ciprofloxacin is effective against most anaerobes.

The critical physician will be only too aware of pharmaceutical false dawns, and clinical roles for the newer orally administered quinolones have yet to be established and defined. They are unlikely to constitute optimal therapy in severe cases of pneumococcal pneumonia.

### Chloramphenicol

Chloramphenicol was the first broad-spectrum antibiotic to be discovered. It is now produced synthetically having been originally obtained from a soil *Streptomyces*. It is a predominantly bacteriostatic but nevertheless potent antimicrobial, being particularly effective against *H. influenzae* and *Salmonella typhi*. However, its original wide-ranging use has been severely curtailed in developed countries because of its potential to cause bone marrow toxicity.

The mode of action of chloramphenicol involves the inhibition of bacterial protein synthesis. Although active against a wide range of respiratory pathogens, including most Gram-positive and Gram-negative aerobic and anaerobic bacteria, antibiotics that are equally effective in the clinical setting but less potentially toxic are now available for use against most of these. Bacterial resistance to chloramphenicol may occur and can include organisms such as *H. influenzae* and *S. typhi*, although this is rare in Western practice. The unrestricted sale of chloramphenicol in developing countries has probably been a factor in promoting resistance in these organisms [272].

Chloramphenicol is available in oral form, including a

more palatable but less rapidly absorbed ester for children, and as a solution for intravenous administration. The drug diffuses well and achieves therapeutic concentrations in the brain. It is metabolized by the liver and the bulk of renal excretion is as inactive metabolites so that dose reduction in renal insufficiency is unlikely to be needed, although it may be necessary in hepatic disease [273]. It is possible to assay chloramphenicol in the blood, in which case the level of the drug should be maintained between 10 and 25 µg/mL. The usual oral dose is 500 mg 6-hourly, while the intravenous dose is 50 mg/kg daily in divided doses every 6 h.

Adverse effects include a common dose-related reversible form of marrow suppression, in which anaemia, leucopenia and thrombocytopenia may occur due to inhibition of protein synthesis [274,275]. A much rarer and usually fatal form of marrow suppression may occur. This is not dose-related, occurring idiosyncratically, sometimes even with topical application, and usually producing aplastic anaemia [249]. Epidemiological evidence from the USA suggests that this complication occurs once every 24 500–40 800 systemic prescriptions [276]. This is approximately 13 times the expected occurrence of aplastic anaemia in the general population as a whole. It is usual for this complication to occur not during but some weeks or even months after completion of the course of treatment.

Systemic chloramphenicol should not be prescribed for trivial infections and is now seldom used for respiratory disease in developed countries. It has been used as an alternative to tetracycline for treating spotted fevers due to rickettsial infection in pregnancy and in young children. It is much more widely used in countries where the choice of antibiotics is limited as a result of cost. In such circumstances, it may be used for serious infections caused by *H. influenzae*, *Salmonella*, *Ps. pseudomallei* and in both pneumococcal and meningococcal infection when the patient is allergic to penicillin. The physician who uses chloramphenicol must be able to justify the choice on good grounds in view of the small but real possibility of severe marrow aplasia.

## Antimicrobial agents for use in fungal infections

The applications of these drugs in respiratory disease are discussed in Chapter 21. As the prevalence of immunosuppression in patients has increased so has the incidence of opportunistic fungal infection, particularly in those undergoing intensive cytotoxic chemotherapy, bone marrow and solid organ transplantation and in the AIDS population. The use of systemic antifungal antibiotics has increased in parallel. Antifungal agents are also used in the treatment of endemic mycoses, including blastomycosis, coccidioidomycosis and histoplasmosis. These agents

include amphotericin (intravenous); the azole antifungals ketoconazole (an oral imidazole, miconazole being an older and more toxic parenteral member of this group), fluconazole (an oral or intravenous triazole) and itraconazole (a newer oral triazole); and the older fluorinated pyrimidine analogue flucytosine (intravenous in the UK, oral in the USA). Reliable therapeutic data comparing the use of amphotericin with the newer azoles in serious infections are unfortunately sparse but it has become clear that some of the chronic indolent endemic mycoses, such as histoplasmosis, blastomycosis and coccidioidomycosis, may respond well to ketoconazole or itraconazole; that itraconazole is effective for treating aspergillosis and sporotrichosis; and that fluconazole is an effective treatment for candidaemia and for meningeal involvement in cryptococcosis and coccidioidomycosis.

The reader will realize that although *Pneumocystis carinii* may be regarded as a fungus in terms of taxonomy, in terms of therapeutics it is not, so that in practice the main causes of fungal pneumonia in compromised hosts are *Aspergillus* spp. and *Cryptococcus neoformans*.

### Amphotericin

Amphotericin (amphotericin B, Fig. 9.7) remains the drug of choice for most serious systemic mycotic infections. Like nystatin it is a polyene antifungal antibiotic, being the only member of this group that can be given parenterally. It is produced by the soil streptomycete *Streptomyces nodosus* and apparently has its effects by binding to sterols in the fungal cell membrane, increasing the permeability of this biological barrier and causing the normal cell contents to leak out.

#### Spectrum of activity against respiratory pathogens

Amphotericin is active against most fungi, including opportunists such as *Aspergillus* spp., *Cryptococcus neoformans*, *Candida* spp., *Sporothrix schenckii* and the causes of endemic mycoses, found mainly but not exclusively in North American central river valleys and Latin America, such as *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomycetes dermatitidis* and *Paracoccidioides brasiliensis*.

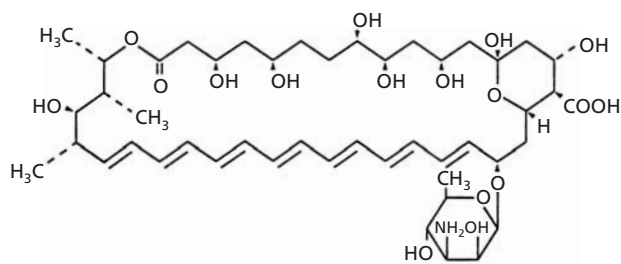


Fig. 9.7 Structure of amphotericin B.

#### *Administration, distribution and excretion*

Amphotericin is insoluble in water, having detergent-like properties with hydrophobic and hydrophilic regions; thus the standard formulation is presented as a deoxycholate complex that provides a colloidal suspension for intravenous administration. The drug is widely distributed and highly protein-bound, particularly to lipoproteins, and is poorly dialysable. It is seemingly concentrated extravascularly in poorly defined sites that may include the liver, spleen, kidneys and lungs, undergoing degradation *in situ*, with less than 10% being excreted in biologically active form in the urine. Blood levels are not significantly affected by hepatic or renal failure. The plasma half-life of the drug is over 24 h but plasma levels do not necessarily relate to therapeutic efficacy and the total elimination half-life is over 2 weeks so that small quantities of the drug may be detected in the urine for over a month after completion of a course of treatment [277].

A number of lipid formulations of amphotericin have been produced in an attempt to decrease renal toxicity without reducing efficacy. These formulations seemingly transfer the amphotericin from the liposome or lipid complex to the fungal cell wall more efficiently with less attachment to host cell membranes. The compounds include an encapsulated phospholipid vesicle or liposome compound (AmBisome), a sodium cholesteryl complex (Amphocil) and a further amphotericin–lipid complex (Abelcet). All these formulations are less nephrotoxic but probably have no advantage in terms of efficacy and are extremely costly. They may be used in circumstances when renal toxicity precludes conventional amphotericin therapy.

#### *Dosage*

After a test dose (see below), an initial dose of 0.25 mg/kg daily infused in 5% dextrose (10 mg/dL), *not* saline, over 2–4 h is recommended, increasing by 10–15 mg daily to the usual dose range of 0.5–1.0 mg/kg according to individual patient tolerance and response. Higher doses of 1.0–1.5 mg/kg daily may be used in severely ill, often neutropenic patients with invasive aspergillosis until improvement is seen. Prolonged courses of treatment are sometimes necessary in order to prevent relapse, according to clinical circumstances. In such cases, and as the drug has a long half-life, a dosage schedule of say 0.5 mg/kg daily is sometimes switched to 1.0 mg/kg on alternate days for convenience [278].

#### *Adverse effects*

Nausea, anorexia, vomiting, headache and febrile reactions may occur in most patients, particularly at the onset of treatment, but respond to symptomatic measures and

may be reduced by using a 4-hourly infusion rate. Anaphylactic reactions are rare but it is nevertheless recommended that a test dose is given before the first full infusion of any new course, 1 mg in 10 mL 5% dextrose being infused over 20 min and the patient observed for a further 30 min [278]. The most important dose-limiting adverse effects are renal, amphotericin both reducing glomerular filtration rate and causing renal arteriolar vasoconstriction that may lead to renal failure, particularly if used in combination with other potentially nephrotoxic drugs or in the presence of volume depletion or hypotension. Some degree of azotaemia is to be expected (80% of patients); however, if the serum creatine exceeds three times the upper limit of normal in severe or life-threatening fungal disease it is advisable to discontinue amphotericin for 1 day, thereafter resuming at half the previous dosage, followed by a gradual increase to the previous dose over 2–3 days if renal function permits [278]. Adequate hydration should be ensured until renal function improves. Electrolytic abnormalities such as hypokalaemia and hypomagnesaemia may occur. Mild normochromic normocytic anaemia may also occur, usually as a result of marrow suppression. Thrombophlebitis at a peripheral infusion site may cause problems and may be minimized by avoiding slower infusion rates and concentrations of greater than 0.1 g/L or by using a central line. Neurotoxic side-effects include peripheral neuropathy as well as rare central effects such as fitting. Cardiotoxicity with dysrhythmias is also described [277].

#### *Principal uses in respiratory medicine*

Because of its toxicity, parenteral amphotericin is only used when progressive, potentially fatal fungal infection (other than *Pneumocystis carinii*) has been confirmed or is strongly suspected. It has been described in North American practice as ‘the drug that we all love to hate but use when the going gets tough’ and it remains the antifungal agent of choice in the extremely ill patient. Such ‘tough’ situations usually arise in patients who are immunocompromised as a result of either cytotoxic or immunosuppressive therapy, particularly those undergoing chemotherapy for neoplastic disease, those who have had organ transplants and those with HIV infection. Major risk factors are therefore neutropenia, systemic corticosteroid use and AIDS, fungal pneumonia being suspected in any immunocompromised host with lung infiltrates who is not responding to conventional antibiotics. Such fungal infections include those caused by *Aspergillus* spp., *Cryptococcus neoformans* and *Candida* spp.

Amphotericin remains the drug of choice in the following situations:

1 immunocompromised and/or neutropenic patients with invasive aspergillosis;

2 immunocompromised and/or neutropenic patients with blastomycosis, also being used in the immunocompetent patient with life-threatening illness;

3 in life-threatening progressive disseminated histoplasmosis (at least for induction), usually in immunocompromised patients especially those with AIDS;

4 for induction in severe paracoccidioidomycosis, usually in immunocompromised patients especially those with AIDS;

5 for initial treatment of life-threatening cases of sporotrichosis [279].

It is used in severe chronic pulmonary coccidioidomycosis, although itraconazole or ketoconazole may be preferred [279,280]. It may be used with flucytosine support in severe pulmonary cryptococcosis and this combination is also the treatment of choice in cryptococcal meningitis [280]. When cryptococcal meningitis occurs in AIDS, fluconazole is an effective primary therapy and is used anyway as 'long-term' maintenance once remission has been achieved [279]. Amphotericin is the treatment of choice for serious disseminated candidal infection, any vascular cannulae that may have been colonized also being removed. Flucytosine is sometimes added initially for synergism, depending on the severity of the situation [280]. Fluconazole is a less toxic alternative that may be used in patients without neutropenia [281]. When fungi are recovered from bronchoscopic lavage fluid it should not be inferred that they are necessarily the cause of pneumonia and the finding of *Candida* spp. in lavage fluid is of little value as they are common colonists. *Candida* pneumonia does not occur in isolation but rather as part of a disseminated invasive candidiasis associated with candidaemia. Critically ill patients who have been treated with broad-spectrum antibiotics and whose immunity may have been impaired by a number of factors including corticosteroid use are at risk of disseminated candidal infection [282]. The decision to treat fungal pneumonia is based on clinical features, e.g. cavitating infiltrates and haemoptysis (see Chapter 21), unless tissue invasion has been demonstrated in lung tissue obtained transbronchially or by other means.

### Itraconazole

Itraconazole (Fig. 9.8), like fluconazole, is a triazole with a better safety profile than the earlier imidazoles such as ketoconazole. As with all azoles, it has its effect by blocking an enzyme concerned with the synthesis of ergosterol, the main fungal cell wall sterol, which damages this membrane with resultant impaired cell growth and replication [280].

#### Spectrum of activity against respiratory pathogens

Itraconazole is active *in vitro* against most fungal

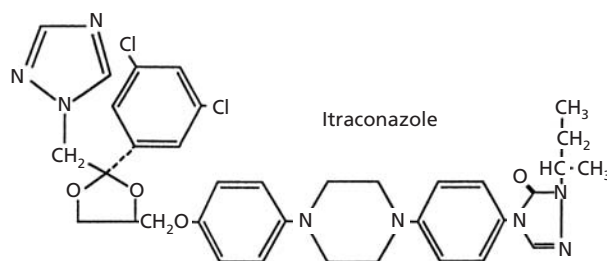


Fig. 9.8 Structure of itraconazole.

pathogens. It is the only azole with good activity against *Aspergillus* spp., comparing favourably in this regard with amphotericin. Other susceptible fungi include *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Cryptococcus neoformans* and *Candida* spp. although *Candida* other than *C. albicans* and other yeasts may be less susceptible.

#### Administration, distribution and excretion

Itraconazole, like ketoconazole and amphotericin but unlike fluconazole, is highly insoluble in water and is available only in oral form. Absorption is very significantly improved if it is taken immediately after food, and is also improved by the presence of acid and therefore diminished by  $H_2$  antagonists and the like. As with ketoconazole but unlike fluconazole, itraconazole is highly bound to plasma proteins (99%), particularly to lipoproteins, and is poorly dialysable. Plasma concentrations of itraconazole are therefore low but tissue concentrations are higher. Like ketoconazole but unlike fluconazole, cerebrospinal fluid (CSF) concentrations are negligible, even in the presence of meningitis. Itraconazole is metabolized in the liver, the metabolites being excreted in the faeces and negligible amounts are found in the urine. No dosage adjustment is therefore needed in renal insufficiency but the drug may accumulate in the presence of significant hepatic dysfunction. The half-life of itraconazole is about 24 h, so that once-daily dosing is possible in appropriate circumstances [279,283].

#### Dosage

The total daily dose and duration of treatment vary according to severity and nature of the infection and the response to the drug. Invasive or disseminated fungal infections may be treated with 200 mg twice daily, although in patients with serious infections many prefer to use 200 mg three times daily for the first 3 days in order to achieve serum concentrations high enough to exert a pharmacological effect more quickly. Thereafter doses of 100–400 mg daily may be used. A long-term maintenance dose of 200 mg daily is usual in AIDS and the same dose



may be used prophylactically in neutropenic patients. Doses greater than 200 mg are conventionally divided.

#### *Adverse effects and interactions*

One of the principal advantages of itraconazole over ketoconazole is its lower rate of toxicity [284]. The commonest adverse effect is nausea and vomiting (<10% of patients) but this does not often necessitate discontinuance of the drug. Tolerance may be improved in such cases by division of the dose. A mineralocorticoid effect with hypokalaemia and oedema may occur at higher doses. Abnormalities of liver function (aminotransferase elevation) have been observed in less than 5% of patients receiving long-term itraconazole but these appear to be reversible on discontinuance and serious hepatotoxicity is rare [284]. Allergic rashes and pruritis sometimes occur.

The effect of drugs that reduce gastric acid has already been mentioned in the context of absorption. Drugs that induce hepatic cytochrome P450-dependent enzymes may increase the metabolism of itraconazole and therefore reduce its bioavailability, with increased levels of the interacting drug. These include rifampicin, phenytoin, carbamazepine and phenobarbital (phenobarbitone). Drugs that are themselves metabolized by the cytochrome P450 enzyme system are potentiated by azoles including itraconazole. These include the antihistamines terfenadine and astemizole and the gut motility stimulant cisapride, with the potential for serious cardiac dysrhythmias including torsades de pointes. Cyclosporin levels may be increased with subsequent renal damage so that the dose of cyclosporin should be reduced by half and levels monitored more closely if the two have to be used together [285]. The effect of warfarin, simvastatin and digoxin may be potentiated.

#### *Principal uses in respiratory medicine*

Itraconazole may be used as an effective alternative to the more toxic amphotericin in the treatment and control of chronic necrotizing aspergillosis [286]. Itraconazole has also been used successfully to treat invasive aspergillosis [287], although amphotericin is generally used in the iller patient. Itraconazole has been proposed as an adjunctive therapy for patients with allergic bronchopulmonary aspergillosis who are corticosteroid dependent [288].

Encouraging results have been obtained with itraconazole at doses of 200 mg daily for approximately 6 months in the treatment of less severe cases of blastomycosis without meningeal involvement [280,289]. Once again, amphotericin remains the treatment of choice in patients whose infection is life-threatening, although once control has been achieved, continued treatment with oral itraconazole may be appropriate [290].

Acute pulmonary coccidioidomycosis occurring end-

emically in an immunocompetent host is usually self-limiting and requires no treatment. Those who develop the more chronic form of pulmonary disease that resembles tuberculosis and those who are immunosuppressed need treatment and itraconazole has been used successfully in this context [291]. Good comparative data comparing itraconazole with ketoconazole and amphotericin in the treatment of coccidioidomycosis are lacking but itraconazole is currently the drug of choice [280]. Itraconazole is not regarded as a first-line drug in patients with meningeal infection because of its poor CSF penetration, although it has been used for this purpose [292].

Some small series have also claimed to show that itraconazole can be effective in cryptococcal meningitis [293], fluconazole or amphotericin ordinarily being used in this situation [280]. In patients unable to take fluconazole, it has been used as consolidation therapy once cryptococcal meningitis in AIDS patients has been controlled [294].

Acute primary pulmonary histoplasmosis in an immunocompetent patient usually takes the form of a mild self-limiting illness so that no specific antifungal treatment is required [295]. Itraconazole is often the drug of choice in cases when symptoms are more severe or the disease becomes chronic, mimicking tuberculosis, or in disseminated disease in immunodeficient patients such as those with AIDS, although amphotericin remains preferable for initial treatment in more severe life-threatening disease [279,280,289]. Itraconazole is also the drug of choice in AIDS for maintenance therapy once a remission has been obtained [296,297]. Paracoccidioidomycosis may produce serious pulmonary infection in immunodeficient patients such as those with AIDS; in severe disease treatment with amphotericin is required, whereas in less severe illness itraconazole may be used and may also be effective in maintaining a remission [282]. Itraconazole may be more effective than fluconazole for treating pulmonary sporotrichosis [298], amphotericin as usual being reserved for severe infections. Itraconazole with flucytosine has been used for the treatment of oesophageal candidiasis when the organism has developed fluconazole resistance [299].

#### *Fluconazole*

Fluconazole (Fig. 9.9), like itraconazole, is a triazole with the same cell membrane destabilizing action common to all azoles. It also has a better safety profile than the earlier imidazoles such as ketoconazole.

#### *Spectrum of activity against respiratory pathogens*

Fluconazole has good activity against *Candida albicans*, although a few candidal species may be resistant and resistance may emerge when it is used as long-term prophylaxis [280]. It is also effective against *Cryptococcus*

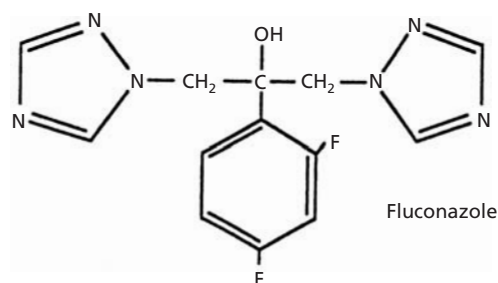


Fig. 9.9 Structure of fluconazole.

*neoformans* and *Coccidioides immitis* but is inactive against *Aspergillus* spp. and cannot be relied upon for infections caused by *Histoplasma capsulatum* and *Blastomyces dermatitidis* [280,290,300,301].

#### Administration, distribution and excretion

Fluconazole, unlike itraconazole, ketoconazole and amphotericin, is a small molecule, with lower lipophilicity and high solubility in water. It is available in both oral and intravenous formulations. In contrast to ketoconazole and itraconazole, absorption does not require the presence of acid and is therefore unaffected by  $H_2$  antagonists, antacids, etc. Fluconazole, unlike itraconazole and ketoconazole, is minimally bound to plasma proteins and is dialysable. It is widely distributed and high CSF concentrations are achieved. The elimination half-life of fluconazole is usually well over 24 h, so that once-daily dosing is possible [279,283]. Unlike itraconazole, fluconazole is largely (80%) excreted unchanged in the urine, so that dosage adjustment is recommended by the manufacturer if the creatinine clearance is 40 mL/min or less.

#### Dosage

The total daily dose and duration of treatment vary according to the type and severity of infection and response. Once-daily dosing is used, except in renal failure in which case the dosing interval may be lengthened. Invasive or disseminated fungal infections may be treated with oral or intravenous fluconazole 400 mg on the first day and 200–400 mg daily thereafter until completion of the course, which in the case of cryptococcal infections may be at least 6 weeks. Prevention of relapse of cryptococcal infection in AIDS may be achieved by lifelong maintenance doses of 100–200 mg daily. According to an assessment of risk, doses of 50–400 mg daily may be used prophylactically in neutropenic patients who have received cytotoxic chemotherapy/radiotherapy for cancer (although survival benefit in this context is questionable). Oropharyngeal and oesophageal candidiasis may be treated with 50–100 mg daily for 7–14 days, or longer in

severely immunocompromised patients [300].

#### Adverse effects and interactions

Fluconazole is well tolerated. The commonest adverse effects are nausea and other gastrointestinal symptoms but these occur in less than 5% of patients [300]. Rashes, including Stevens–Johnson syndrome, may occur but are uncommon. Mild abnormalities of liver function (amino-transferase elevation) have been reported in less than 7% of patients but severe hepatotoxicity is extremely rare.

Of the drugs that induce the hepatic cytochrome P450-dependent enzyme system, rifampicin increases the metabolism of fluconazole and therefore reduces its bioavailability. Drugs that are themselves metabolized by the cytochrome P450-dependent enzyme system may be potentiated by azoles including fluconazole. Because of this, the antihistamines terfenadine and astemizole and the gut motility stimulant cisapride are also best avoided with fluconazole in view of the possibility of serious cardiac dysrhythmias, including torsades de pointes. Cyclosporin levels may be increased in transplant patients and should be monitored particularly if higher doses of fluconazole have to be used. The effects of warfarin, theophylline, rifabutin (risk of uveitis), phenytoin, zidovudine and oral sulphonylurea hypoglycaemic agents may be potentiated [279,300].

#### Principal uses in respiratory medicine

Pulmonary cryptococcosis in immunosuppressed patients is usually treated with amphotericin, with or without flucytosine, although fluconazole has been used as a less toxic alternative, being effective in meningitis [279,302,303]. In AIDS patients, lifelong maintenance fluconazole is necessary once the primary cryptococcal infection has come under control [304]. Amphotericin is also often used for the first 2 weeks for induction therapy when cryptococcal infection involves the meninges, as it commonly does in AIDS, after which treatment is usually maintained with fluconazole, which is the drug of choice in this situation [294].

There are few data on the relative efficacy of the azoles and amphotericin in the treatment of pulmonary coccidioidomycosis but fluconazole is appropriate if the meninges are involved [305].

Fluconazole may be used as a less toxic alternative to amphotericin for treatment in the intensive care unit of the severely ill non-neutropenic patient with disseminated candidiasis but without any major immunodeficiency, in which situation *Candida albicans* is the usual pathogen [306,307]. Amphotericin remains the preferred agent in the management of other patient groups with candidaemia and haematogenously disseminated candidiasis [306]. Fluconazole is a highly effective agent when used to treat

oropharyngeal or oesophageal candidiasis in patients with AIDS and in cancer patients with neutropenia [300]. There appears to be no clear survival benefit when antifungal agents such as fluconazole are used as so-called 'primary prophylaxis' in cancer patients with neutropenia [308] or in patients with advanced HIV infection ( $CD4^+$  lymphocytes  $\leq 0.05 \times 10^9/L$ ), although in the latter group reduced morbidity from candidiasis and cryptococcosis was shown [309]. The use of prophylactic fluconazole may encourage the emergence of resistant potentially pathogenic yeasts such as *Candida krusei* [310].

Fluconazole is not an effective treatment for aspergillosis [280].

### Ketoconazole

Ketoconazole (Fig. 9.10) was the first oral azole that was useful for treating systemic infections. It is an imidazole with a shorter half-life and narrower spectrum than the newer more expensive triazoles such as itraconazole and fluconazole. It also has more adverse effects than the newer drugs fluconazole and itraconazole but is less expensive, which may be important for patients receiving long-term treatment. As with the other azoles, it has its effect by blocking an enzyme concerned with ergosterol synthesis so that the integrity of the fungal cell membrane is impaired.

#### Spectrum of activity against respiratory pathogens

Ketoconazole has activity against *Candida*, although species other than *C. albicans* and other yeasts may be resistant. It also has activity against *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*. It has some activity against *Coccidioides immitis* but is inactive against *Aspergillus* spp. and *Cryptococcus neoformans*.

#### Administration, distribution and excretion

Ketoconazole, like itraconazole and amphotericin but unlike fluconazole, is highly insoluble in water. It is avail-

able only in oral form. As with itraconazole, absorption requires the presence of acid and is therefore diminished by  $H_2$  antagonists, proton pump inhibitors, etc. As with itraconazole but unlike fluconazole, ketoconazole is highly bound to plasma proteins (99%) and is not dialysable. Penetration to most tissues is good but CSF concentrations, as with itraconazole but unlike fluconazole, are negligible even in the presence of meningitis [311]. Ketoconazole is metabolized in the liver, the metabolites being excreted in the faeces, so that negligible amounts are found in the urine. No dosage adjustment is therefore needed in renal insufficiency but the drug may accumulate in the presence of significant hepatic dysfunction and, since it may itself cause idiosyncratic hepatotoxicity, is best avoided in this situation.

#### Dosage

When used for serious systemic mycoses, the usual dose is 400 mg once daily with food to reduce nausea.

#### Adverse effects and interactions

Adverse effects with ketoconazole include anorexia, nausea, vomiting and other gastrointestinal symptoms, which occur in about 17% of patients taking 400 mg (two tablets) daily [312]. Rashes may also occur. Asymptomatic mild elevation of the transaminases is not uncommon and is usually transient. The most serious potential adverse effect is symptomatic hepatitis, which is rare but occurs idiosyncratically at any time during treatment and which may progress rapidly, being accompanied by profound derangement of liver function tests with jaundice and occasionally a fatal outcome. It is recommended that liver function tests be checked before treatment, after 14 days and monthly thereafter until completion of the course. Whether this protects patients is unproven, but at least it serves to keep both the physician and the patient alert for the complication. In contrast to the newer triazoles itraconazole and fluconazole, ketoconazole has endocrine effects by inhibiting the cytochrome P450 enzymes needed for adrenal and gonadal steroid hormone production; thus production of both cortisol and testosterone may be suppressed, particularly if the 400 mg daily dose is exceeded. Impotence, infertility, gynaecomastia, dysfunctional uterine bleeding and, rarely, adrenal insufficiency may result [313].

Drug interactions are broadly similar to those described for itraconazole. Isoniazid may also cause increased metabolism of ketoconazole and cyclosporin levels are more likely to be raised by ketoconazole than by itraconazole and fluconazole [280]. This observation has led some to combine ketoconazole with cyclosporin deliberately after transplantation in order to reduce the requirement and therefore the cost of cyclosporin [314].

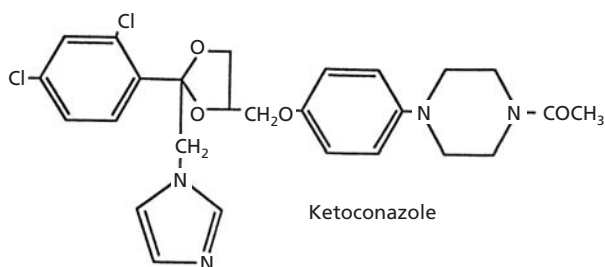


Fig. 9.10 Structure of ketoconazole.

*Principal uses in respiratory medicine*

Ketoconazole may be used for the treatment of chronic pulmonary histoplasmosis or blastomycosis in immunocompetent hosts, provided there is no meningeal involvement, and is cheaper though less well tolerated than itraconazole. Improvement may take a month to become evident and treatment is continued for 6 months to 1 year [280,290,312]. It is not effective in histoplasmosis when this occurs in association with AIDS [297]. Ketoconazole is also effective in paracoccidioidomycosis [315]. It may control disseminated coccidioidomycosis temporarily but relapse usually occurs on discontinuance of the drug [301].

Ketoconazole is ineffective for the treatment of both aspergillosis and cryptococcosis and for any disseminated mycosis involving the meninges. Rapidly progressive deep mycoses are more reliably treated with amphotericin. Systemic ketoconazole should not be used for superficial fungal infections in view of its potential for causing adverse effects, particularly hepatitis.

*Flucytosine*

Flucytosine is a synthetic fluorinated pyrimidine analogue that has a relatively narrow spectrum of antifungal activity. The drug is metabolized to its active form, 5-fluorouracil, which interferes with fungal protein synthesis. Flucytosine is active against many yeasts and yeast-like organisms. Although well absorbed by mouth and with excellent distribution, which includes the CSF, the only formulation available in the UK is for intravenous infusion. The usual daily dose is 150–200 mg/kg i.v. divided as four doses over 24 h. It is not usually used alone because of the emergence of resistance (which is more likely than with fluconazole) but may be used in combination with amphotericin for deep-seated infection by susceptible organisms, this being standard therapy in the treatment of seriously ill patients with cryptococcal meningitis; fluconazole is used for milder cases and for maintenance therapy in AIDS. Flucytosine may also be combined with amphotericin to treat systemic candidiasis, particularly when the CNS is involved. It has weak activity against *Aspergillus* spp. and *Histoplasma capsulatum*. *Blastomyces dermatitidis* and *Coccidioides immitis* are resistant. It is largely excreted unchanged by the kidneys, so that the dose must be adjusted in renal impairment according to creatinine clearance. Bone marrow suppression may occur, with leucopenia and thrombocytopenia, and this may be more problematical in patients with AIDS in whom the bone marrow may already be suppressed as a result of other factors. Nausea, vomiting and diarrhoea may also occur [316].

**Antimicrobial agents for use in viral infections**

Antiviral chemotherapy poses considerable problems compared with antibacterial treatment, in which the metabolism of the invading organism is sufficiently different from that of the host cells to enable the development of agents toxic to the bacterium but not to the patient. As virus particles manipulate the host's cellular structures for their own ends, such a clear separation of the target organism from the host becomes more difficult; nevertheless, recent developments in molecular biology have permitted the synthesis of various compounds, the majority of which are intended to interfere with the viral replicative process in infected host cells without interfering with nucleic acid synthesis in normal cells. A number of these substances either show promise or are of established, although limited, clinical value.

Viruses that may be targeted in adult respiratory medicine include members of the Herpesviridae family, HIV and the influenza A virus. The Herpesviridae contains herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV) and cytomegalovirus (CMV), all of which may cause severe illness in immunocompromised patients. VZV may also cause severe pneumonia in immunocompetent adults (see Chapter 13). Increased understanding of the structure and pathogenicity of HIV, responsible for AIDS [317], has given impetus to further developments in the field of antiviral chemotherapy. As with antibacterial agents, resistance may emerge with antiviral agents as a result of the occurrence, during replication, of mutations in the genes that code for the drug target or activator [318]. A description of some antiviral agents currently relevant to respiratory medicine follows.

**Aciclovir in VZV and HSV infections**

Aciclovir (acyclovir) is an antiviral purine nucleoside analogue that is the agent of choice in the treatment of infection by both HSV types 1 and 2 and VZV.

*Mode of action*

Aciclovir (Fig. 9.11) is activated *in vivo* by virally produced thymidine kinase, which phosphorylates it to form aciclovir monophosphate in infected cells [319]. Further intracellular phosphorylation takes place to form aciclovir triphosphate, which reaches sufficient concentration in infected cells to inhibit viral DNA polymerases, which in turn prevents the production of new viral DNA chains [320,321]. As the action of this drug is to prevent replication of viral DNA, it is unlikely to eradicate latent infection.

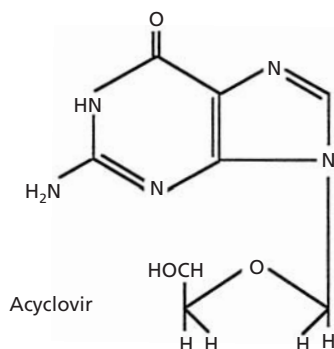


Fig. 9.11 Structure of aciclovir.

#### *Spectrum of activity*

Aciclovir is active against HSV infections, controlling rather than eradicating the virus. It is active against VZV but has little activity against Epstein–Barr virus (EBV) and CMV is resistant [322,323]. Neither EBV nor CMV produce thymidine kinase and this probably accounts for their relative immunity. Aciclovir-resistant strains of HSV have been demonstrated in immunocompromised patients and these too lack thymidine kinase [324]. These HSV mutants remain sensitive to drugs such as foscarnet that do not require thymidine kinase for activation [325]. Clinical studies of aciclovir have shown it to be effective in both HSV and VZV infections and to be more effective than another antiviral nucleoside, vidarabine, which is no longer available for systemic use [326,327].

#### *Administration, distribution, excretion and dose*

Aciclovir may be taken orally but only 20% of the dose is absorbed. This may produce adequate blood levels for mucocutaneous HSV infections and for chickenpox in immunocompetent adults but for any serious infection the intravenous route is preferred. The drug is widely distributed and reaches the CSF, permitting one of its principal extrathoracic uses, the treatment of HSV encephalitis. The plasma half-life is 2–3 h and most of the drug is excreted unchanged in the urine, so that the dose should be reduced in renal insufficiency [328], an estimated creatinine clearance of less than 50 mL/min being an indication for dosage reduction according to the manufacturer's recommendations [325,329].

The oral dose for treating mucocutaneous HSV in immunocompromised patients is 200–400 mg five times daily for 5–10 days [325]. The oral dose for HSV prophylaxis in immunocompromised patients, such as those undergoing induction chemotherapy or transplantation, is 200–400 mg four times daily. The oral dose for VZV infections is 800 mg five times daily for 7 days.

The usual intravenous dose for HSV infections in

immunocompromised patients is 5 mg/kg infused over 1 h and repeated 8-hourly. The dose may be increased to 10 mg/kg i.v. 8-hourly in severe VZV infection. This higher dose is also used in HSV encephalitis [325]. The treatment is normally continued for 5 days for uncomplicated HSV infection and up to 10 days for more serious infections, including encephalitis.

Topical preparations exist for skin (cream, not for mucous membranes) and eyes (eye ointment).

#### *Adverse effects*

Aciclovir shows a remarkable lack of toxicity at standard doses. Intravenous infusions may produce local irritation. Bolus intravenous injection may produce crystal formation in the renal tubules. Infusions of more than 5 mg/kg may have a similar effect, with a reversible rise in plasma creatinine [330]. If such high doses are required, then adequate hydration should be ensured. Nausea, vomiting and encephalopathy have been reported with higher doses. Disturbances of liver function tests may occur.

#### *Principal uses in respiratory medicine*

The application of aciclovir to immunocompetent adult patients with respiratory disease is largely confined to the hospital treatment of chickenpox pneumonia, as other susceptible viral infections in this group are usually mild and self-limiting [331], although a recent study has shown that adults with uncomplicated chickenpox recover quicker when treated with aciclovir and that this is cost-effective management [332]. A retrospective controlled trial involving 38 patients was conducted to determine if aciclovir was effective in the early treatment of varicella pneumonia in otherwise healthy adults, better results being obtained in the treatment group [333]. In immunosuppressed patients, such infections are more likely to be life-threatening; however, provided that treatment is started within 72 h of the onset of zoster or chickenpox, there is evidence that cutaneous and visceral spread is limited [325,334]. A placebo-controlled trial of aciclovir in immunosuppressed children with chickenpox has shown the drug to be effective in preventing the development of pneumonia [335]. Once disease is fully established, the results are poor [335]. There is evidence to suggest that aciclovir was clinically more effective than vidarabine in VZV infection, the latter drug being no longer available for systemic use [326,336]. Aciclovir has been shown to be effective both prophylactically and as treatment for mucocutaneous HSV lesions in immunocompromised hosts [325,337–339]. Aciclovir does not alter the clinical course of CMV and EBV infections [325].

Valaciclovir is an ester of aciclovir. Famciclovir is a prodrug of penciclovir, which is pharmacologically related to aciclovir. Both drugs are available for the oral

treatment of mucocutaneous HSV infections and have to be taken less frequently than aciclovir.

## **HIV: principles of antiretroviral therapy**

### **General principles**

HIV infection is mainly caused by HIV-1, HIV-2 being largely confined to West Africa. Both are RNA-containing retroviruses that target CD4+ T lymphocytes. Replication of the virus results in the destruction of these lymphocytes so that the CD4+ count (normal  $0.6\text{--}1.5 \times 10^9/\text{L}$ ) falls progressively, leaving the patient open to those opportunistic infections and neoplasms that characterize AIDS. Rates of opportunistic infection rise significantly when the CD4+ count falls below  $0.2\text{--}0.3 \times 10^9/\text{L}$ . Two viral enzymes that are important in HIV replication have been targeted by antiretroviral drug therapy: (i) viral reverse transcriptase (DNA polymerase) and (ii) viral protease. Reverse transcriptase uses viral RNA as a template to produce DNA that is then incorporated into the host's DNA and transcribed to make more viral RNA. This RNA produces precursor polyproteins that are split by viral protease to produce proteins essential for viral maturation. Those drugs that interfere with DNA transcription by acting on reverse transcriptase of HIV-1 and HIV-2 are the nucleoside analogues, including zidovudine, didanosine (ddI), zalcitabine (ddC), stavudine (d4T) and lamivudine (3TC). The more recent non-nucleoside reverse transcriptase inhibitors such as nevirapine inhibit HIV-1 reverse transcriptase. Those that inhibit HIV protease include ritonavir, indinavir, nelfinavir and saquinavir [340]. Other protease inhibitors and non-nucleoside reverse transcriptase inhibitors (such as nevirapine) have been released or are under investigation [341].

As experience in the management of HIV infection has accumulated, it has become evident that HIV replicates rapidly and has the capacity to become resistant to antiviral agents by spontaneous mutation; when this happens, cross-resistance to drugs of the same class may arise. The use of single drugs is likely to select resistant organisms within days or weeks, hastening treatment failure, so that recent drug strategies making use of more than one agent (along the lines of antituberculous therapy) have emerged in order to forestall this [341,342]. These recommendations have been made largely on the basis of randomized clinical trials and short-term disease activity marker studies [341]. In addition to the CD4+ count, changes in the plasma level of HIV-1 RNA ('viral load') has emerged as an important disease activity marker and thus change in viral load 8–12 weeks after the introduction of treatment may be used as a measure of therapeutic efficacy [341,342]. Although expensive, viral load assays should be con-

ducted, starting with two baseline measurements and then every 3–6 months in untreated HIV-infected patients and more frequently in those receiving antiretroviral therapy [341,342].

Clinical trials are ongoing but three-drug combinations that include two nucleoside analogues and an HIV protease inhibitor (e.g. zidovudine/didanosine/indinavir or zidovudine/lamivudine/indinavir) show promise, the rationale being to suppress viral replication maximally before the immune system is irreparably damaged [343–345]. Although still an area of debate, current opinion has leaned towards this initial three-drug approach and away from recent two-drug recommendations [346]. These recommended the combination of two nucleosides or a nucleoside plus a protease inhibitor, with the option of the addition of a protease inhibitor to the first combination or a nucleoside to the second if the patient fails to respond [342,347]. More recently it has been recommended that the initial treatment of all HIV-infected patients should include an HIV protease inhibitor plus two nucleoside analogues unless contraindicated [340,348]. Debate also surrounds the dilemmas of when treatment should best be started, the initial choice of drugs and when to switch from, or add to, this combination. In the USA, it is considered prudent to start treatment when the CD4+ count falls below  $0.5 \times 10^9/\text{L}$  or if the plasma HIV RNA concentration (viral load) is more than 5000–10000 copies/mL even if the CD4+ count exceeds  $0.5 \times 10^9/\text{L}$ , disease in patients with much heavier viral loads having been found to progress faster than in those with lower viral loads [340,341,346].

Antiretroviral drugs in general are toxic and the manufacturer's summary of product characteristics should be consulted before use.

### **Accidental exposure of staff (needlestick injuries)**

Antiretroviral drugs are also used to treat healthcare workers who have experienced accidental percutaneous exposure to HIV-infected blood, such as might occur with a needlestick injury. The average risk of transmission of HIV infection in this situation is estimated at 0.3% [349]. The data on the effectiveness of postexposure prophylaxis are limited but a retrospective case-control study indicates that risk is related to the size of the inoculum and that zidovudine appears to provide an 81% reduction in the risk of occupational infection [349,350]. In the UK, the Chief Medical Officer's Expert Advisory Group on AIDS has published guidance recommending 24-h access to advice for healthcare workers with prompt (within 24 h, preferably 1–2 h) postexposure prophylaxis using a combination of three antiretroviral drugs for 4 weeks [351,352]. In the USA, guidelines have also been promulgated.



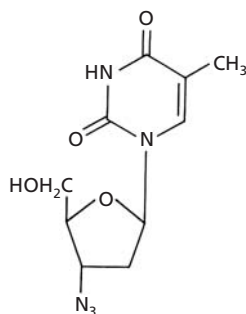


Fig. 9.12 Structure of zidovudine.

### Nucleoside analogues: reverse transcriptase inhibitors

#### Zidovudine

Zidovudine (azidothymidine, AZT, Fig. 9.12) is an analogue of the naturally occurring DNA nucleoside thymidine. It was licensed for use in HIV infection in the UK in 1987 [353]. It is now current practice to use it as a constituent part of combination chemotherapy in the treatment of HIV infection (see above).

#### Mode of action

Zidovudine was found to inhibit the *in vitro* replication of a cytopathic retrovirus, now known as HIV, in human T cells [354,355]. It is active against a broad spectrum of retroviruses including HIV-1 and HIV-2. Zidovudine enters cells and is converted into zidovudine triphosphate. This competes with thymidine triphosphate for a nucleoside-binding site on the growing chains of viral DNA that are being produced by reverse transcriptase, the drug thereby acting as a 'chain terminator' and preventing reverse transcriptase from making DNA copies of viral genomic RNA [354,356].

#### Administration, distribution and excretion

The drug is usually taken orally and is well absorbed, being distributed widely in body fluids including the CSF [354], so that it may be potentially useful in preventing the AIDS dementia complex. It is cleared rapidly from the blood, being metabolized mainly in the liver, and about 25% is excreted unchanged in the urine so that some dose adjustment may be necessary in advanced renal failure. The half-life is very short (about 1 h) but may be prolonged in liver disease because of impaired metabolism. A formulation of the drug is available for intravenous infusion if it cannot be taken orally.

#### Dosage

The dosage schedule from early trial work was 250 mg

orally every 4 h [357], although it soon became apparent that lower doses were as effective but less toxic [358]; thus 500–600 mg daily in two to five divided doses is acceptable, the commonest regimen being 200 mg three times daily. In order to protect the fetus, pregnant women (over 14 weeks' gestation) with HIV infection should be prescribed 100 mg five times daily until the onset of labour, then 2 mg/kg intravenously over 1 h and then 1 mg/kg/h by continuous infusion until the cord is clamped, the infant then continuing oral zidovudine for 6 months. This approach reduces the risk of perinatal transmission from 26% to 8% [359]. The intravenous dose is 1–2 mg/kg every 4 h.

#### Adverse effects

Zidovudine is associated with significant toxicity, the most important manifestations of which are haematological. Anaemia (usually macrocytic) and neutropenia were experienced in almost half the patients receiving the drug in one large early trial [360]. These effects, serious enough to require blood transfusion in some patients and to prevent further treatment with the drug, usually started soon after the onset of treatment and reversed within about 2 weeks of stopping therapy, so that it was possible to recommence at a lower dose. Bone marrow suppression has been found to be dose dependent, also occurring more commonly in patients with advanced disease (CD4+ count  $<0.1 \times 10^9/L$ ), but the blood count should nevertheless be monitored. It is less common nowadays as the drug is used at lower doses than in early studies, so that neutropenia may be found in about 9% of patients with less advanced disease. Neuropathy and myopathy have also been reported but are unusual. Other side-effects include nausea, headache, myalgia and insomnia but usually pass off without stopping treatment. Lactic acidosis may rarely occur, in which case the drug must be stopped.

#### Clinical role

The clinical role of zidovudine is under continuous review, the trend having shifted from monotherapy [357] to two-drug therapy [361,362] and more recently to triple-drug therapy [340,344,345,348], zidovudine being one of a number of possible constituents in these regimens (see above). In the early days of its use as monotherapy, the results of a multicentre, prospective, double-blind, placebo-controlled study involving over 280 patients was published [357]. Those patients entered either had AIDS, with a first episode of *Pneumocystis carinii* pneumonia within the last 4 months, or satisfied inclusion criteria for the AIDS-related complex, which included positive serology for AIDS with either (i) 10% weight loss in the preceding 3 months or (ii) oral candidiasis and one of



the following: unexplained fever, extrainguinal lymphadenopathy, oral hairy leucoplakia, unexplained night sweats, herpes zoster or unexplained diarrhoea. These selection criteria would have tended to exclude patients who were more debilitated as a result of having had clinical AIDS for a longer period. The results of this study showed a highly significant reduction in mortality in the treated group over a period of 24 weeks, probably as a result of a significant reduction in opportunistic infection, which became evident after the sixth week of treatment [357]. There was also improved quality of life in terms of Karnofsky scoring [357,363].

### *Didanosine*

Didanosine (ddI, DDI) is an orally administered purine nucleoside analogue with antiretroviral activity but with relatively little toxicity for bone marrow. It has a half-life of about 12 h and may therefore be given twice daily. It is unstable in acid and has to be taken 1 h before or 2 h after a meal. All formulations contain buffering agents to reduce gastric pH. It reaches the CSF, although less well than zidovudine. About 50% of the drug is excreted unchanged in urine so that dose adjustment is necessary in renal failure. Like zidovudine, it inhibits the replication of HIV by blocking the reverse transcriptase-mediated synthesis of viral DNA. The tablet dose is 125 mg twice daily for patients weighing less than 60 kg and 200 mg twice daily for those weighing more than 60 kg. The main dose-limiting adverse effects are painful peripheral neuropathy and pancreatitis. These are unusual with currently recommended dose levels but the drug should not be used in patients with a previous history of either condition. Nausea, vomiting, diarrhoea and, rarely, liver failure may occur. It was initially used singly, subsequently in double-drug combinations and more recently has been under investigation as triple therapy in combination with zidovudine and a protease inhibitor such as indinavir [364].

### *Zalcitabine*

Zalcitabine (ddC, DDC) is an orally administered nucleoside analogue with antiretroviral activity that also inhibits the replication of HIV by blocking the reverse transcriptase-mediated synthesis of viral DNA. It is usually well absorbed and distributed but reaches the CSF less well than zidovudine; 75% is excreted unchanged in the urine so that dose reduction is necessary if the creatinine clearance is less than 40 mL/min. The usual dose is 0.75 mg 8-hourly. The main dose-limiting side-effect is painful sensorimotor peripheral neuropathy, which occurs in about 20% of patients and necessitates discontinuance when it does. As with didanosine, pancreatitis may also occur but is uncommon. Mouth and oesophageal ulceration

can occur as can disorders of gastrointestinal tract motility. Cardiomyopathy is described. It has been found to be more effective when used in combination with zidovudine than either drug alone [365]. More recently it has been shown to be more effective when used as triple therapy in combination with zidovudine and the protease inhibitor indinavir compared with zidovudine and lamivudine alone [344].

### *Stavudine*

Like zidovudine, stavudine (d4T) is an orally administered thymidine nucleoside analogue that competes with thymidine triphosphate for a nucleoside-binding site on the growing chains of viral DNA being produced by reverse transcriptase; it therefore acts as a 'chain terminator' and prevents reverse transcriptase from making DNA copies of viral genomic RNA. It is well absorbed and about 40% is excreted unchanged in the urine. The usual dose is 40 mg 12-hourly for patients weighing more than 60 kg and 30 mg 12-hourly for those weighing less than 60 kg. The main dose-limiting adverse effect is a painful sensory neuropathy, which is more likely to occur at high doses and in patients with advanced disease. This is ordinarily reversible if the drug is stopped, as are changes in liver function. Stavudine is less toxic to bone marrow than zidovudine, neutropenia occurring in about 5% of patients with less advanced disease. Thrombocytopenia is still less common. Acute pancreatitis may occur but, as with zalcitabine, this is less common than with didanosine. Stavudine is another promising antiretroviral agent whose efficacy has been demonstrated in comparison with zidovudine [366]. Further evaluation in trials of combination chemotherapy are ongoing.

### *Lamivudine*

Lamivudine (3TC) is another relatively new orally administered nucleoside analogue. Like zidovudine it is a reverse transcriptase inhibitor active against HIV-1 and HIV-2. It has good bioavailability. The usual recommended dose is 150 mg 12-hourly. Adverse effects appear to be uncommon with long-term use but, as with other nucleoside analogues, there have been reports of peripheral neuritis and pancreatitis. Headache, nausea, vomiting, diarrhoea, abdominal pain and disturbances of liver enzymes have also been described [367]. The clinical benefit of lamivudine when added to previously available nucleoside analogues has been shown [368], as has its benefit in triple therapy regimens with indinavir and zidovudine [344,345].

### **HIV protease inhibitors**

Members of this newer class of antiretroviral drug inhibit

viral protease by competing with it for its binding site [340]. These drugs, including ritonavir, indinavir, saquinavir, nelfinavir and others [342,343], act on the process of viral replication at a later stage than the reverse transcriptase inhibitors, preventing the cleavage of HIV precursor proteins in infected cells and thereby blocking the maturation of viral particles and impeding further waves of infection. These compounds are used in combination with nucleoside analogues. All of them are inhibitors of the hepatic cytochrome P450 enzyme system, ritonavir being the most potent in this respect, so that great care should be taken to avoid drug interactions and the manufacturers' summaries of product characteristics should be consulted. As an example, ritonavir substantially increases plasma levels of rifabutin (used to treat *Mycobacterium avium-intracellulare* complex) and its metabolites, thereby increasing the risk of uveitis, so that these two drugs should not be used together. Competitive inhibition of terfenadine, astemizole and cisapride may also occur with the risk of cardiac dysrhythmias, including torsades de pointes. The addition of a P450 inhibitor such as ketoconazole may substantially increase the availability of the protease inhibitor, especially in the case of saquinavir [340]. Haemophiliacs receiving protease inhibitors should be warned that they may increase their bleeding tendency. The following drugs belong to this group and others are under development or investigation:

#### ***Ritonavir***

This orally administered protease inhibitor is currently taken in combination with nucleoside analogues at a recommended dose of 600 mg twice daily, preferably with food. The drug is principally metabolized and eliminated by the liver. At the commencement of treatment, nausea, vomiting, abdominal pain and diarrhoea are common and patients should be forewarned [340]. A gradual build-up of the dose is recommended to prevent this and an antiemetic may be necessary. Headache, disturbances of taste and flushing may also be complaints, and circumoral and digital paraesthesiae are not uncommon, usually resolving despite continued treatment. Elevated liver enzyme levels and hypertriglyceridaemia may be found on blood testing but pancreatitis is not a recognized complication. Hyperglycaemia and fat redistribution ('buffalo hump') have been reported. Other adverse effects and a myriad of drug interactions are listed in the summary of product characteristics [340].

#### ***Indinavir***

This orally administered protease inhibitor is currently taken in combination with nucleoside analogues, such as zidovudine and lamivudine, at a recommended dose of

800 mg 8-hourly 1 h before or 2 h after food or with a low-fat snack [344,345]. Metabolism and excretion of the drug is mainly hepatic, only 20% being excreted unchanged or as metabolites in the urine. Gastrointestinal side-effects may occur as for ritonavir. Patients may complain of headache, a dry skin, rashes and taste disturbance. Liver function changes may include hyperbilirubinaemia, which is reversible and occurs in 10% of patients; 3–4% of patients develop renal calculi with loin pain, this being the most important side-effect so that a high fluid intake (at least 1.5 L per 24 h in addition to normal intake) is advised to counter this tendency [340]. Episodes of severe haemolysis have been reported. Hyperglycaemia and fat redistribution ('buffalo hump') have been reported. Other adverse effects are listed in the summary of product characteristics.

#### ***Saquinavir***

This orally administered protease inhibitor with relatively low bioavailability is currently taken in combination with nucleoside analogues at a recommended dose of 600 mg three times daily within 2 hours after a meal [369]. Newer soft gel capsules increase bioavailability but at the price of increased gastrointestinal side-effects. The principal route for metabolism and excretion is the liver. Diarrhoea, nausea, vomiting and abdominal discomfort, oral ulcers and peripheral neuropathy may occur. Minor disturbances of liver function, hyperglycaemia and fat redistribution ('buffalo hump') have been reported. Rifampicin and rifabutin reduce blood levels of saquinavir significantly. Other adverse effects and precautions are listed in the summary of product characteristics.

#### ***Nelfinavir***

This orally administered protease inhibitor has improved bioavailability and is currently taken in combination with nucleoside analogues at a recommended dose of 750 mg three times daily, with or shortly after meals. The principal route of metabolism is the liver. The dose-limiting side-effect is diarrhoea, which can usually be controlled with an ant motility drug such as loperamide. Nausea, vomiting, fatigue and paraesthesiae may all occur. Biochemical abnormalities such as raised serum transaminases, triglyceride and glucose may occur [340].

#### **Other antiviral drugs in HIV infection**

A number of non-nucleoside reverse transcriptase inhibitors are under investigation or in use. These include nevirapine (now licensed in the UK and USA), delavirdine (licensed in the USA), loviride and the investigational non-nucleoside reverse transcriptase inhibitor efavirenz. The field of drug research and development surrounding HIV infection is one of strenuous activity as the search for

effective clinical regimens continues pending the possible development of a vaccine.

### Drugs active in CMV infection

HIV-related research extends beyond the development of antiretroviral drugs to the development of drugs to combat superadded viral infection in AIDS. The following antiviral drugs have so far been shown to be clinically effective in delaying the progression of CMV retinitis, a complication that may affect about 40% of patients with AIDS and with an incidence similar to *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex infection [370,371].

#### Ganciclovir

Ganciclovir, a nucleoside analogue of guanosine, is structurally related to (but much more toxic than) aciclovir (Fig. 9.13). It is active against herpes viruses and was the first drug shown to be effective against CMV in humans. Infection with CMV is the commonest cause of intraocular infection in AIDS and, if untreated, leads to progressive retinal destruction, with or without retinal detachment, and blindness. It tends to occur in patients with a CD4+ count of less than  $0.05 \times 10^9/L$ .

#### Mode of action

Phosphorylation of ganciclovir takes place by virally produced thymidine kinase, with the formation of ganciclovir monophosphate in cells infected by CMV. Further phosphorylation produces ganciclovir triphosphate, which reaches sufficient concentration in infected cells to inhibit viral DNA polymerases, which in turn prevents the production of new CMV DNA chains and thereby slows viral replication [372]. Ganciclovir triphosphate reaches a much higher concentration in CMV-infected cells than aciclovir triphosphate and also has a longer half-life, accounting for its much improved CMV inhibitory effect [372].

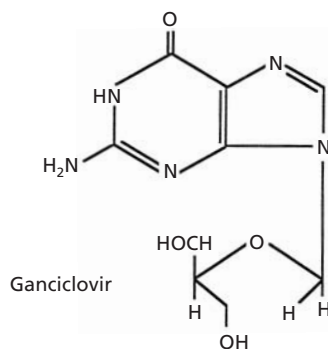


Fig. 9.13 Structure of ganciclovir.

#### Spectrum of activity

Although shown to be active in tissue culture against various herpes viruses, including HSV and VZV, it is much more toxic than aciclovir and its only clinical application has been in the management of CMV infection.

#### Administration, distribution, excretion and dose

Ganciclovir was initially available only as a solution for intravenous infusion, now used for induction and 'salvage' (repeat induction) therapy. Later, an oral preparation became available for maintenance treatment, once the retinitis was considered stable [373], and most recently an intraocular implant has become available [374]. Sub-retinal fluid levels similar to plasma levels are achieved after intravenous administration and the drug crosses the blood-brain barrier. More than 90% of the drug is excreted unchanged by the kidneys and the dose is reduced progressively for estimated creatinine clearances below 70 mL/min.

The intravenous formulation is typically administered for induction by infusion over 1 h at a high dose of 5 mg/kg every 12 h for 2–3 weeks [371]. After intravenous induction therapy, lifelong maintenance doses of 5 mg/kg every 24 h intravenously for 7 days per week or 6 mg/kg for 5 days per week are prescribed. Oral therapy using ganciclovir 1000 mg three times daily (12 capsules per day) is an alternative to parenteral treatment. This formulation may be almost equivalent in its maintenance effect to parenteral treatment, with a much lower incidence of severe neutropenia and no risk of central venous catheter-related sepsis. However, it is very costly and sufficient doubt about relative efficacy remains for it to be usual to prescribe the intravenous formulation, especially for central retinitis which is more likely to cause blindness [371].

More recently, an intraocular ganciclovir-releasing device, which may be implanted as an outpatient procedure, has been developed. This results in higher intravitreal drug levels than those achieved with intravenous therapy. It remains therapeutically active for up to 8 months (but is usually replaced after 6 months), although initial enthusiasm has been tempered by concerns about a possible increased incidence of early retinal detachment and the potential for the development of manifestations of CMV infection in the unimplanted eye and elsewhere in the body [371,372]. Implants may be suitable for patients with central retinitis who have so far retained good vision in the infected eye.

#### Adverse effects

Although many adverse effects have been described, the principal dose-limiting side-effects of ganciclovir are neu-

tropenia and thrombocytopenia. Anaemia may also occur with prolonged treatment but is less common. These side-effects may be summative, particularly during induction, if other marrow-depressing drugs such as zidovudine are used in parallel, so that profound myelosuppression may occur and dose modification is required [372]. It is usual to titrate the dose so that the neutrophil count is in the range  $0.5\text{--}1.0 \times 10^9/\text{L}$  and to treat with a recombinant human granulocyte colony-stimulating factor, such as filgrastim, if the count drops below  $0.5 \times 10^9/\text{L}$ . Ganciclovir should be stopped if the platelet count drops below  $20 \times 10^9/\text{L}$ . Myelosuppressive effects usually reverse within a week of stopping the drug but occasionally fatal bacteraemias have resulted. It is advisable to check the blood count twice weekly during induction and every 1–2 weeks during maintenance treatment. Rises in serum creatinine may be seen with prolonged treatment, so that this should be checked monthly. Intravenous ganciclovir has a tendency to cause local pain and thrombophlebitis at the site of the infusion.

#### *Principal uses in respiratory medicine*

The principal use of ganciclovir is the treatment and control of CMV retinitis in patients with AIDS [372]. Over 80% of patients are expected to respond to intravenous treatment, most lesions stabilizing within 2 weeks and healing within 1 month; 65% of patients have unilateral disease when the retinitis is first detected and treatment prevents involvement of the unaffected eye. However, without treatment most patients become blind or severely visually impaired in the affected eye within 4–6 months, the disease becoming bilateral in 60% [372]. Treatment must be lifelong. CMV resistance to ganciclovir may emerge during treatment, necessitating either an increase in dosage or a switch in therapy to an alternative drug such as foscarnet or cidofovir [371].

Prophylactic oral ganciclovir 1000 mg 8-hourly may be used in an attempt to prevent CMV infection in AIDS patients with a CD4+ count of less than  $0.1 \times 10^9/\text{L}$ , although the limited efficacy of such use has to be set against adverse effects and high cost [372,375]. The drug has also been used prophylactically in CMV-seropositive transplant recipients [372].

Ganciclovir has also been used to treat CMV colitis and polyradiculopathy in patients with AIDS and CMV pneumonia in transplant recipients [372].

#### *Foscarnet*

Foscarnet is an intravenously administered inorganic pyrophosphate analogue that directly inhibits the activity of viral DNA polymerase, an enzyme essential for the replication of CMV. It also has a weak antiretroviral effect by inhibiting HIV reverse transcriptase, an observation

that may have accounted for a small but significant survival advantage (8.5–12.6 months) in a comparative CMV retinitis trial with ganciclovir [376]. Its spectrum of activity covers most ganciclovir-resistant CMV and also aciclovir-resistant HSV and VZV strains. Over 80% of the drug is excreted unchanged by the kidney so that progressive dose reductions have to be made in renal insufficiency.

The principal dose-limiting adverse effect is nephrotoxicity, an increase in serum creatinine occurring after the first week of treatment in about half of patients. Numerous other side-effects have been recorded, including paraesthesiae, headache, nausea and tetany, which may result from the drug's ability to transiently chelate ionized calcium during infusion, the rate of which should therefore be carefully regulated. There may also be disturbances of phosphate, potassium and magnesium so that it is recommended that monitoring should include serum creatinine, calcium, phosphate and potassium twice weekly during induction and once weekly thereafter [371]. Genital ulceration may occur and, as with ganciclovir, there is a risk of central venous catheter-related sepsis.

Foscarnet is significantly more costly than ganciclovir and is diluted according to the manufacturer's instructions and infused by pump over 2 h at a usual induction dose of 90 mg/kg every 12 h for 2 weeks in those with normal renal function. The maintenance dose is 90 mg/kg as a single daily infusion. Treatment must be lifelong. As with ganciclovir, resistant CMV mutants may emerge during treatment.

Although mainly used to treat CMV retinitis [371], foscarnet may also be effective in the treatment of aciclovir-unresponsive serious HSV and VZV infections.

#### *Cidofovir*

Cidofovir is an intravenously administered nucleoside phosphate analogue of cytosine that undergoes intracellular phosphorylation to cidofovir diphosphate, resulting in viral DNA polymerase inhibition and thereby slowing down the synthesis of viral DNA. In contrast to ganciclovir and aciclovir, this phosphorylation is dependent on host rather than viral enzymes.

It has been shown to be active *in vitro* against a number of herpes viruses, including HSV-1 and HSV-2, VZV and CMV. It has also been shown to be effective *in vivo* against CMV and to delay the progression of CMV retinitis in patients with AIDS [377]. It is currently licensed for the treatment of CMV retinitis in patients with AIDS without significant renal dysfunction (see below) and in whom other agents are considered unsuitable.

The active intracellular metabolites of cidofovir have unusually long half-lives, up to 65 h for the diphosphate, so that the compound has a prolonged antiviral effect and

needs administration at 1–2 weekly intervals. This is clearly more convenient than daily infusions of ganciclovir or foscarnet and obviates the need for indwelling catheters.

The major side-effect is dose-dependent nephrotoxicity with the risk of renal tubular necrosis. The chance of this may be reduced by prehydration and concomitant administration of high-dose probenecid, which competes with cidofovir for uptake in the proximal renal tubules. The recommended dose of cidofovir for induction is 5 mg/kg infused at a constant rate over 1 h once per week for two consecutive weeks; for maintenance, the same dose is given once every 2 weeks. To reduce the potential for nephrotoxicity, 1 L of normal saline is infused over 1 h prior to dosing and 2 g probenecid is taken orally 2 h before commencement of the infusion and 1 g taken 2 and 8 h after completion of the infusion, to a total of 4 g. A further litre of saline may be given during or after the cidofovir infusion. Probenecid itself may cause nausea, fever and rashes. Cidofovir is presently contraindicated in patients with pre-existing renal impairment, defined as serum creatinine greater than 133  $\mu\text{mol/L}$  (>1.5 mg/dL) or creatinine clearance less than 55 mL/min or proteinuria greater than 100 mg/dL (2+ or more by dipstick). Cidofovir should not be used with other nephrotoxic drugs. It may interfere with the renal tubular excretion of many drugs and the manufacturer's summary of product characteristics should be consulted before use.

The efficacy of cidofovir is probably similar to that achieved by standard intravenous ganciclovir or foscarnet but long-term treatment may be limited by toxicity [371]. As with ganciclovir and foscarnet, resistant CMV mutants may emerge during treatment.

### Combined therapy for CMV infection

A combination of standard-dose ganciclovir and foscarnet for CMV retinitis was found to be more effective in delaying disease progression than high doses of either drug alone but there was a higher patient fall-out from the combined regimen as a result of drug intolerance [378]. Other trials of combined therapy are likely to be published and further anti-CMV drugs, such as a valine ester of ganciclovir, are under development.

## Antiviral agents in influenza prophylaxis

### Adamantanes: amantadine and rimantadine

Amantadine (Fig. 9.14) is a crystalline primary amine and has long been in use as an antiparkinsonian drug. It is also known to have some activity against influenza A virus infection. Rimantadine (Fig. 9.14) is a closely related derivative, having an additional methyl group attached to the

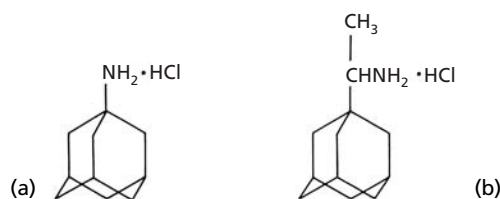


Fig. 9.14 Structure of (a) amantadine hydrochloride and (b) rimantadine hydrochloride.

same cage-like structure. Amantadine and rimantadine have no activity against influenza B virus, which accounts for about 35% of all cases. Rimantadine is not generally available in the UK

### Mode of action

Both drugs are thought to act at low concentrations at an early stage of replication by blocking the ion channel function of a viral structural protein and preventing the uncoating of virus particles [379,380]. Although the drugs have weak *in vitro* activity against some other viruses, including rubella, parainfluenza and respiratory syncytial viruses, their only practical use is against influenza A virus.

### Administration, distribution and excretion

The drugs are well absorbed after oral administration and are widely distributed. The mean half-life of amantadine is about 15 h but may vary widely between patients. It is excreted unchanged in the urine, so that accumulation tends to occur in renal failure and dose reduction is necessary for significantly reduced creatinine clearances, according to the manufacturer's instructions. Rimantadine mainly undergoes hepatic metabolism so that dosage reductions only need be made in liver disease or severe renal failure (creatinine clearance <10 mL/min). It has an even longer half-life than amantadine of about 30 h.

### Dosage

Amantadine may be used at a dose of 100 mg daily for influenza prophylaxis in 'at-risk' unimmunized people for as long as protection is required (usually about 6 weeks) or for 2–3 weeks following immunization to allow the vaccine to take effect. Half this dose may be used in patients over the age of 65 years by giving the same dose every second day. Some authorities recommend twice these dosages [381]. Reduced doses should also be given in renal insufficiency according to the creatinine clearance [379,380]. A recommended dosage schedule for rimanta-

dine prophylaxis is 100 mg twice daily, reducing to 100 mg daily in elderly nursing home residents [382].

#### *Adverse effects*

Adverse effects are few and are dose related, although particular care needs to be taken in patients with renal insufficiency and in the elderly [383,384]. CNS side-effects have been recorded, particularly in the elderly, and may include dizziness, lethargy, insomnia, headaches, anxiety and depression; if high blood levels are allowed to develop, toxic psychoses may occur. Livedo reticularis may rarely occur. Amantadine is contraindicated in epilepsy as patients may have their seizure tendency enhanced [385]. Rimantadine has been reported to have fewer CNS side-effects [380,386].

#### *Principal uses in respiratory medicine*

Early studies of prophylactic amantadine showed that the drug could reduce the incidence of influenza A infection or diminish the symptoms of those who developed infection when taking the drug [387–389]. Amantadine (100–200 mg daily) has also been used in the treatment of influenza A and has been shown to reduce the duration of fever by 1–2 days if started within the first 48 h of symptoms [390,391].

There are obvious difficulties in making a clinical diagnosis of influenza in view of the similar symptoms that may be produced by other community-acquired respiratory viral infections; furthermore, the drug has been shown to be useful only in influenza A infection and not in influenza B [392]. Although the widespread use of amantadine has been recommended, it is probably best reserved for occasions when there is known to be a high prevalence of influenza A infection in the community. In the UK, this is indicated by Public Health Laboratory Service reports of isolation of influenza A virus and by clinical returns collated by the Birmingham research unit of the Royal College of General Practitioners. Amantadine (or rimantadine) may be used in influenza A virus infection in the following situations.

**1** Prophylactically for those at particular risk, such as unvaccinated persons living in a home or institution in which influenza has already broken out (postexposure prophylaxis), particularly the elderly and those with chronic debilitating illnesses [393]. Such people should be vaccinated but may also be given amantadine for at least 2 weeks while the vaccine takes effect. In such situations, these drugs are about as effective as influenza vaccination. They should not be regarded as a substitute for vaccination and do not interfere with the immune response to influenza vaccines.

**2** Prophylactically for unvaccinated healthcare workers

and other key personnel during epidemics in order to prevent disruption of the services that they provide.

**3** As treatment in patients in whom a clinical diagnosis of influenza has been made, particularly those in whom complications might be expected to occur such as the elderly or those with chronic cardiac or respiratory disease [394,395]. It is reasonable to treat for up to 1 week in such circumstances. It is unwise to use these drugs for both postexposure prophylaxis and treatment in the same home as the selection and transmission of resistant influenza A virus may occur [385].

Amantadine and rimantadine are broadly similar both structurally and in their mechanism of action. Both are about as effective as available vaccines in preventing influenza A virus infections and when used as treatment shorten the illness by about a day.

#### *Zanamivir: a drug for influenza A and B virus infections*

Zanamivir is a sialic acid analogue that selectively inhibits both influenza A and B virus neuraminidases (sialidases) [396]. These enzymes are essential in allowing the virus to attack the host cell surface, thereby permitting the release of virus particles from infected cells. The drug is currently undergoing clinical investigation and has recently become available for clinical use. It has been administered topically as a dry powder both to the nasal passages and by inhalation and has been shown (i) to protect adults from developing illness when experimentally infected with influenza A virus [397] and (ii) to reduce the duration of illness of naturally acquired influenza (both types A and B) by 1–2 days when used as antiviral treatment within 48 h of the patient becoming symptomatic [398]. It is available as a metered dose dry powder oral inhalation to be taken at a dose of 5 mg twice daily for 5 days. Studies have been carried out in otherwise healthy patients with influenza and beneficial effects in more vulnerable groups have yet to be shown. There are as yet no comparative trials of amantadanes and zanamivir. Other neuraminidase inhibitors, some of which may be administered orally, are also at early stages of investigation [396].

#### **Other antiviral agents**

Numerous other antiviral substances are being investigated under laboratory conditions or are being applied to clinical situations with varying degrees of success.

*Interferons* are a group of naturally produced glycoproteins that are important in host cellular defences against viral infection. They are active *in vitro* against a variety of DNA and RNA viruses, as well as showing some antitumour effects. Three major types are recognized ( $\alpha$ ,  $\beta$  and  $\gamma$ ), of which interferon  $\alpha$  has received the most attention. They have their effect indirectly by inducing other

antiviral enzymes and by modifying and stimulating the host's immune responses. Large quantities may now be produced by bacterial and yeast clones of interferon genes as a result of advances in recombinant DNA technology. They have been used, with some success, as a topical nasal spray to prevent rhinovirus infections, and have also been given in parenteral form with moderate success for virus infection in immunocompromised hosts, e.g. VZV in children [390,399]. Side-effects of systemic therapy include flu-like symptoms, with myalgia and fever, and also marrow toxicity [400].

*Tribavirin* (ribavirin) is an antiviral nucleoside that is available for use as a small particle aerosol in the treatment of respiratory syncytial virus bronchiolitis and pneumonia in infants, being thought to accelerate clinical recovery in this situation [401]. This drug is now available in the UK for the treatment of infants and young children with severe respiratory syncytial virus bronchiolitis.

## Drugs used in the management of airflow limitation

### Sympathomimetic bronchodilators

Sympathomimetic bronchodilators [402] have been in use for several thousand years, an ephedrine-containing extract derived from the plant *Ephedra equisetina* having been used in ancient China. Modern sympathomimetics (syn. adrenoceptor stimulants, adrenergic receptor agonists), as used in the treatment of asthma, are synthetic derivatives, or analogues, based on the structure of epinephrine (adrenaline). This naturally occurring catecholamine is both an  $\alpha$ - and  $\beta$ -adrenergic agonist that acts as a neurotransmitter in the sympathetic nervous system,  $\alpha$  receptors being predominantly stimulatory (vasoconstriction) and  $\beta$  receptors predominantly inhibitory (relaxation of smooth muscle in the respiratory tract, vasculature and uterus) [403]. Epinephrine was used as a bronchodilator for a large part of the twentieth century until it became obsolete as a result of the development of isoprenaline (USA, isoproterenol), which stimulates only  $\beta$ -adrenergic receptors. Isoprenaline itself largely fell from use (and is no longer easily obtainable in the UK) following the discovery that  $\beta$ -adrenergic receptors could be divided into types 1 and 2 and with the development of more selective  $\beta$ -adrenergic receptor agonists (or  $\beta$  agonists), the effects of which are directed more specifically to the  $\beta_2$  receptors, which produce bronchodilatation (as well as vasodilatation), and less to  $\beta_1$  receptors that stimulate heart muscle [404]. In skeletal muscle,  $\beta_2$  stimulation is responsible for the tremor that is a common unwanted effect of  $\beta$ -agonist bronchodilator use.

A common biochemical feature shared by the majority of the sympathomimetic bronchodilators is the possession of a six-carbon (or benzene) ring with an ethanolamine

side-chain in the C-1 position. Various substitutions can be made at the C-3, C-4 and C-5 positions on the ring and at positions  $R_1$  and  $R_2$  on the side-chain (Fig. 9.15). These substitutions affect the properties of an individual group member, such as its potency, selectivity, duration of action and metabolic fate. Three groups of sympathomimetic bronchodilator have been described on the basis of their closely related chemical structures: catecholamines (e.g. epinephrine, ephedrine, isoprenaline, rimeterol), saligenins (e.g. salbutamol, salmeterol) and resorcinols (e.g. terbutaline and fenoterol, which was derived from orciprenaline). Eformoterol (formoterol) is classed as an *N*-arylalkylamine, having a formamide group at the C-3 position of the benzene ring and an *N*-arylalkyl side-chain (Fig. 9.16). The molecular structures of epinephrine, salbutamol (USA, albuterol), terbutaline, isoprenaline and orciprenaline (USA, metaproterenol) are shown in Figs 9.17–9.20. The similarities are striking and such is the case with most of the sympathomimetic bronchodilators in current use.

#### Selectivity

Table 9.6 lists some of the sympathomimetic bronchodilators presently available. Those in the first column have been shown to be more selective  $\beta_2$  agonists, although concerns have been expressed about fenoterol in this regard. Those in the second column, although effective bronchodilators to varying degrees, are non-selective or poorly selective and are more likely to produce unwanted effects. As a general rule, the larger the substitution at the  $R_2$  position on the side-chain, the greater the selectivity displayed by the drug (Figs 9.17–9.20). This also accounts in part for the relative non- $\beta_2$  selectivity of orciprenaline, which has the same  $R_2$  substitution as isoprenaline and is therefore

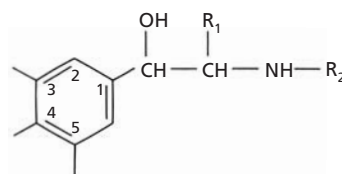


Fig. 9.15 Sympathomimetic bronchodilators: common benzene ring and ethanolamine side-chain (see text).

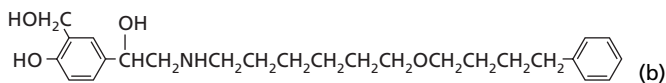
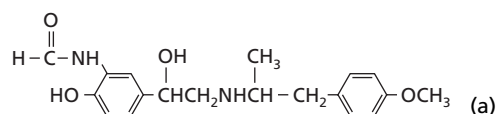


Fig. 9.16 Structure of (a) eformoterol and (b) salmeterol.



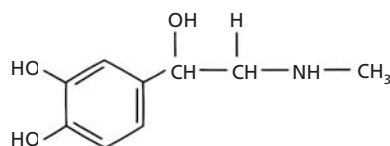


Fig. 9.17 Structure of epinephrine (adrenaline).

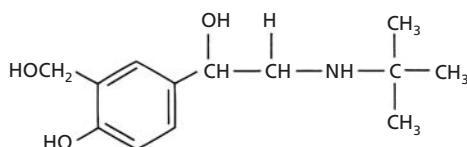


Fig. 9.18 Structure of salbutamol (albuterol).

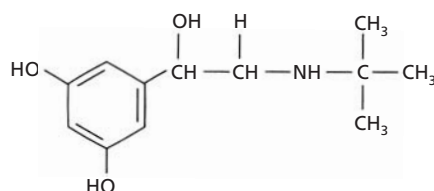


Fig. 9.19 Structure of terbutaline.

also more apt to cause direct cardiac stimulation if standard doses are exceeded [405].

It should be noted that  $\beta_2$  selectivity diminishes as dose increases, so that a high plasma level following oral, inhaled or particularly intravenous dosage produces cardiac stimulation with tachycardia. However, such effects do not occur following standard inhaled doses using a metered-dose inhaler (MDI) [406].

#### Duration of action

The older catecholamine bronchodilators like epinephrine (adrenaline) and isoprenaline are degraded enzymatically by catechol-*O*-methyltransferase and are relatively short-acting, their bronchodilator effect lasting 1–3 h after inhalation. Movement of the hydroxyl groups from the C-3,C-4 configuration on the catechol nucleus (Fig. 9.15) to the C-3,C-5 configuration on the resorcinol nucleus produces the intermediate duration of action (3–6 h) seen with orciprenaline, terbutaline and fenoterol (Figs 9.17–9.20). The substitution at the C-3 position also accounts for the intermediate duration of action of the saligenin salbutamol (4–6 h). These more selective  $\beta_2$  agonists have a slightly slower onset of action than isoprenaline. Two  $\beta_2$  agonists have a duration of action that exceeds 12 h, salmeterol and eformoterol (Fig. 9.16). Each compound has an extended side-chain and is highly lipophilic. It has been postulated that the long lipophilic side-chain of the salmeterol molecule anchors it to an 'exo-site' in close proximity to the active  $\beta$ -receptor site in such a way that prolonged

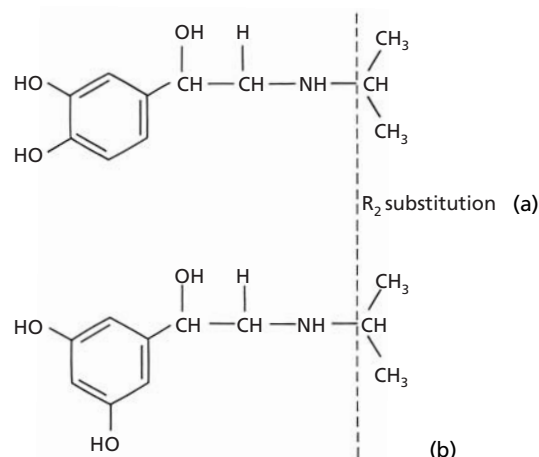


Fig. 9.20 Structure of (a) isoprenaline (isoproterenol) and (b) orciprenaline (metaproterenol).

Table 9.6 Sympathomimetic bronchodilators.

$\beta_2$ -selective	Non-selective
Salbutamol	Epinephrine (adrenaline)
Terbutaline	Ephedrine
Fenoterol*	Isoprenaline
Reproterol	Orciprenaline
Pirbuterol†	
Salmeterol†	
Eformoterol†	

\* Full agonist for cardiac  $\beta_2$  receptors.

† Longer-acting.

‡ not available in UK

activation by the saligenin head takes place. However, this has been questioned and it has been proposed that both salmeterol and eformoterol interact with, and are gradually released from, the cell membrane lipid bilayer (plasmalemma) over a prolonged period [407,408]. The speed of onset of action of eformoterol is similar to that for salbutamol, with peak bronchodilatation occurring at about 30 min, whereas salmeterol is slower, taking 1–2 h to achieve its maximal effect [409,410].

#### Mode of action

The  $\beta$  agonists produce bronchodilatation by stimulating  $\beta_2$  receptors situated in the smooth muscle of the bronchial tree, from the trachea down to the terminal bronchioles. This activates the enzyme adenyl cyclase [411], facilitating the conversion of ATP to cyclic AMP and resulting in the relaxation of smooth muscle in the bronchial wall. The cellular chemistry is complex but probably involves the activation of protein kinase with a reduction in ionic calcium concentration in bronchial smooth muscle [412]. Other potentially beneficial non-bronchodilator  $\beta_2$  effects include enhanced mucociliary transport, diminished

release of histamine and other chemical mediators of asthma from mast cells, inhibition of cholinergic neurotransmission and a possible increased ventilatory response to hypercapnia and hypoxia [407,413–416]. As a consequence of  $\beta$ -agonist activity, bronchoconstriction in response to both allergen challenge and exercise is reduced and the effect of corticosteroids tends to be potentiated [417,418]. Small increases in bronchial reactivity may be seen after the bronchodilating effect of  $\beta$  agonists has worn off [419,420]. It has not been possible to gauge the clinical significance of this but there is the theoretical risk of a serious asthmatic reaction to a given trigger factor in a patient whose airways are already hyperreactive [421]; this might be a particular concern in patients with labile asthma who were relying too heavily on  $\beta$ -agonist therapy and complying poorly with inhaled steroid treatment. All the  $\beta_2$  agonists currently available are racemic mixtures containing stereoisomers (enantiomers) of the same molecule. Research is currently ongoing to see if specific pharmacological effects can be related to individual stereoisomers, which if produced commercially in pure form might select desirable qualities and dispense with undesirable ones [422].

Regularly taken, long-acting  $\beta_2$  agonists do not have any significant anti-inflammatory actions and should not be used as substitutes for inhaled steroids.

### Potency

The potency of sympathomimetic bronchodilators can be expressed in terms of  $ED_{50}$ , i.e. the dose that produces a standard measured effect in 50% of subjects; the lower the  $ED_{50}$ , the greater the potency. Although the potency of the  $\beta_2$  agonists in Table 9.6 may vary according to the configuration of the chemical substitutions in the benzene ring and ethanolamide side-chain, this is of little practical consequence since the dose contained in one 'puff' of MDI 'A' is manipulated by the manufacturer to achieve the same effect as one 'puff' of a lesser dose of a slightly more potent compound 'B'. The same applies to tablet formulations: a 4-mg tablet of salbutamol is equipotent to a 5-mg tablet of terbutaline and 400  $\mu$ g of salbutamol by MDI is for practical purposes equipotent to 500  $\mu$ g of terbutaline. The discrepancy is much greater for eformoterol, the usual dose of which is only 12  $\mu$ g.

Although prolonged use of  $\beta$  agonists may lead to some  $\beta_2$ -receptor downregulation, there is no convincing evidence that tolerance (subsensitivity or tachyphylaxis) develops to the extent of presenting a significant clinical problem [407,423–428]. Tolerance to muscle tremor, increased heart rate and other systemic adverse effects has been observed [429,430].

Bronchodilatation following an oral or parenteral dose of  $\beta_2$  agonist is a function of the plasma level achieved, whereas this is not the case following an inhaled dose.

This has obvious and important implications for avoiding the tiresome systemic side-effects by inhaled rather than systemic administration of the drug [431].

### Administration

*Inhalation.* The  $\beta_2$  agonists may be taken in a variety of ways but the preferred route is inhalation from an MDI. About 10% of the fraction leaving the device reaches the lungs, the remainder impacting in the oropharynx and being swallowed. These small quantities nevertheless quickly (depending on the drug used) produce the desired bronchodilator effect in a responsive patient and although absorbed from the lungs, systemic side-effects are generally insignificant by comparison with an orally administered drug because of the microgram quantities involved. One of the principal disadvantages of this method is that it requires a modicum of coordination on the part of the patient, each dose being ideally inhaled from about functional residual capacity by a slow inspiratory manoeuvre with a breath-hold to the count of 10 at total lung capacity. The very young and the very old may not possess the necessary neuromuscular coordination to achieve this with conventional 'press and breath' inhaler devices, and arthritis or severe dyspnoea may also prevent proper administration by this route. Various methods have been devised to escape these difficulties: the inhalation of dry powder preparations; the use of 'spacer' devices of various shapes and sizes; the use of breath-actuated MDIs; and administration of drugs by wet nebulized aerosol. The last method of administration has become the standard method of bronchodilator delivery for patients with attacks of acute severe asthma, usually being as effective as parenteral therapy [432]. Used on a regular basis at home, compressed air nebulizers delivering  $\beta$  agonists and antimuscarinic bronchodilators are often popular with patients who have severe COPD, although objective evidence that they are more effective than MDIs is hard to come by, particularly if the latter are used with spacer devices [433–435]. These matters have been reviewed in detail elsewhere [436,437].

Inhaled therapy has the advantage of a rapid onset of action compared with the same drug taken orally; thus the inhaled non-catecholamine  $\beta_2$  agonists bronchodilate within 3–6 min, achieving 80% bronchodilatation in 5 min and reaching a peak in 30–60 min, with the effect wearing off over about 3–6 h. Those inhaled bronchodilators belonging to the catecholamine group, such as epinephrine (adrenaline) and isoprenaline have an even more rapid onset of action, bronchodilating within 1–3 min and peaking at about 5 min, so that isoprenaline has been useful in the lung function laboratory. However, their duration of action is shorter, so that their effect lasts for only 1–3 h. The only  $\beta_2$ -selective bronchodilator belonging to the catecholamine group was rimeterol and this shared the group

characteristic of being shorter-acting than the other  $\beta_2$  agonists, which are all non-catecholamines. However, it is no longer generally available. The rapidity of onset of isoprenaline and even epinephrine may account in part for the reluctance of the diminishing band of long-standing asthmatics, settled onto older bronchodilator preparations, to switch to newer and more selective  $\beta_2$  stimulants such as salbutamol, the onset of action of which is not quite so rapid. It used to be worth trying the effect of the selective catecholamine rimeterol (no longer available in the UK) in such patients. Another possible reason for the failure to achieve such a change in therapy is the CNS stimulating effect of some of the earlier unselective bronchodilators.

*Oral medication.* A very small proportion of patients need to take their sympathomimetic bronchodilator medication orally because of their inability to manage inhaled therapy. Oral medication has a slow onset of action, producing bronchodilatation after about 30 min and reaching a peak at 1–2 h. The plasma half-lives of some  $\beta_2$  agonists that are adequately absorbed from the gut and available in oral form are shown in Table 9.7. It should be noticed that terbutaline and fenoterol have relatively long half-lives so that twice-daily dosage may be adequate in some patients and this might be an advantage with regard to compliance. Fenoterol is not available as an oral preparation in the UK. Oral formulations of catecholamines such as isoprenaline are inadvisable as they undergo gastrointestinal inactivation by monoamine oxidase. The only exception is ephedrine but the non-selectivity and low potency of this drug argue against its use in modern practice.

Controlled-release oral formulations of terbutaline (7.5 mg) and salbutamol (8 mg) exist [438]. When taken on retiring at night, these sometimes prove to be a useful supplement to regular inhaled  $\beta_2$ -agonist and corticosteroid therapy in patients who continue to experience nocturnal symptoms despite optimal adjustment of their other therapy [439], alternatives being eformoterol, salmeterol and sustained-release theophylline. Bambuterol is a prodrug of terbutaline, with activity spanning 24 h; taken as a once-daily dose of 20 mg at night it may produce similar bronchodilatation to 5 mg terbutaline (standard release) three times daily [440] and may also be useful in nocturnal asthma [441].

*Parenteral medication.* The  $\beta_2$  agonists salbutamol and terbutaline are both available for parenteral administration in severe exacerbations of asthma. Both compounds behave similarly when administered by these routes. The onset of action is rapid, occurring within a few minutes, and the peak effect reached sooner than by inhalation, the duration of action being about 4 h [431]. Subcutaneous  $\beta_2$  agonists have also been given by continuous infusion at doses of 1–12 mg terbutaline per 24 h in ambulant but brittle severe asthmatics using small, portable, battery-powered mechanical pumps (e.g. Graseby MS26) connected to a short 25-gauge ‘butterfly’ needle, or by four equally divided injections spread over 24 h [442–445]. This continuous ambulatory method of administration has been found to be less successful in patients with chronic, severe, systemic steroid-dependent non-variable asthma [443]. The most rapid onset of action follows intravenous administration by slow bolus, followed, if required, by intravenous infusion (Table 9.8). The general clinical experience is that most patients with attacks of acute severe asthma respond as well to nebulized bronchodilator as to the same bronchodilator when given parenterally [432]. However, some patients with acute severe asthma who have a poor response to nebulized bronchodilator, possibly as a result of bronchial plugging, nevertheless respond to a parenteral  $\beta_2$  agonist [446].

Metabolism and excretion

Selective  $\beta_2$  agonists, if swallowed, may undergo some conjugation in the gut wall as well as in liver. Most are relatively resistant to metabolism by catechol-O-methyl-transferase, the enzyme that together with monoamine oxidase account for the shorter duration of action of members of the catecholamine group, such as epinephrine, isoprenaline and rimeterol. Those that are administered parenterally initially circulate in the plasma largely unchanged. Inhaled drugs also enter the circulation, but usually only in microgram quantities. Relatively small quantities of these drugs are excreted unchanged by the kidneys and dosage modification is unnecessary in renal insufficiency. They may slightly penetrate the blood–brain barrier and also cross the placenta so that oral medication is perhaps better avoided in pregnancy, although there is

Table 9.7 Oral  $\beta_2$ -sympathomimetic bronchodilators.

	Plasma half-life (h)	Usual oral dose	Tablet/capsule size (mg)
Salbutamol	4	4 mg t.d.s.–q.d.s.	2, 4
Terbutaline	11	5 mg b.d.–t.d.s.	5 (scored)
Orciprenaline	2	10–20 mg q.d.s.	20 (scored)
Fenoterol*	7	2.5–7.5 mg b.d.–t.d.s.	2.5

\* Not available in UK.  
Smaller doses may be needed in the elderly.

**Table 9.8** Parenteral  $\beta_2$ -sympathomimetic bronchodilators.

	s.c. bolus	i.v. bolus	i.v. infusion
Terbutaline	250–500 $\mu$ g	250–500 $\mu$ g	1.5–5 $\mu$ g/min
Salbutamol	500 $\mu$ g	250 $\mu$ g	5 $\mu$ g/min initially, then 3–20 $\mu$ g/min

For subcutaneous infusion, see text.

no evidence that administration of  $\beta_2$  agonists by MDI in this situation is harmful [447].

*Adverse effects*

The principal dose-limiting adverse effect of the selective  $\beta$ -agonist drugs is skeletal muscle tremor, particularly affecting the hands [448]. This is a consequence of  $\beta_2$ -receptor stimulation in skeletal muscle and is most commonly encountered following oral medication or high-dose inhaled therapy. It is seldom a problem with conventional quantities taken by MDI. Other problems that might arise with forms of administration producing high blood levels are muscle cramps and tachycardia, although serious dysrhythmias are rare. With the selective ( $\beta_2$ ) agonists, tachycardia is thought to be mainly a consequence of reduced peripheral vascular resistance, vasodilatation occurring as a result of the stimulation of receptors in vascular smooth muscle [449], although direct cardiac stimulation may occur as a result of some cardiac  $\beta_2$  receptors [407]. Patients who develop a tachycardia may feel generally unwell, with sweating, light-headedness and headache. Prolonged headache may be an occasional reason for patients refusing to take the long-acting  $\beta_2$  agonists salmeterol and eformoterol. Pre-existing angina pectoris may be aggravated, although this is seldom a practical problem [450]. Short-term metabolic effects of intravenous dosage include hypokalaemia, probably brought about by stimulation of pancreatic  $\beta_2$  receptors, resulting in increased insulin release and an intracellular potassium shift [451]. These adverse effects have led some to recommend that the plasma potassium and ECG should be monitored when intravenous  $\beta_2$  agonists are used in the treatment of asthma [452]. Similar fears have been voiced regarding large doses of nebulized  $\beta_2$  agonists [453], although these metabolic responses diminish with regular administration [454]. Non-specific effects of inhalation include dryness of the mouth, nausea, vomiting and gagging, but these are unusual. There have been a number of reports of paradoxical bronchoconstriction occurring after patients have taken  $\beta$  agonists by pressurized MDI or nebulization [455–457]. Such happenings, which are unusual, may be caused by the drug itself, some constituent of the propellant or its physical characteristics (pH, osmolality, temperature) [455–458]. It has been

pointed out that the potential exists for  $\beta_2$  agonists to worsen ventilation–perfusion mismatch in the short term. This may arise if pulmonary vessels that were previously reflexly constricted in response to local hypoxia are dilated by  $\beta_2$ -receptor stimulation so that blood is shunted into areas of lung still relatively poorly ventilated [459]. In cases where this might matter, this problem should be overcome by the administration of oxygen as a routine. The  $\beta_2$  agonists are uterine relaxants and have been used to prevent premature labour. In connection with this, profuse uterine bleeding has been reported in an asthmatic woman taking salbutamol prior to a termination of pregnancy [460]. Urinary retention is a largely theoretical risk but may occur if high blood levels are achieved in men with prostatic hypertrophy. Local dermal collagen necrosis may occur with prolonged subcutaneous administration of terbutaline [445].

*Asthma deaths and  $\beta$  agonists*

Non-selective adrenergic drugs (see Table 9.6) are more likely to cause cardiovascular side-effects than the  $\beta_2$ -selective preparations and wariness about  $\beta$ -agonist use in general has grumbled on since the retrospective association, made in a number of countries including the UK, New Zealand and Australia, between the asthma death epidemics of the 1960s and the widespread use at that time of a high-dose formulation (Medihaler Iso Forte) of the non-selective  $\beta$ -agonist isoprenaline, which contained five times the standard isoprenaline (Medihaler Iso) metered dosage (120  $\mu$ g) [461].

A similar epidemic of asthma deaths commencing in the mid-1970s was noted in New Zealand and was temporally linked by case–control studies with fenoterol, a  $\beta$  agonist that at the time was marketed only in a high-dose (200  $\mu$ g/puff) device [462]. Semantic argument continues as to whether this increased mortality was a consequence of the particular pharmacological properties of fenoterol itself or whether it represented a class effect that might arise from the excessive use of  $\beta$  agonists in general [463,464]. Discussion also continues about whether the subsequent decline in asthma mortality following the withdrawal of fenoterol as a prescription medicine in New Zealand in 1989 was a consequence of that action or of other variables, such as increased inhaled steroid use [465]. This decline in mortality occurred despite the sales of other  $\beta$  agonists continuing to increase, and no bronchodilators other than high-dose isoprenaline and fenoterol have been epidemiologically associated with increased asthma death rates. High doses of inhaled fenoterol in normal subjects have been shown to increase regional differences in myocardial repolarization as measured by the surface ECG interlead variability in corrected QT interval (so-called QTc dispersion) and it has been postulated that this might predispose to cardiac dysrhythmias, particularly in the presence of

hypoxia [466]. No significant differences in  $\beta_1/\beta_2$  receptor selectivity have been demonstrated between salbutamol and fenoterol in normal subjects [467], although fenoterol has been shown to be more potent on a microgram-for-microgram basis with regard to the production of systemic effects, such as hypokalaemia, muscle tremor and increase in heart rate, but not with regard to bronchodilator response, which is similar in the two drugs [468,469]. These observations are supported by *in vitro* data showing that fenoterol is a full agonist and is more potent on cardiac  $\beta_2$  receptors than salbutamol, which is a partial agonist [470]. The circumstantial evidence is strong that overuse of high-dose fenoterol in acute severe asthma in the 1970s and beyond carried with it a similar risk to that ascribed to high-dose isoprenaline in the 1960s [471].

A recent small case-control study found that patients admitted to intensive care units with attacks of asthma were more than twice as likely to be taking salmeterol than asthmatic patients admitted to ordinary hospital wards. However, it seems that this apparent association was discovered because (i) these patients had more severe asthma in the first place and were thus prescribed salmeterol and (ii) they were more likely to have severe exacerbations, these two variables not being causally connected [472,473].

With regard to the indisputably unselective agents, both epinephrine (adrenaline) and ephedrine may produce strong CNS stimulatory effects as well as peripheral effects such as pallor, tremor, palpitations and urinary retention. A study comparing 0.5 mg subcutaneous epinephrine with the same dose of subcutaneous terbutaline nevertheless found epinephrine to be equally effective and without serious side-effects in a small group of patients treated for acute severe asthma [474].

#### Dosage

The dosages of various  $\beta_2$  agonists are given in Tables 9.7–9.9. With the exception of the long-acting  $\beta$  agonists eformoterol and salmeterol, it is current practice to recommend that  $\beta_2$  agonists taken by MDI in asthma should be used 'as needed' rather than on a regular basis [475,476]. When peak expiratory flow was used as the main outcome measure, control of asthma was equally effective in a group of mild asthmatics, taking only  $\beta_2$ -agonist therapy, when salbutamol was taken 'as needed' rather than regularly [477]. The dose of epinephrine (adrenaline) in anaphylaxis is given below.

#### Principal uses in respiratory medicine

The clinical applications of  $\beta_2$  agonists and other bronchodilators are discussed in Chapters 23 and 35. It should be noted that in addition to relieving wheeze, they may be used to prevent or reduce it in patients with exercise-

**Table 9.9** Doses of inhaled  $\beta_2$ -sympathomimetic bronchodilators by metered-dose inhaler (MDI) and as nebulizer solution.

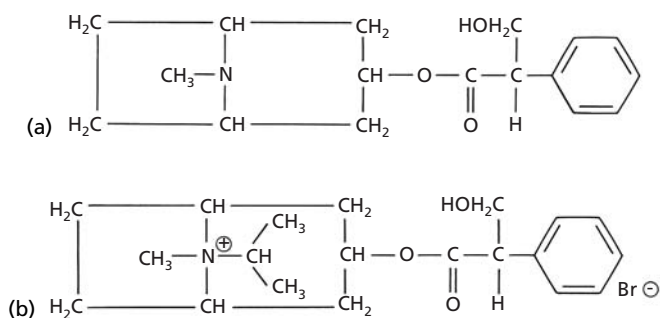
	MDI (1–2 puffs)	Nebulizer solution
Salbutamol	100–200 $\mu$ g	2.5–5 mg
Terbutaline	250–500 $\mu$ g	5–10 mg
Fenoterol	100–200 $\mu$ g	–
Reproterol	500–1000 $\mu$ g	–
Pirbuterol*	200–400 $\mu$ g	–

\*Not available in UK.

induced asthma [478]. This also applies to the long-acting  $\beta_2$  agonists eformoterol and salmeterol, eformoterol having a more rapid onset of action (see p. 245) [478–480]. These long-acting bronchodilators may also be useful as a single dose before bedtime for patients who continue to experience nocturnal wheeze despite otherwise optimal treatment, as an alternative to an oral sustained-release  $\beta_2$  agonist. The non-selective sympathomimetic agent epinephrine (adrenaline) is the drug of choice for treating anaphylaxis [481]. This may occur in a sensitized person following a bee or wasp sting, following a drug or after the administration of radiographic contrast medium. Epinephrine should be given to patients who develop bronchospasm, serious upper airway narrowing or hypotension with collapse. The dose is 3–5 mL of 1:10000 epinephrine intravenously if this route is accessible. If venous access cannot be achieved or if self-injection is used, then 0.3–0.5 mL of 1:1000 epinephrine is given subcutaneously or intramuscularly and is repeated after 15 min as required, since in severe anaphylaxis epinephrine by any parenteral route is better than none. About 10% of patients may require a second injection. Prompt treatment is usually met with a gratifying response, whereas delay may result in a fatal outcome.

#### Anticholinergic bronchodilators

The potential usefulness of anticholinergic drugs in the treatment of wheeze has long been recognized. Strümpell in the nineteenth century, while mentioning the beneficial effects of atropine and belladonna, stated that the 'stramomium cigarettes to be had in most drug stores are much praised' [482]. Stramomium, an atropine-related substance, is found in the leaves of the plant *Datura stramonium*. A major problem with atropine as a bronchodilator is its ability to cross the blood-brain barrier, with adverse neurological consequences such as restlessness, confusion, hallucinations, etc. With the availability of  $\beta$  agonists such remedies received little attention in modern times until the development of less-soluble synthetic quaternary ammonium analogues of atropine that could be taken by inhalation and which had fewer side-effects than the parent compound. The structures of



**Fig. 9.21** Structure of (a) tertiary ammonium compound atropine and (b) its quaternary ammonium derivative ipratropium bromide.

the synthetic substance ipratropium bromide and of the parent tertiary ammonium compound atropine are shown in Fig. 9.21 in order to illustrate the similarities between the two.

### *Ipratropium bromide and oxitropium bromide*

#### *Mode of action*

Atropine-like bronchodilators are anticholinergic, being competitive antagonists of acetylcholine, the neurotransmitter released at the effector surfaces of the parasympathetic vagal nerve endings. Acetylcholine acts on muscarinic (or smooth muscle) receptors situated in the airways causing bronchoconstriction and mucous secretion. Anticholinergic bronchodilators therefore oppose this action and result in smooth muscle relaxation within the airways, leading to bronchodilatation.

Experimental work has shown that electrical stimulation of the vagi produces mucous secretion and airway narrowing from the trachea to the large bronchi and that some narrowing is potentiated by anticholinesterase inhibitors and prevented by atropine [483,484]. Further work has shown that histamine and other mediators, chemical or mechanical irritation, and dust all produce bronchoconstriction, and that in some cases this may be experimentally abolished or diminished by vagotomy or anticholinergics [485–491]. There is therefore a reflex autonomic pathway by which irritant bronchial stimuli result in the passage of afferent signals to the vagal nuclei in the brainstem, from which efferent signals return to the lungs via the vagus nerve, causing release of acetylcholine at the neuromuscular junction. It is at this point that anticholinergic bronchodilators act by opposing vagally mediated bronchoconstriction. Improved understanding of the pharmacology of muscarinic receptors has led to the identification of three types in the lung. Blockade of two of these types, known as M<sub>1</sub> and M<sub>2</sub> receptors, opposes acetylcholine-mediated bronchoconstriction, whereas blockade of M<sub>3</sub> receptors may be counterproductive by

increasing acetylcholine release. The knowledge that both ipratropium and oxitropium are unselective muscarinic receptor antagonists has stimulated a search for more selective drugs in the hope that these will prove more effective bronchodilators. One such investigational drug is triatropium bromide, which has a prolonged action on M<sub>1</sub> and M<sub>2</sub> receptors and offers the promise of once-daily dosing [492].

Studies in normal subjects have implied that some normal bronchial tone is provided by the release of acetylcholine from vagal motor nerve endings and that atropine can variably inhibit reflex bronchoconstriction produced by irritants such as sulphur dioxide [493]. Anticholinergic drugs have also been shown to provide some protection from the effects on the airways of the muscarinic agonist methacholine, in both normal subjects and asthmatics [494]. Reports of their protective effect in bronchoconstriction caused by exercise and cold air are conflicting, some subjects being protected and others not [495,496]. Similarly reports of their protective effect in antigen challenge are contradictory, and  $\beta_2$  agonists have been found to be more effective [497].

Inhalation of anticholinergic agents produces a slower onset of bronchodilatation than that seen following  $\beta_2$  agonists, the maximum bronchodilator effect occurring between 60 and 120 min [498]. Half this response is achieved within 3 min and 80% of it by 30 min [499]; after peaking, the duration of action wanes gradually over the space of 6 h, lasting somewhat longer than most  $\beta_2$  agonists [499]. The rate of onset of action of oxitropium is similar to that of ipratropium. It has been claimed to have a longer duration of action, enabling twice-daily dosing, but this could reflect the relatively higher dose of oxitropium delivered by a single actuation of the MDI (100  $\mu$ g oxitropium vs. 20–40  $\mu$ g ipratropium). One study that compared the use of the two compounds in asthma found no difference in duration of bronchodilator effect [500].

#### *Administration, absorption and metabolism*

Ipratropium bromide is available for administration only by inhalation, either by pressurized and dry-powder MDIs or in the form of a 0.025% solution for use with a jet nebulizer. Oxitropium is available for administration only by pressurized MDI. Unlike their parent compound atropine, they are relatively lipid insoluble. This property has largely overcome the adverse effects encountered as a result of the absorption of inhaled atropine sulphate when this substance was used as a bronchodilator [501]; furthermore, unlike atropine, ipratropium and oxitropium do not cross the blood–brain barrier and produce no central effects [502]. The minute amounts absorbed from the respiratory and gastrointestinal tracts are metabolized and excreted both in inactive form and as the parent compound in the urine.

### *Dosage*

Ipratropium bromide is an effective bronchodilator when given by MDI (pressurized or dry powder) at a standard dose of 40 µg three to four times daily. As the drug is well tolerated, its effect may sometimes be augmented by doubling the dose. This may be achieved by using a proprietary inhaler that delivers 80 µg per two inhalations. The drug is also available as a 0.025% solution for administration of up to 500 µg (2 mL) 6-hourly by nebulizer. The dose of oxitropium bromide is 200 µg three or four times daily by pressurized MDI.

### *Adverse effects*

The effects of belladonna poisoning have long been recognized [503], systemic absorption of atropine producing tachycardia, blurring of vision, urinary retention, drying of mucous secretions and central effects including mental confusion. Fortunately the lipid solubility of ipratropium prevents significant absorption and avoids most of these problems. However, an unpleasant taste and dryness of the mouth are sometimes noticed with this drug. There has been concern that ipratropium might cause drying of the respiratory secretions, resulting in impaired mucociliary clearance, but work using radioactively labelled inhaled particles in patients with airflow obstruction has failed to show that this occurs even at high inhaled doses of ipratropium [504]. Occasional paradoxical bronchoconstriction has occurred [505]; this was probably the result of the hypotonicity of the original nebulizer solution, a physical property that has now been corrected [506]. Others have suggested that the bromide radical contained in the molecule (Fig. 9.21) may cause an idiosyncratic hypersensitivity reaction in some patients [507], although this has not been confirmed. Later work showed that preservatives such as benzalkonium chloride and EDTA present in earlier formulations of ipratropium bromide solution could cause bronchoconstriction [508]. These have now been removed by the manufacturers. The acidity of the nebulizer solution has been suggested as a possible cause of bronchoconstriction in infants [509].

Just as respiratory physicians see patients who wheeze as a result of the topical ocular application of  $\beta$ -blocking drugs such as timolol prescribed by ophthalmologists for glaucoma, so our colleagues in the eye clinic occasionally see patients with the ocular emergency of acute angle closure glaucoma caused by nebulized ipratropium [510]. The problem arises because nebulized ipratropium escapes around the edge of a face mask and comes into contact with the eyes [511]. This relaxes the smooth muscle of the iris, dilating the pupil and causing the iris to come into contact with the lens. This blocks the flow of aqueous humour from its site of production in the ciliary body through the pupil into the anterior chamber, so that pres-

sure builds up in the posterior chamber [512]. Patients may complain of misty vision and headache, and sometimes coloured haloes (caused by corneal oedema) may be seen around bright lights. These patients may be found to have a red eye and semi-dilated fixed or sluggish pupil. The cornea may appear cloudy. One or both eyes may be affected. Treatment is by lowering the intraocular pressure medically and an urgent referral to an ophthalmologist is made. Failure to treat may result in permanent visual loss or blindness. Predisposed individuals are hypermetropic (long-sighted) with a shallow anterior chamber and may be identified by holding their convex distance lenses close to small print, which will be magnified [513]. The problem may be avoided by using a mouthpiece rather than a mask for nebulization or, if this is impracticable, by taping the top of the mask to the face at the level of the eyes.

### *Principal uses in respiratory medicine*

Anticholinergic drugs only act on the vagally mediated component of reflex bronchoconstriction, whereas  $\beta$  agonists relax smooth muscle irrespective of the nature of the constrictor stimulus and are more effective as bronchodilators in asthma, in which condition a variety of non-neurally mediated bronchial challenges might act as triggers. Despite these considerations, ipratropium bromide has been shown to have a significant bronchodilator effect in patients with asthma in the acute and non-acute setting [514–516], and also in patients with COPD with some potential for reversibility of airflow limitation [499,517], which in this group may partly result from increased vagal tone. The maximal bronchodilator effect of anticholinergic agents is achieved more slowly than that seen with  $\beta_2$  agonists [498], and the peak bronchodilator effect achieved with  $\beta_2$  agonists is probably somewhat greater in asthma than is the case with ipratropium [518]. For these various reasons, ipratropium bromide is not a first-choice bronchodilator in the treatment of asthma. The value of ipratropium in the prophylaxis of exercise-induced asthma is also limited [495,519] and it is common experience that  $\beta_2$  agonists are more effective. Differences in airway responsiveness between ipratropium and  $\beta_2$  agonists are likely to be small and of doubtful clinical significance in COPD [520], a clinical state in which 'reversibility' itself is likely to be small as a result of the underlying pathological processes. There is nevertheless retrospective evidence to suggest that extended treatment with an inhaled anticholinergic agent produces improved lung function in patients with COPD [521].

The combination of a  $\beta_2$  agonist with an anticholinergic drug is pharmacologically enticing, as an additive effect might be expected. A number of studies, over both the short and longer term, have claimed to show benefit from



combination therapy in both asthma and COPD. Again, such improvements are usually small so that some workers report no benefit whereas others report 'trends' that fail to reach statistical significance [522]. This suggests that in most patients any improvement in either ventilatory capacity or duration of action resulting from combination therapy is likely to be of dubious clinical significance and that anticholinergic agents such as ipratropium are not first-line agents in conditions presenting with airflow limitation [495,522,523]. However, there are data which suggest that nebulized ipratropium and salbutamol given together sometimes produce a better response than either drug alone in severe asthma [524]. In the same clinical situation, it has also been claimed that sequential nebulized ipratropium given 2 h after nebulized salbutamol produces a greater effect than simply repeating the same dose of salbutamol [525]. A comparison of nebulized salbutamol and ipratropium with salbutamol alone found no benefit from the combination in hospitalized patients treated for acute exacerbations of COPD [526], so that a better practice might be to give the  $\beta_2$  agonist first and to add ipratropium later if the patient is not progressing satisfactorily. Whatever the evidence, it has been common hospital practice in severely breathless patients admitted with either acute severe asthma or COPD to give a combination of nebulized  $\beta_2$  agonist and ipratropium, and hard-pressed house staff may find the 2-hourly check for sequential treatment theoretically attractive but often practically unachievable.

There also seems, on present evidence, to be no good reason for using a combination dose of a  $\beta_2$  agonist and ipratropium in a single proprietary MDI as a first choice in the treatment of asthma or COPD; these inhalers currently provide 90–100  $\mu\text{g}$ /puff salbutamol and 18–20  $\mu\text{g}$ /puff ipratropium (USA and UK) or 100  $\mu\text{g}$ /puff fenoterol and 40  $\mu\text{g}$ /puff ipratropium as marketed in the UK [527]. A double-blind trial comparing the effect of a metered-dose combination of salbutamol 100  $\mu\text{g}$ /puff and ipratropium 20  $\mu\text{g}$ /puff with either drug alone in a large group of patients with moderately severe COPD found significantly greater improvements in  $\text{FEV}_1$  in patients receiving the combination, although in absolute volumetric terms the improvements were small and there were no significant improvements in peak expiratory flow or symptom scores [528].

The discrepancies in the responsiveness of patients with asthma or COPD to ipratropium may be explained by individual differences in the contribution of the parasympathetic nervous system to bronchoconstriction. Thus in some patients neural reflexes may be potent, and it is possible that chronic bronchial inflammation or respiratory epithelial damage may provoke a bronchial smooth muscle response by neural pathways rather than by the local release of cellular mediators [529]. Clearly, parasympathetic neural responses only represent one of many

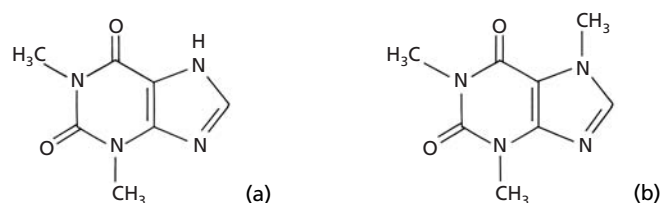


Fig. 9.22 Structure of (a) theophylline and (b) caffeine.

different pathways of bronchial airway responsiveness [484,530].

Ipratropium may be effective for watery rhinorrhoea when used as a topical nasal spray at a dose of 42  $\mu\text{g}$  (two sprays) to each nostril two to four times daily [531].

### Theophylline and related compounds

Theophylline is a naturally occurring member of a group of compounds known as methylxanthines and is the oldest asthma medication still in routine use. It is found in the leaves of the tea plant and is closely allied chemically to caffeine, another methylxanthine also found in tea, coffee and chocolate (Fig. 9.22). Strong coffee was recognized as an asthma remedy in the nineteenth century and theophylline continues to be widely prescribed for the relief of wheeze. The use of theophylline waned with the discovery of a seemingly safe and effective method of bronchodilatation in the form of inhaled  $\beta_2$  agonists and because of the side-effects encountered with earlier more rapid release xanthine preparations. However, there was a revival of interest in this drug following the introduction of various sustained-release preparations, which have been increasingly used particularly when  $\beta_2$  agonists or other treatment has produced an inadequate response [532]. Aminophylline is a salt of theophylline that has been made more soluble than the parent compound at neutral pH by the addition of an otherwise therapeutically useless ethylenediamine radical, and for many years has had an 'add on' parenteral role in patients with severe airflow limitation. Choline theophyllinate is a further salt of theophylline that has no particular advantage over the parent compound.

#### Mode of action

The clinical effects of theophylline appear to result from the inhibition of phosphodiesterases, the antagonism of adenosine receptors and other molecular mechanisms that are as yet ill understood [533,534]. Methylxanthines have been known for years to inhibit cyclic nucleotide phosphodiesterase (PDE), thereby retarding the hydrolysis and breakdown of cyclic AMP and cyclic GMP. The increased intracellular concentrations of cyclic AMP (cf. mode of action of sympathomimetic bronchodilators) and cyclic

GMP that result are associated with smooth muscle relaxation in the bronchial walls and it was thought that this mechanism was sufficient explanation for the action of theophylline [535]. One problem with this explanation for the effects of theophylline is the experimental evidence suggesting that for PDE inhibition to occur, much higher levels of theophylline would need to be attained than are clinically possible [536]. It is now recognized that PDE comprises several families of isoenzymes that not only act on airway smooth muscle but also have effects on those inflammatory cells implicated in the processes by which airways become hyperactive in diseases such as asthma [537]. Theophylline is an unselective PDE inhibitor and the knowledge that certain PDE isoenzymes, such as types 3 and 4, are more potent than others at relaxing airway smooth muscle [538] has led to the search for specific PDE isoenzyme inhibitors [539], a quest that has not so far borne clinical fruit. PDEs are also present in inflammatory cells and PDE-4 is the predominant isoenzyme in this regard, being found in eosinophils, neutrophils, monocytes, alveolar macrophages and T lymphocytes [537,540]. This knowledge has given added impetus to pharmaceutical efforts to exploit any anti-inflammatory and immunomodulatory effects of specific PDE-4 inhibitors that might prove to be clinically significant [492]. Another mechanism of action other than PDE inhibition is the antagonism of adenosine receptors [541]. This may not cause bronchodilatation *per se* but could have some clinical effects by reducing diaphragmatic muscle fatigue, as well as acting centrally to increase ventilation during hypoxia and also reducing mediator release from mast cells [534,542–545]. Other effects of doubtful significance include prostaglandin and other mediator inhibition [542,546], and the alteration of intracellular calcium ion concentrations [542,547].

*Administration, metabolism and excretion*

Xanthines are usually administered orally in one of three chemical formulations: theophylline, aminophylline (theophylline and ethylenediamine) and choline theophyllinate. In addition to the ‘plain’ preparations, there are currently six different proprietary modified-release formulations listed in the *British National Formulary* [58]. These have been designed to maintain therapeutic plasma levels for up to 12 h, so that not more than two doses are required daily.

Absorption of ‘plain’ preparations from the gut is rapid and complete, the peak plasma level being achieved in about 1.5 h. The plasma half-life is very variable between subjects but is about 6–8 h on average, so that at least three doses daily are usually needed for a continuous effect. Modified-release preparations tend to achieve a peak plasma level about 4–6 h after a morning dose. Absorption may be slower during the night so that the peak level may

be achieved 8 h after a bedtime dose. The half-life is also variable but allows twice-daily dosage, a relatively steady state being achieved after 3 days on a given dose. Once-daily dosing does not provide adequate plasma concentrations for 24 h, levels tending to fall outside the therapeutic range by about 14 h, so that this approach is best adopted when treating nocturnal symptoms [548]. Ordinary (short-acting) formulations peak at about 2 h and elixirs after about 15 min. About half the drug is protein-bound and the average volume of distribution is 0.5 L/kg, an observation used when calculating the dose from plasma levels (see below).

Xanthines undergo metabolism by the P450 microsomal enzyme system in the liver, with quite wide variations in rate between individuals. Less than 20% of the oral drug is excreted in the urine unchanged, the remainder being accounted for by relatively inactive metabolites [549]. The plasma half-life of all the xanthine bronchodilators can be affected by the various factors listed in Table 9.10. For example, tobacco (or cannabis) produces a shorter theophylline half-life as a result of microsomal liver enzyme induction and thus theophylline clearance may remain enhanced for over 3 months after tobacco abstinence [550,551]. Clearance is also enhanced by liver enzyme-inducing drugs such as rifampicin, phenobarbital (the level of which may itself be lowered by theophylline) and other anticonvulsants. On the other hand, clearance is reduced and the half-life prolonged with increasing age, with liver disease including congestion or hypoxia due to heart failure, in febrile illness, if the diet is low in carbohydrate and high in protein, and if the patient takes various drugs, including cimetidine, macrolides, ciprofloxacin, isoniazid, fluconazole, calcium-channel blockers and the antidepressants fluvoxamine and viloxazine (see Table 9.10), in which situations toxicity is more likely to be

**Table 9.10** Factors affecting theophylline elimination (see text).

Decreased elimination (theophylline level increased)	Increased elimination (theophylline level decreased)
Erythromycin and other macrolides	Tobacco or cannabis smoking
Ciprofloxacin*	Rifampicin
Cimetidine	Phenobarbital
Norfloxacin	(phenobarbitone)
Fluvoxamine*	and primidone
Combined oral contraceptives	Carbamazepine
Diltiazem/verapamil	Phenytoin
Allopurinol (high dose)	Youth
Old age	
Cardiac failure	
Liver disease	
Hypoxaemia	
Viral infection	
Fever	

\* Halve dose of theophylline.

encountered [552–555]. Potentiation of xanthines is particularly strong with ciprofloxacin and fluvoxamine, so that the Committee on Safety of Medicines recommends that if xanthines are used together with either of these then the dose of xanthine should be halved. A 75% reduction in the dose is recommended if theophylline is used in the presence of hepatic cirrhosis. The drug crosses the placenta but there is no evidence of teratogenicity. It also appears in breast milk.

Aminophylline may be given intravenously in the management of severe asthma but safer alternatives such as nebulized  $\beta_2$  agonists should be used first, and parenteral aminophylline omitted if the patient usually takes an oral theophylline preparation, at least until plasma levels are known, so that dangerous toxicity may be avoided. The care with which this situation should be handled highlights the principal drawback of the theophyllines, i.e. their narrow therapeutic index, the margin between a satisfactory therapeutic result and the development of toxic side-effects often being uncomfortably small. This problem can only be adequately addressed by making use of plasma theophylline assays and this is discussed in the following sections.

The pharmacokinetics of parenteral theophylline are apparently unaffected by oral corticosteroid therapy [556].

#### *Oral dosing and plasma theophylline levels*

Sustained (modified)-release preparations are preferred if an oral xanthine drug is used. The modified-release preparations [58] are all similar in their effects but individual brands are not interchangeable dose for dose because of their different theophylline release mechanisms. Many patients are put on one or two such tablets once or twice daily and left to take them indefinitely, often with no objective assessment of effect on the part of the physician and without any clear subjective improvement on the part of the patient, many of whom are undertreated. As well as theophylline having a narrow therapeutic index, there are also wide intersubject variations in the rate at which it is metabolized, so that if these drugs are to be useful then the maximum bronchodilator effect has to be sought by measuring plasma levels and manipulating the dosage within the usual therapeutic range of 10–20 mg/L. Chemistry laboratories in the UK have long been wedded to SI rather than mass units, even for reporting drug levels, despite the merciful fact that drugs are still prescribed in mass units. Conversion from mass units to SI is obtained by multiplying by 5.5, giving a therapeutic range of 55–110  $\mu\text{mol/L}$ ; the opposite conversion is achieved by multiplying by 0.18. The American Thoracic Society, recognizing that significant benefits may occur within a lower dose range, has recommended that clinicians should initially aim for plasma concentrations of 5–15 mg/L (27.5–82.5  $\mu\text{mol/L}$ ) [557]. The therapeutic range for theophyllines is intended

for guidance only, as useful bronchodilatation may occur below this range in some patients and will continue without side-effects if the upper figure is exceeded in others. However, it is clear that dosages may be safely increased at concentrations below 10 mg/L (55  $\mu\text{mol/L}$ ) and that serious toxicity is much more likely if blood levels are allowed to exceed 20 mg/L (110  $\mu\text{mol/L}$ ) and that fatal accidents may occur at 25 mg/L (137.5  $\mu\text{mol/L}$ ) or more [532,558]. Toxicity becomes unusual at levels below 15 mg/L (82.5  $\mu\text{mol/L}$ ), but may occur in about 15–20% of patients within the usual therapeutic range of 10–20 mg/L (55–110  $\mu\text{mol/L}$ ). As patients vary widely in the dose required to keep the plasma level therapeutic [559], a 'recipe book' approach is inappropriate and theophylline levels should be measured. These may be taken 2–3 days after onset of treatment or change in dose. An initial dose of about 10 mg/kg daily is used [560], peak plasma levels being measured 4–6 h after the morning dose of a sustained-release product, so that the drug may be swallowed in the morning and the sample taken in the afternoon. Trough levels may be obtained immediately before the next dose is due but are in practice seldom measured. When the trough level is low with a long-acting preparation, attempts should not be made to increase the level by upward adjustment of the dose before ensuring that the peak level is not approaching the upper limit of the therapeutic range, otherwise peak level toxicity may be produced [561]. A linear relationship has been obtained between the logarithm of the plasma theophylline concentration within the range 3–20 mg/L (16.5–110  $\mu\text{mol/L}$ ) and  $\text{FEV}_1$  [562], so that incremental increases in concentration of the drug at levels below 10 mg/L (55  $\mu\text{mol/L}$ ) produce only small changes in  $\text{FEV}_1$ , whereas above this level more substantial increases in  $\text{FEV}_1$  are produced.

It is of some importance that patients who are already stabilized on one brand of modified-release theophylline or aminophylline should stay on the same brand as there are variations in bioequivalence between different makes, and thus the brand name rather than the generic name should therefore be stated on prescriptions.

#### *Intravenous dosing and plasma theophylline concentrations*

Patients who are ill enough to require admission to hospital with asthma or COPD and who do not respond to nebulized bronchodilators and other measures are frequently considered for treatment with intravenous aminophylline by infusion. Before commencing such an infusion, a loading dose may be given over the space of 30 min in order to achieve a therapeutic level without undue delay, while at the same time exercising sufficient caution to avoid the untoward effects that may follow a more rapid injection. It should first be established that the patient was not taking xanthines, including certain 'over the counter' proprietary preparations, prior to admission. If there is

doubt about this, an urgent level should be requested. In order to make the calculations, the volume of drug distribution ( $\text{Vol}_D$ ) is assumed to be 0.5 L/kg (i.e. half the patient's body weight in kg =  $\text{Vol}_D$  in litres) and the loading dose ( $\text{Dose}_L$ ) can be calculated according to the equation:

$$\text{Dose}_L = \text{Conc}_{PD} \times \text{Vol}_D \quad [9.3]$$

where  $\text{Conc}_{PD}$  is the desired plasma theophylline concentration (mg/L). As  $\text{Vol}_D$  may vary according to the state of hydration and other factors, it is suggested that the lower end of the therapeutic theophylline range is aimed for, i.e. 10 mg/L (55  $\mu\text{mol/L}$ ). Thus for a 60-kg patient on no xanthine treatment within the last 24 h:

$$\text{Dose}_L (\text{mg}) = 10 \times 30 = 300 \text{ mg aminophylline}$$

In the case of patients who have already been taking oral theophylline or in whom there is any suspicion that they might have done so, the plasma theophylline level must be obtained before any loading dose is given, otherwise the chance of serious toxicity is increased [563]. Once the plasma theophylline level is available, the reduced loading dose can be calculated according to a modification of Eqn 9.3 as follows:

$$\text{Dose}_{LM} = (\text{Conc}_{PD} - \text{Conc}_{PM}) \times \text{Vol}_D \quad [9.4]$$

where  $\text{Dose}_{LM}$  is the modified loading dose (mg) and  $\text{Conc}_{PM}$  is the measured plasma theophylline concentration (mg/L) before the modified loading dose. Once again, as  $\text{Vol}_D$  may vary according to the patient's state of hydration and other factors, it is suggested that the lower end of the therapeutic theophylline range is aimed for, i.e. 10 mg/L (55  $\mu\text{mol/L}$ ). Thus for a 60-kg patient in whom  $\text{Conc}_{PM}$  is found to be 5 mg/L (27.5  $\mu\text{mol/L}$ ):

$$\text{Dose}_{LM} = (10 - 5) \times 30 = 150 \text{ mg aminophylline}$$

This dose may be infused over 30 min before commencing the maintenance infusion. A further theophylline estimation may be carried out 15 min after completing the loading dose to determine the peak level. In practice, although more rapid analytical techniques are being developed [564], by the time the pre-dose plasma theophylline measurement has been obtained from the laboratory, many patients will have responded to a nebulized  $\beta_2$  agonist or a parenteral  $\beta_2$  agonist (subcutaneous or intra-

venous terbutaline or salbutamol) and the aminophylline infusion may prove unnecessary. Assuming that this is not the case and that the post-loading dose level is therapeutic, then a maintenance infusion may be commenced at a rate of 0.5 mg/kg/h. This dose may need adjustment upwards to about 0.9 mg/kg/h in children or young adult smokers, or reduction by about half in patients with right heart failure or liver disease [558,565,566]. Plasma theophylline levels may be checked 4–6 h into the infusion or at any time if toxicity is suspected.

Rectal administration of aminophylline in suppository form, although used in the past to improve nocturnal wheeze, produced inadequate blood levels [567], sometimes causing irritant proctitis, and has been superseded by the administration of a modified-release oral preparation at night-time, if indeed a xanthine preparation rather than a long-acting  $\beta_2$  agonist is chosen for this purpose.

In general, oral theophyllines are as effective bronchodilators as oral  $\beta_2$  agonists but carry the same disadvantage that their therapeutic effect is, unlike inhaled bronchodilators, directly related to their plasma level so that adverse effects are more liable to occur.

#### Adverse effects

Theophylline has a narrow therapeutic index, i.e. significant adverse effects (Table 9.11) may occur at plasma concentrations close to those needed to produce bronchodilatation. The most common side-effects of xanthines are nausea, insomnia, nervousness and headache (as might be experienced after taking too much tea or coffee). Such symptoms are more likely to occur if the plasma theophylline concentration increases rapidly above 10 mg/L (55  $\mu\text{mol/L}$ ) and may be avoided if care is taken to increase the dose gradually [568]. Other gastrointestinal symptoms include anorexia, vomiting and diarrhoea. About 5% of patients may experience unacceptable gastrointestinal symptoms at plasma concentrations below 14 mg/L (77  $\mu\text{mol/L}$ ) [569]. These symptoms usually abate quickly if a dose is omitted and subsequent downward adjustment made. The most serious adverse effects are major seizures and ventricular tachydysrhythmias. These are rare at levels below 55 mg/L (110  $\mu\text{mol/L}$ ), tending to occur with blood levels exceeding 30 mg/L

**Table 9.11** Adverse effects of theophylline.

Gastrointestinal	Neurological	Cardiovascular	Allergic
Nausea	Headache	Cardiac dysrhythmias	Rashes
Anorexia	Tremor	Flushing	Pruritis
Vomiting	Irritability		Fever
Abdominal pain	Insomnia		
Diarrhoea	Confusion		
	Dizziness		
	Tinnitus		
	Major seizures		

(165  $\mu\text{mol/L}$ ). Such levels may be the result of gradual overdosage from an infusion, slow-release oral product or an inappropriately rapid intravenous bolus injection. Clearly, in an already hypoxic patient struggling to breathe as a result of severe bronchoconstriction, a grand mal seizure may deliver the *coup de grâce* and should be avoided at all costs. Rarely, an allergic reaction to the ethylenediamine component of aminophylline may occur, with an erythematous or urticarial rash; occasionally exfoliative dermatitis has been reported [570].

As with any oral medication, deliberate overdosage may occur [571,572]. When recent oral overdosage has occurred and the patient is conscious, gastric lavage or emetics may be used and can be followed by repeated oral doses of activated charcoal [573]. If this proves impracticable, charcoal haemoperfusion may need to be considered [574]. Serious overdosage can produce ventricular tachydysrhythmias and convulsions and may result in fatality [532,575,576].

#### *Principal uses in respiratory medicine*

Theophyllines are widely used in the management of asthma (see Chapter 35) and COPD (see Chapter 23). In the UK, their usual application in asthma is as supportive oral treatment in more chronic asthmatics whose symptoms are inadequately controlled with a  $\beta_2$  agonist and inhaled steroid alone [577] and also in patients with nocturnal wheeze [578], modified-release preparations being used in both cases. A recent study of patients with moderate asthma who had persistent symptoms showed that the addition of theophylline to low-dose inhaled glucocorticosteroid produced similar benefits to changing to high-dose inhaled steroid [579].

Intravenous aminophylline may be effective in acute severe asthma or exacerbations of chronic obstructive lung disease in those patients who remain profoundly ill despite treatment with nebulized or parenteral  $\beta$  agonists. However, it should be used with caution, as outlined above, because of the risks of serious toxicity [580].

The place of oral theophylline in COPD is more controversial, some studies having found improved effort tolerance, others not [581–584].

### **Non-steroidal prophylactic drugs for use in asthma**

#### *Sodium cromoglicate*

Sodium cromoglicate (sodium cromoglycate, cromolyn sodium) is a synthetic bis-cromone with a distinctively symmetrical molecular structure (Fig. 9.23). It was synthesized in the UK in 1965 following the observation that a related botanical substance, khellin, contained in folk medicines had asthma-relieving properties [585]. Sodium

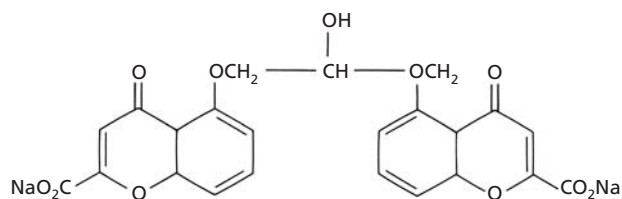


Fig. 9.23 Structure of sodium cromoglicate.

cromoglicate has no direct bronchodilator properties but has nevertheless proved very useful in certain aspects of prophylactic asthma management.

#### *Mode of action*

The mode of action of sodium cromoglicate is incompletely understood. It is known to have a stabilizing effect on mast cell membranes so that the release of various chemical mediators of asthma within the airway wall is inhibited [586]. As a result of the practical observation that sodium cromoglicate was particularly effective in asthma in which extrinsic allergic factors were clinically obvious, it was thought that mast cell stabilization might be due to a direct blocking action on early-phase IgE antibody-antigen reactions. However, it has subsequently become clear that sodium cromoglicate can also prevent or reduce non-allergic bronchoconstriction, such as that following exercise [587,588], exposure to cold air [589] or chemical irritants such as sulphur dioxide [590]. It has been suggested that mast cell stabilization may be brought about by the phosphorylation of a high molecular weight protein that results in the blocking of ionic calcium transport across the cell membrane [591]. The view that mast cell stabilization cannot account for all the actions of sodium cromoglicate is supported by the observation that other more potent mast cell stabilizing substances may be clinically ineffective in asthma [592]. There is some experimental evidence to suggest that sodium cromoglicate may exert a possible neural effect, suppressing the activity of sensory nerve endings in the lungs [593]. Studies carried out on the bronchial secretions and blood of asthmatics treated with sodium cromoglicate have shown that this form of therapy may be associated with a reduction in eosinophil counts in the blood, sputum and bronchoalveolar lavage fluid, as well as a reduction in allergen-specific plasma IgE. It is also evident that, in addition to its early-phase mast cell stabilizing effect, sodium cromoglicate also reduces those late-phase asthmatic responses mediated by other inflammatory cells such as neutrophils, eosinophils and monocytes [594].

#### *Administration and excretion*

Sodium cromoglicate was originally made available as a

dry micronized powder contained in capsules and administered using a pocket-sized tubular device into which the powder was released automatically and from which it was sucked by the patient through a small turbine. This method of administration is still useful in children who are not old enough to master the pressurized MDI. A 1% aqueous solution of sodium cromoglicate is available for nebulization and has a limited application for patients (usually small children) who are too young to use either of the other devices.

As with all medications administered by inhalation, most of the dose becomes impacted in the mouth and throat and is subsequently swallowed, being excreted unchanged in the faeces. Approximately 1–2 mg of the standard 20 mg inhaled powder dose reaches the lungs [595]. This is absorbed into the blood and excreted unchanged, about half in the urine and the remainder in bile [588]. The plasma half-life is about 80 min. It does not cross the placenta or blood–brain barrier. A sodium cromoglicate nasal spray is available for the treatment of allergic rhinitis, as are ophthalmic drops for conjunctivitis.

#### *Dosage and modes of use*

The standard inhaled dry powder dose is one 20 mg capsule four times daily initially. In addition to the active drug, each capsule also contains 20 mg of lactose carrier. Two inhalations (2 mg) four times daily from the MDI is considered a clinically equipotent dose, although the manufacturers have substituted a higher-strength MDI in Europe that delivers 5 mg per actuation. A solution containing 20 mg sodium cromoglicate in 2 mL of water is also available and has to be taken using a nebulizer.

Ideally, when sodium cromoglicate therapy is commenced the preparation should be taken regularly four times daily, with peak flow charting to assess the response. The treatment should not be abandoned unless there has been no improvement at 3–4 weeks despite good patient compliance. If a good response is achieved, then small decremental dose reductions may be possible but patients, or their parents, need to be discouraged from being over-hasty about this and it is common, when a clear response has been achieved, for a twice, three or four times daily dose to be continued for months or years. The most encouraging results occur in children with obviously allergic asthma, although good results may be obtained in some adults. Response is difficult to predict [596] and if objective improvement is not achieved then sodium cromoglicate should be discontinued. Patients need to be told that an improvement may take a good 2 weeks to become evident.

Patients whose symptoms occur seasonally should start regular sodium cromoglicate a few weeks before the anticipated onset of wheeze and should continue regularly until the end of their 'season'.

In addition to regular prophylactic use, sodium cromoglicate can also be taken to forestall exercise-induced asthma, 20 mg of powder or a 10-mg metered-dose inhalation being taken about 30 min before the anticipated exertion. Occasionally a higher dose of sodium cromoglicate is required to prevent exercise-induced asthma, using the MDI that delivers 5 mg per actuation. Sodium cromoglicate is commonly 'added on' to a separately inhaled  $\beta_2$  agonist if control of exercise-induced asthma with the latter alone is poor.

There is no good pharmacological indication for taking sodium cromoglicate and a  $\beta$  agonist in combined dry powder form. However, some clinicians have prescribed such formulations as a ruse to get preventive medication into the lungs of patients who would be unlikely to comply with prophylactic treatment but who can be depended upon to 'dose up' with bronchodilator.

#### *Adverse effects*

Sodium cromoglicate must be one of the safest medications available for prescription and this is an important reason for its attraction in paediatric practice. Side-effects have been reported in about 2% of patients. These are mild and may take the form of pharyngeal irritation, occasionally the dry powder form producing cough and wheeze, in which case a  $\beta_2$  agonist may be taken first or the patient switched to the pressurized MDI. Skin rashes may rarely occur [597].

The place of sodium cromoglicate in the wider scheme of asthma management is discussed in Chapter 35.

#### *Nedocromil sodium*

Nedocromil sodium is the disodium salt of a paraquino-line tricyclic dicarboxylic acid (Fig. 9.24). Although chemically unrelated, it has a somewhat similar profile of action to sodium cromoglicate, also affecting both the early and late responses in asthma.

#### *Mode of action*

The mode of action of nedocromil is not fully understood. Like sodium cromoglicate, it has been shown to stabilize mast cells and to inhibit *in vitro* mediator release and activation of other inflammatory cells [598,599]. It has been

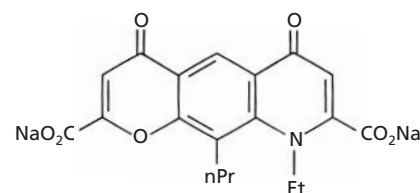


Fig. 9.24 Structure of nedocromil sodium.

shown to inhibit antigen-induced inflammatory mediator release from bronchoalveolar lavage cells in experimental animals [600]. As with sodium cromoglicate, it has also been found to inhibit the bronchoconstrictor response to various immunological and non-immunological stimuli in humans [598,599]. It may protect against exercise-induced asthma and against bronchoconstriction induced by both antigen challenge and other non-specific stimuli including sulphur dioxide [599,601–604]. It has been speculated that, like sodium cromoglicate, nedocromil may also have an effect on sensory nerve ending in the lungs [604]. Improvement in the control of bronchial asthma in humans was achieved when it was administered four times daily for 1 month [605]. In one study, 2–16 weeks of treatment with nedocromil 16mg daily appeared to have a similar inhibitory effect on methacholine challenge to that provided by 400µg daily of beclometasone (beclomethasone) dipropionate [606].

#### *Administration, excretion and dosage*

Nedocromil is administered by MDI. It is absorbed from the lung and undergoes no metabolism, being rapidly excreted unchanged in both the bile and urine. The present recommended dose is two inhalations (4mg) four times daily at first, decreasing to two inhalations twice daily if symptomatic control permits. It is licensed for use in both adults and children over the age of 6 years.

#### *Modes of use*

Published work in patients with asthma who were not receiving inhaled steroids has shown that, compared with placebo, nedocromil may improve daytime and nocturnal symptoms and reduce the requirement for existing treatment with  $\beta$  agonists [599,607,608]. Clinical trials comparing nedocromil with sodium cromoglicate in terms of symptom control and lung function have shown nedocromil to have similar or somewhat greater efficacy than sodium cromoglicate [609,610]. On the basis of improvements in peak expiratory flow, 16mg of nedocromil daily has been found to be therapeutically equivalent to 400µg daily of beclometasone dipropionate in some patients [611], albeit at greater economic cost, so that nedocromil may be an alternative for the few patients who are intolerant of low-dose inhaled steroids [599]. However, a low-dose inhaled steroid is likely to be more effective in terms of overall symptom control and also gives the option of upward dose adjustment [607,611]. Claims have been made that the addition of nedocromil enables a reduction in dose of prednisolone in those requiring systemic steroids, although the evidence is conflicting and this effect is unlikely to be strong [599,612,613]. Nedocromil may have an inhaled steroid-sparing effect, in the sense that, compared with placebo, it

produces a better effect on symptoms and peak flow when added to a treatment regimen in which the inhaled steroid dose had been reduced [614]. Increasing the dose of nedocromil beyond 16mg daily does not appear to augment any inhaled corticosteroid-sparing effect [615]. Symptomatic benefit and small improvements in peak flow measurements have been demonstrated by the addition of nedocromil to the regimens of patients with asthma who had troublesome symptoms despite high doses of inhaled steroids [616]. Nedocromil 4mg taken 20min before exercise may attenuate the exercised-induced decline in measured lung function to the same degree as 20mg sodium cromoglicate but its duration of action may be shorter [617].

As with sodium cromoglicate, nedocromil may be regarded as a regular adjunctive therapy in patients with relatively mild persistent asthma whose symptoms are not adequately controlled by  $\beta$  agonists alone. Comparisons of nedocromil with established treatments of known efficacy in clearly defined clinical groups are few in number and have shown no clear-cut clinical advantage of nedocromil over other forms of maintenance therapy. Most clinicians, particularly in adult practice, use an inhaled steroid as initial anti-inflammatory prophylaxis in asthma; nevertheless, sodium cromoglicate or nedocromil may sometimes be used as alternatives for the milder case, particularly those who regard 'steroids' as the devil's own medicine. Patients need to be told that an improvement may take 1–2 weeks to become evident and patient compliance is a problem in medication that may need to be taken four times daily.

Nedocromil is also available as a 1% solution in a metered-dose spray and as a 2% solution for topical use in allergic rhinitis and conjunctivitis respectively.

#### *Adverse effects*

The drug has a rather bitter taste that some patients found unpleasant. This has been quite successfully masked by an added mint flavour. Cough, irritation of the throat and headache are occasional complaints but, as with sodium cromoglicate, the drug appears to be very safe [599,618].

#### *Leukotriene modifiers*

Leukotrienes, like prostaglandins, thromboxane (TX) $A_2$  and prostacyclin, are members of a group of lipid mediators known collectively as eicosanoids. These have inflammatory properties and are liberated from various cells such as mast cells, eosinophils and basophils. The production of eicosanoids is dependent on the arachidonic acid cascade, one branch of which (the cyclooxygenase pathway) produces prostaglandins, TX $A_2$  and prostacyclin, whereas the other (the lipoxygenase pathway) leads to the production and liberation of leukotrienes from



inflammatory leucocytes. A number of eicosanoids, particularly the leukotrienes, are known to play varying roles in the production of inflammation, mucous secretion, reduced mucociliary clearance and tissue injury in asthma. Cysteinyl leukotrienes are known to be extremely potent bronchoconstrictors [619] and much pharmaceutical research effort has recently been centred on this area, with attempts to develop chemicals that either interrupt the synthesis of leukotrienes by interfering with the 5-lipoxygenase pathway or block their action at a common receptor known as the cysteinyl leukotriene type 1 receptor on bronchial smooth muscle. These drugs may be collectively termed 'leukotriene modifiers' or 'antileukotrienes'.

Those orally administered agents that interrupt cysteinyl leukotriene production do so by inhibiting the enzyme 5-lipoxygenase or an associated protein, 5-lipoxygenase-activating protein. Zileuton is an example of a potent 5-lipoxygenase inhibitor, whereas montelukast, zafirlukast and pranlukast are all cysteinyl leukotriene receptor antagonists. These agents only affect one set of inflammatory mediators, and there appears to be much variation in response to these drugs between individual asthmatic subjects. This implies that there is probable patient heterogeneity with regard to the importance of leukotrienes in each individual's asthmatic response and as yet there is no method of identifying those patients in whom leukotrienes may play a more central role.

The limited amount of clinical data currently available gives the impression that these agents will have a relatively weak effect in asthma compared with inhaled steroids or  $\beta_2$  agonists. The effects of these antileukotriene drugs have been initially evaluated against allergen and cold air challenge as well as in exercise-induced and aspirin-sensitive asthma; thus in a group of atopic asthmatics 40 mg zafirlukast taken orally attenuated the early and late responses to allergen challenge in most but not all subjects [620,621]. It also produced a reduction in exercise-induced bronchoconstriction in asthmatics, with quite wide variation between subjects [622]. The addition of zafirlukast to  $\beta$  agonists in a group of patients with mild to moderate asthma was found to be more effective than  $\beta$  agonists alone in a North American randomized, double-blind, multicentre, placebo-controlled trial [623]. The usual intervention in such a group would be to add an inhaled steroid but there is little published work comparing leukotriene-modifying therapy with low-dose inhaled steroids in mild asthma. Some of the data have recently been reviewed [624,625]. It has been suggested that in patients with more severe asthma antileukotriene drugs might enable adequate control of symptoms with a lower dose of inhaled steroid than might otherwise be possible. A more recent controlled trial has shown an inhaled steroid-sparing effect with montelukast in stable asthmatic patients [626]. However, no such steroid-sparing

effect was found in two studies in which the effect of zafirlukast was compared with placebo in patients with asthma taking 400–2000 mg of inhaled steroid daily [627,628]. There is some evidence that leukotriene antagonists may be effective in asthmatics with sensitivity to aspirin and other non-steroidal anti-inflammatory drugs, bronchopulmonary reactions in such patients being associated with hypersecretion of urinary leukotriene (LT) $E_4$  [629,630].

Montelukast is licensed in the UK as an 'add-on' for use in patients with mild to moderate asthma whose symptoms are inadequately controlled by inhaled steroids and inhaled  $\beta$  agonists, and as prophylaxis in exercise-induced asthma [631,632]. It has a 24-h duration of action and is taken as a once-daily dose of 10 mg at bedtime, half this dose being used in children aged 6–14 years. It is rapidly absorbed and extensively metabolized, being excreted by the biliary route. The dose need not be modified in renal insufficiency or in mild to moderate hepatic disease. It should not be taken with food.

Zafirlukast has usually been administered as an oral dose of 20 mg twice daily [633]. It is well absorbed, having a terminal half-life of about 10 h. It is extensively metabolized and mainly excreted in the faeces. It may be used in patients with renal insufficiency but is not advised in those with liver disease. No major adverse effects have been reported. Minor side-effects have included sore throat and headache but these were not significantly more frequent than found with placebo.

Other oral antileukotriene agents currently under investigation include zileuton (available in the USA) and pranlukast [634,635]. These and other leukotriene modifying drugs are still being evaluated and any long-term benefit has yet to be established. On present evidence, they should certainly not be used as 'add-on' therapy in uncritical fashion and may be best introduced in an asthmatic whose control is less than satisfactory but sufficiently stable to enable an objective assessment of the effect of the new drug to be made so that responders may be separated from non-responders, enabling the leukotriene modifier to be continued or discarded as the case may be [636].

## Glucocorticosteroids

Glucocorticosteroid hormones, hereafter referred to simply as 'steroids', are widely used in respiratory medicine, particularly in the treatment of asthma, for which they are still the most effective agents for reducing both airway inflammation and bronchial hyperresponsiveness (see Chapter 35), and in a variety of other pulmonary disorders. All steroids in clinical use are synthetic but are chemically based on the naturally occurring corticosteroids, such as cortisol (hydrocortisone), produced in the adrenal cortex from cholesterol. All steroids, both naturally occurring and synthetic, share the same molecular

configuration of four carbon rings containing 21 carbon atoms. Their clinical and pharmacokinetic properties (potency, distribution, metabolism, duration of action, etc.) depend upon variations on this central structure, so that those compounds with effective anti-inflammatory activity must possess the following:

- 1 a double bond between C-4 and C-5;
- 2 a ketone ( $=O$ ) group in the C-3 position;
- 3 a hydroxyl group (OH) in the C-11 position;
- 4 a two-carbon side-chain in the C-17 position with a ketone ( $=O$ ) group in the C-20 position and a hydroxyl group (OH) in the C-21 position (Fig. 9.25).

Such steroids are known to chemists as 17-hydroxycorticoids. The main endogenously produced steroid is cortisol (hydrocortisone, Fig. 9.26), which is produced by the adrenal cortex. The inactive steroid cortisone, also produced in small quantities by the adrenal, is converted to cortisol in the liver. Similarly, prednisolone, a synthetic analogue of hydrocortisone, is produced in the liver from its synthetic and inactive parent prednisone. Both the beneficial and adverse clinical effects of steroids result from their administration in doses that far exceed the plasma levels achieved by their naturally occurring adrenal glucocorticoid analogues.

### Mode of action

The biological mechanisms by which steroids have their clinical effects remain incompletely understood, despite the fact that they have been in use as therapeutic agents for over 50 years. This relative state of ignorance stems from the considerable complexity of their interactions with

many different biochemical pathways. The summary that follows attempts to concentrate on areas of apparent clinical relevance.

### Gene-modulating effects

Therapeutically administered steroids diffuse passively across cell membranes and selectively bind to glucocorticoid receptors, proteins contained within the cytoplasm of the cells [637,638]. This results in the formation of activated glucocorticoid-receptor complexes, which then migrate across the cell to enter the nucleus where they interact with so-called glucocorticoid-response elements (GREs) in the nuclear chromatin (DNA). Binding of a glucocorticoid-receptor complex with a GRE affects transcription of the mRNA for the specific gene which that GRE regulates, which in turn increases or decreases the output of gene products that modify pre-existing cellular processes [639]. These gene-modulating effects of steroids may have a variety of outcomes. One such outcome is the inhibition or downregulation of a complex network of soluble molecules that act as intercellular messengers (cytokines), thought to be of much importance in the inflammatory response in asthma. Examples of such cytokines are interleukins (ILs), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interferon  $\gamma$  (IFN- $\gamma$ ). Another outcome is the production of anti-inflammatory proteins, such as lipocortin 1 (or, being a member of the annexin family, annexin 1). Levels of this protein in the respiratory tract have been shown to increase following the administration of exogenous systemic steroids. It is thought that lipocortin 1 has its anti-inflammatory effect by reducing the activity of phospholipase  $A_2$ , an enzyme that plays a key role in a number of inflammatory responses (see below) [640,641]. It is perhaps because such protein synthesis cannot be immediately accomplished that the effects of steroids do not show clinically for 1–3 h after their administration.

### Inhibition of arachidonic acid cascade

One biochemical sequence of events considered important in the development of those changes in the bronchial tree that produce symptoms of asthma is the arachidonic acid cascade. Steroids are believed to be important in inhibiting this chain of events, which is shown in simplified form in Fig. 9.27. The first stage that has been proposed is the disruption of inflammatory-cell membranes, which may result from a variety of immunological, neurological, physical or other forms of insult. This may produce a loss of cell membrane integrity, allowing the influx of calcium ions into the cell. The raised intracellular ionic concentration of calcium may in turn activate the calcium-dependent enzyme phospholipase  $A_2$ . This rate-limiting

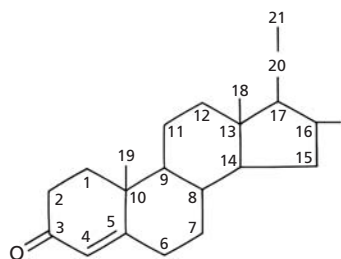


Fig. 9.25 Structure of the 21-carbon corticosteroid molecule.

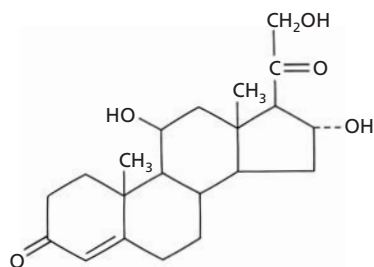
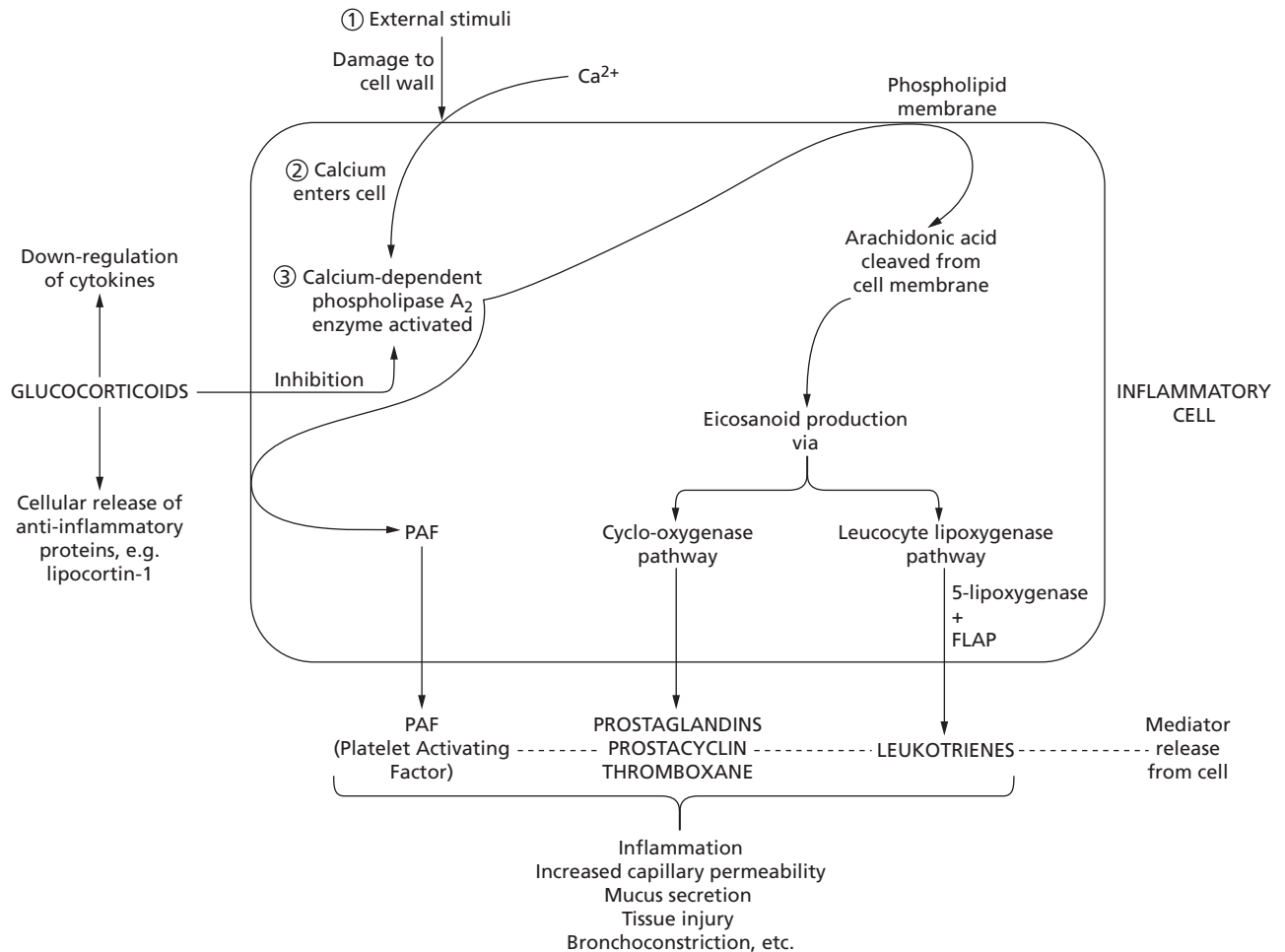


Fig. 9.26 Structure of hydrocortisone (cortisol).



**Fig. 9.27** Inhibition of inflammatory mediator release by corticosteroids.

enzyme cleaves arachidonic acid, a polyunsaturated fatty acid, from the cell membrane phospholipids of which it is a component. Arachidonic acid is a precursor of a large number of lipid mediators, known collectively as eicosanoids, which have inflammatory properties. Prostaglandins,  $\text{TXA}_2$ , prostacyclin and leukotrienes are all eicosanoids and are liberated from various inflammatory cells, such as mast cells, eosinophils, basophils and macrophages. One route by which eicosanoids are produced is the cyclooxygenase pathway, which leads to the production of thromboxanes, prostaglandins and prostacyclin. Another major route for eicosanoid production is the leucocyte lipooxygenase pathway, which leads to the production of leukotrienes. The entity formerly known as slow-reacting substance of anaphylaxis belongs to this class of compound and is now known to comprise a number of different cysteinyl leukotrienes ( $\text{LTC}_4$ ,  $\text{LTD}_4$  and  $\text{LTE}_4$ ) [642]. A number of eicosanoids, particularly the

leukotrienes, probably play varying roles in the production of inflammation, mucous secretion and tissue injury. Steroids may have a limiting effect on these injurious events by suppressing the production of eicosanoids via both pathways of arachidonic acid metabolism (cyclooxygenase and leucocyte lipooxygenase). It is possible that this limitation is partly achieved through the glucocorticoid-stimulated release of inhibitory proteins such as lipocortin 1, arachidonic acid release being retarded by its inhibition of the enzyme phospholipase  $\text{A}_2$  [640,641,643,644]. Specific leukotriene modifying drugs have been referred to in the previous section and are the subject of current research.

#### ***Inhibition of platelet-activating factor***

In addition to various eicosanoids, platelet-activating factor (PAF) is another lipid inflammatory mediator that is less powerful *in vitro* than cysteinyl leukotrienes. It may also be released from inflammatory cells such as eosinophils and macrophages as a result of phospholipase  $\text{A}_2$  activity on cell membrane phospholipid precursors

[645,646]. PAF may be important in recruiting further eosinophils and may lead to a prolonged increase in bronchial hyperresponsiveness as well as microvascular leak in asthma. PAF is also inhibited as a result of the suppression of phospholipase A<sub>2</sub> by steroids. The experimental development of specific PAF antagonists has so far had disappointing results in asthma.

### *Inhibition of histamine release*

Histamine is one of the mediators of bronchoconstriction that is released by mast cells and basophils after both immediate IgE-mediated allergic reactions and following non-immune stimuli. It is a less potent mediator than leukotrienes *in vitro*. Of the three types of histamine receptor in the airways, H<sub>1</sub> stimulation causes bronchoconstriction, H<sub>2</sub> stimulation results in mucous secretion and there is animal evidence to suggest that H<sub>3</sub> receptors may be concerned with histamine release from mast cells. Although oral glucocorticoids do not affect the acute physiological response of allergen challenge to the lung, nasal passages or skin [647], steroids appear to suppress the IgE-mediated release of histamine from basophils [638]. Mast cell activity is probably reduced indirectly by steroids, which diminish the numbers of submucosal T lymphocytes, these in turn liberating interleukin cytokines that may have an inhibitory effect on mast cells [648]. Antihistamines such as the H<sub>1</sub> antagonists chlorphenamine (chlorpheniramine) and loratadine, although effective in allergic rhinitis, are disappointing in asthma.

### *Effects on vasculature*

Steroids act to reduce capillary permeability at sites of inflammation [649] and are potent inhibitors of inflammatory oedema. This can be beneficial in certain inflammatory conditions by preventing the passage of both inflammatory cells and immune complexes from the intravascular space to surrounding tissues. It is not known by what mechanisms steroids produce this effect on capillaries but the suppression of inflammatory mediators (see above), as well as cytokines such as tumour necrosis factor  $\alpha$  and fibroblast growth factors, may be involved. The production of a protein, other than lipocortin 1, that acts on endothelium to reduce permeability is suggested as another mechanism [650].

### *Cellular effects*

Changes in the proportions of the normal white cell constituents of circulating blood can be detected within a few hours of a dose of glucocorticoid. The blood neutrophil count is increased, in part due to increased bone marrow production. These cells are required for acute inflammation and steroids may inhibit their movement into

inflamed tissues, partly by blocking the production of recruitment cytokines, so that neutrophils are redistributed from the tissues back into the circulation [647,651]. Circulating eosinophils, basophils, monocytes and lymphocytes are all reduced [651,652], possibly as a result of their redistribution to other extravascular sites including lymphoid tissues, as fewer of these cells are to be found in inflamed tissues. A reduction in the numbers of tissue-based T lymphocytes is likely to be an important response to steroids, these cells being known to liberate cytokines such as interleukins, which probably play important roles in the activation of other inflammatory cells [647]. Such a reduction has been observed in the lungs of asthmatic patients treated with an inhaled steroid [653]. The suppression of the tuberculin reaction is a further example of the impairment of T cell-mediated immune responses by steroids. Seasonal increases in the numbers of nasal mucosal mast cells are attenuated by long-term administration of topical nasal steroids in patients with allergic rhinitis [654]. Similar observations have been made in the lungs of asthmatic patients treated with an inhaled steroid, not only for T lymphocytes and macrophages but also for mast cells and eosinophils [653]. Steroids may inhibit the proliferation of mucosal mast cells, although they do not inhibit the release of inflammatory mediators from mast cells once they have been challenged by antigen [647]. Activated eosinophils are known to be capable of liberating secretory products that are both cytotoxic to bronchial epithelial cells and that also increase bronchial smooth muscle responsiveness. There is evidence to suggest that treatment with steroids reduces eosinophil proliferation, differentiation and activation, probably indirectly by reducing cytokine production from T lymphocytes, macrophages and endothelial cells, all of which affect eosinophil function [647]. The recruitment of basophils is suppressed by steroids, probably by blocking various recruitment factors such as cytokines and PAF [647]. Thus in addition to alterations in the numbers of individual constituents of the intravascular white cell pool, steroids also inhibit a number of complex cellular functions that contribute to inflammatory or immunological processes.

### *Effects on $\beta_2$ -adrenergic receptors*

The increased sensitivity of  $\beta_2$ -adrenergic receptors to both endogenous catecholamines and to administered synthetic  $\beta_2$  agonists is an important effect of steroids in patients with asthma, becoming evident within about 1 h of intravenous administration [655]. The mechanism by which this occurs is uncertain, but it may involve the enhancement of chemical receptor synthesis or an increase in the sensitivity of existing receptors. The human  $\beta_2$ -adrenergic receptor gene is known to contain a number of GREs (see above) ready to interact with steroid-receptor

complexes, and it may be that  $\beta_2$ -receptor numbers increase as a result of steroids affecting gene transcription [648,656].

### Miscellaneous effects

Glucocorticoids may inhibit the growth of fibroblasts and therefore the laying down of collagen and 'scar tissue' as a consequence of inflammation. The mechanism is unclear, although cytokine downregulation, which may include a reduction in fibroblast growth factors, is possible. Steroids may also modulate calcium ion movements across cell membranes, a process important in the activation of the enzyme phospholipase  $A_2$ . They also modify the effects of many other inflammatory mediators too numerous to mention here but which are reviewed elsewhere [638,648,657]. They reduce bronchial hyperresponsiveness as a result of their anti-inflammatory actions in the airway and are therefore a cornerstone in the management of asthma [658] as well as many other less common inflammatory diseases of the lungs.

### Administration, metabolism, excretion

Corticosteroids are generally rapidly and almost completely absorbed when taken by mouth. They may be divided into short-, intermediate- and long-acting preparations in terms of the length of time that they suppress adrenocorticotrophin (ACTH) production. Hydrocortisone, cortisone, prednisolone, prednisone and methylprednisolone are regarded as short-acting. Triamcinolone is intermediate and both betamethasone and dexamethasone are longer-acting [659]. The majority of steroid preparations are also available for parenteral use, either as freely soluble and rapidly absorbed sodium phosphate or sodium succinate esters or as poorly soluble 'depot' preparations that are completely but slowly absorbed.

### Oral corticosteroid preparations

#### Prednisolone and prednisone

Prednisolone (Fig. 9.28) is a favoured oral steroid preparation. It is largely absorbed within 30 min of ingestion. Metabolism is primarily hepatic, with the production of inactive metabolites. The metabolism of prednisolone and other steroids is enhanced by hepatic enzyme-inducing drugs, such as phenobarbital (phenobarbitone), phenytoin, carbamazepine and rifampicin, so that these reduce the glucocorticoid effects of steroids. The opposite may result from liver disease or impairment of liver function as a result of metabolic disease; furthermore since prednisolone and other steroids are for the most part protein-bound, hypoalbuminaemia increases glucocorticoid activity and its attendant side-effects. The plasma half-life

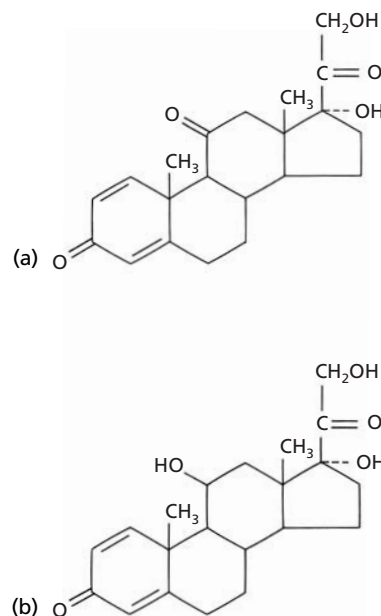


Fig. 9.28 Structure of (a) prednisone and (b) its active metabolite prednisolone.

of prednisolone is about 3 h, whereas the physiological activity (based on duration of ACTH suppression) is about 20 h. Thus a once-daily dosage regimen may allow some degree of adrenal recovery from suppression before the next dose is due. By comparison, a once-daily dose of hydrocortisone (cortisol), of which an oral preparation exists, is not workable as its duration of action is too short. The inactive metabolites of prednisolone are excreted in the urine. Its pharmacokinetics do not vary significantly between night and day [660].

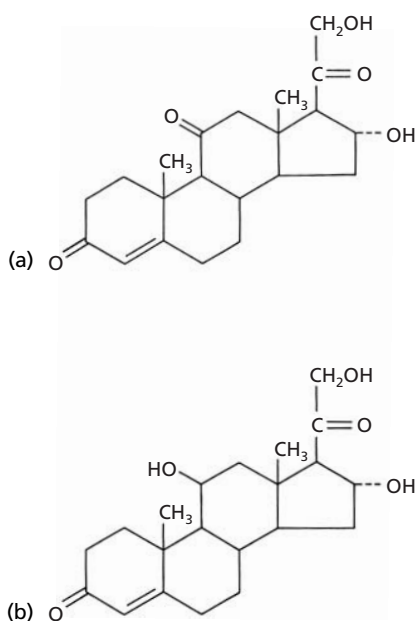
Prednisone is inactive since it is a prodrug with no glucocorticoid activity until it has been metabolized by reduction to prednisolone in the liver. However, this takes place rapidly so that its plasma half-life is only about 1 h. Its onset of action is bound to be slower than its metabolite prednisolone, which differs structurally in having a ketone rather than a hydroxyl group in the C-11 position. Nevertheless, the peak effect is reached after a similar length of time with both preparations and comparable levels of prednisolone appear in the plasma no matter which preparation is given, provided that liver function is normal. However, the same glucocorticoid activity may not be achieved in patients with liver disease, and prednisolone is pharmacologically preferred as the plasma levels achieved are unaffected by hepatic dysfunction [661]. Both these drugs have little mineralocorticoid activity by comparison with hydrocortisone and cortisone and are preferred in the longer term, other than for replacement in adrenal insufficiency. The prodrug prednisone is no longer commercially available in the UK.

*Cortisone and hydrocortisone*

Cortisone was the first naturally occurring corticosteroid to be used. Like prednisone, it is a prodrug that is inactive until converted to hydrocortisone (cortisol) by reduction in the liver, with the substitution of a hydroxyl group for a ketone group in the C-11 position (Fig. 9.29). It has similar pharmacokinetic properties to hydrocortisone, although dose for dose it is about 25% less potent with regard to glucocorticoid effect. Its traditional use was as replacement therapy in Addison's disease, a role for which hydrocortisone is now pharmacologically preferred, both drugs possessing mineralocorticoid as well as glucocorticoid activity.

*Methylprednisolone*

Methylprednisolone differs in structure from prednisolone only by the possession of a methyl group in the C-6 position of the steroid structure (Fig. 9.30). Dose for dose it has slightly greater glucocorticoid effect than prednisolone and little mineralocorticoid effect, which may be of clinical significance by reducing the chance of serious hypokalaemia if high-dose methylprednisolone is used. The speed of onset, peak effect and duration of action are broadly similar to those of prednisolone. Methylprednisolone has been shown to penetrate lung acini better than prednisolone and it has been proposed that this could have practical benefits in the management of potentially fibrotic lung disease [662,663]. This oral preparation is about 10 times the cost of prednisolone.



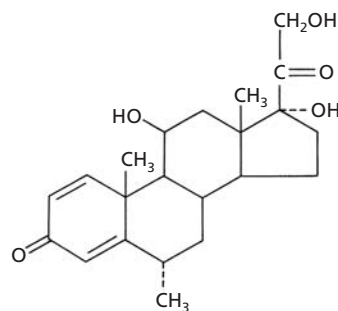
**Fig. 9.29** Structure of (a) cortisone and (b) its active metabolite hydrocortisone.

*Triamcinolone*

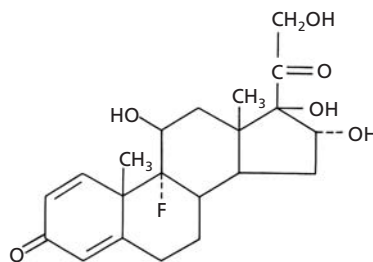
Triamcinolone differs in structure from prednisolone by the possession of a fluorine atom at the C-9 position and an additional hydroxyl group in the C-16 position (Fig. 9.31). The rate of absorption and peak effect are similar to those of prednisolone. Metabolism is also hepatic but slower, as with other fluorinated steroids (betamethasone and dexamethasone), so that its plasma half-life is over 3 h. Its duration of action is also longer and may be about 2 days. Dose for dose it has a slightly stronger glucocorticoid effect than prednisolone, being equivalent in this respect to methylprednisolone. Like betamethasone and dexamethasone it has no significant mineralocorticoid effect.

*Betamethasone*

Betamethasone, like triamcinolone, is a fluorinated steroid but differs from this compound by the possession of a methyl group in place of the hydroxyl group at the C-16 position (Fig. 9.32). The rate of absorption and peak effect are similar to prednisolone. Possession of the fluorine atom results in delayed hepatic metabolism and a plasma half-life of over 3 h. The duration of action of betamethasone is longer than that of triamcinolone and may exceed 3 days. The presence of the methyl group increases its glucocorticoid activity (including adverse effects), so that its potency in this respect is about five times that of prednisolone [664]. Mineralocorticoid effect, as with triamcinolone and dexamethasone, is said to be minimal [649].



**Fig. 9.30** Structure of methylprednisolone.



**Fig. 9.31** Structure of triamcinolone.



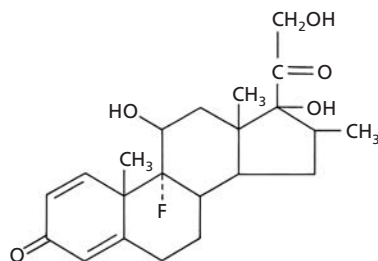


Fig. 9.32 Structure of betamethasone.

### Dexamethasone

Dexamethasone differs structurally from betamethasone only geometrically, in that the methyl group in the C-16 position is in the  $\alpha$  rather than the  $\beta$  position (Fig. 9.33). The rate of absorption and peak effect are similar to prednisolone. The plasma half-life is over 3 h because, like triamcinolone and betamethasone, its hepatic metabolism is slowed by the possession of a fluorine atom in the C-9 position. Its duration of action is similar to that of betamethasone. Weight for weight it also has similar glucocorticoid potency to betamethasone [58], this being about five times that of prednisolone. Mineralocorticoid effect is negligible, as is the case with methylprednisolone and the other two fluorinated corticosteroids triamcinolone and betamethasone. High-dose dexamethasone tends to be favoured in the palliative treatment of raised intracranial pressure due to brain metastases, in which case fluid retention and potassium loss due to mineralocorticoid effect would be a disadvantage.

### Deflazacort

Deflazacort is a more recently introduced orally administered steroid with glucocorticoid activity. It is an oxazoline derivative of prednisolone. Dose for dose it is slightly less potent than prednisolone, so that a 6-mg dose of deflazacort has a similar anti-inflammatory effect to 5 mg prednisolone. Claims that this compound may be less likely to cause steroid-related osteoporosis or diabetes mellitus require substantiation. It is about 20 times the cost of prednisolone.

### Parenteral corticosteroid preparations

#### Hydrocortisone

Hydrocortisone (cortisol) is a favoured short-term parenteral steroid preparation. Its structure is shown in Fig. 9.26. It is usually given intravenously, rather than intramuscularly, as the sodium succinate or sodium phosphate ester. Its onset of action, although more rapid than with prednisolone and other steroids, is by no means immedi-

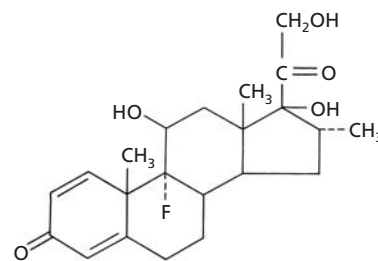


Fig. 9.33 Structure of dexamethasone.

ate [665]. Its peak effect on airway mechanics may be achieved more rapidly, the time between administration and onset of benefit in asthma being thought to be about 5 h compared with about 8 h for prednisolone [666]. Dose for dose, hydrocortisone possesses slightly greater mineralocorticoid activity than prednisolone and this may have some additional benefit in the treatment of acute severe asthma in patients maintained on oral steroids and who may develop relative adrenal insufficiency in situations of stress. Conversely, oral hydrocortisone is avoided in the longer-term treatment of asthma as its mineralocorticoid activity would be more likely to cause fluid retention and potassium loss; indeed care needs to be taken to prevent severe hypokalaemia with associated ventricular tachycardia when high-dose hydrocortisone is given parenterally [667]. Hydrocortisone undergoes hepatic metabolism and its plasma half-life is 1–2 h, which is about half that of prednisolone. Its duration of action based on ACTH suppression is variable, depending on body size, and is about 8–12 h; this is about half that seen with prednisolone and necessitates multiple daily dosage or continuous infusion in asthma management.

#### Cortisone

Cortisone is not available as a parenteral formulation in the UK. A poorly soluble but slowly released and completely absorbed acetate derivative is available in the USA, but has no place in the management of respiratory disease.

#### Prednisolone and prednisone

Prednisolone is available as a poorly soluble acetate derivative for intramuscular depot injection, being slowly absorbed and remaining active for up to 3 weeks. A freely soluble sodium phosphate preparation is available in the USA for rapid-onset intravenous use and may also be given intramuscularly. The pharmacology has been discussed above.

#### Methylprednisolone

Methylprednisolone is available as a freely soluble



sodium succinate ester for intravenous or, less frequently, intramuscular use. The pharmacology is as described above for the oral preparation. A poorly soluble acetate derivative is also available. This intramuscular depot preparation is very slowly absorbed, so that it may take about a week to reach its peak effect and its duration of action may be up to 4 weeks. Pulse treatment, with depot methylprednisolone injections every 2 weeks, has been used in the past in the treatment of asthma [668], although high-dose pulse methylprednisolone is unlikely to be more effective than short-course oral prednisolone in this situation [669]. High-dose treatment with methylprednisolone or other steroids in critically ill patients with septic shock does not appear to prevent adult respiratory distress syndrome and is probably without benefit [670,671].

### *Triamcinolone*

Triamcinolone is available as a poorly soluble acetonide derivative for intramuscular depot injection, being very slowly absorbed. The peak plasma concentration may be achieved in 48 h, the level thereafter gradually declining to become undetectable at about 3 weeks [672]. Such depot injections have been successfully used once monthly in chronic asthmatics [673], the clinical effect lasting up to 6 weeks. A similar slow-release diacetate derivative is available in the USA for intramuscular use. There is no rapidly absorbable parenteral form. The pharmacology is as described above for the oral preparation.

### *Betamethasone*

Betamethasone is available as a freely soluble and rapid-onset sodium phosphate derivative for intravenous or, less frequently, intramuscular use. A mixture of betamethasone sodium phosphate and acetate derivatives is available in the USA for use as a depot intramuscular injection. No such poorly soluble derivatives are available in the UK. The pharmacology has been discussed above.

### *Dexamethasone*

Like betamethasone, dexamethasone is also available as a rapid-onset sodium phosphate derivative for intravenous or, less commonly, intramuscular use. No intramuscular depot preparation is available in the UK but a slow-release intramuscular acetate formulation exists in the USA that is intended for weekly to 3-weekly dosage.

### *Other parenteral preparations*

Other parenteral preparations that are not themselves corticosteroids but which cause corticosteroid release include ACTH, which is obtained from mammalian pituitary and

is no longer commercially available in the UK, and tetracosactrin, which is synthetic but structurally similar to ACTH. When given to a subject with responsive adrenal glands, these substances result in the endogenous production of hydrocortisone (cortisol). This pharmacological effect is useful in the investigation of adrenal function and is the basis of the tetracosactrin test. This effect has also been put to therapeutic use in the treatment of asthma and has been claimed to cause less growth suppression than exogenous corticosteroids in children [674], although the evidence for this is somewhat slender. Such treatment has a number of disadvantages:

- 1 it needs to be given parenterally and this tends to be less acceptable in children;
- 2 the pituitary–adrenal axis may be suppressed at a higher level, so that pituitary rather than adrenal suppression occurs;
- 3 previous treatment with exogenous corticosteroids may have caused adrenal suppression, with consequent lack of response to ACTH or tetracosactrin;
- 4 an undesirable mineralocorticoid effect, with salt and water retention, may occur;
- 5 when depot injections are used, release may be unpredictable and erratic.

Tetracosactrin acetate produces a peak plasma cortisol level 1 h after intramuscular injection, the level returning to basal conditions after 4 h. A more poorly soluble acetate/zinc phosphate complex derivative of tetracosactrin may be used for depot intramuscular administration, achieving a peak cortisol level at 8 h with raised values for over 24 h [675]. This preparation has been used in the treatment of asthma once or twice per week but the limitations in usefulness listed above apply. ACTH is no longer available in the UK but is still obtainable in the USA, being given either as a gelatin preparation subcutaneously or intramuscularly, producing an effect for 12–24 h. A zinc oxide preparation is given similarly and may have a duration of action of 48 h.

### **Dosage of systemic steroids**

This section is confined to general comments only and the reader is referred to chapters dealing with the management of specific diseases or clinical situations for more detailed recommendations about steroid dosage. Table 9.12 shows doses of various steroids with approximately equipotent anti-inflammatory (glucocorticoid) effects. Conversion factors for obtaining an approximately equipotent anti-inflammatory effect with the different drugs are shown in Table 9.13. Thus 30 mg of prednisolone, which is a commonly used starting dose for an oral course of steroid in moderate exacerbations of asthma, is equipotent to 120 mg of hydrocortisone. This order of dosage may achieve a maximum therapeutic response in asthma, although some patients may require

60mg daily to achieve the same effect, this dose corresponding to 240mg of hydrocortisone. For comparison, the baseline physiological requirement for hydrocortisone replacement in an adrenalectomized or Addisonian patient is 20–30mg daily. The practice of gradually reducing the dose of oral corticosteroid in the treatment of exacerbations of asthma has been criticized, and it has been claimed that 0.6mg/kg of prednisolone daily for up to 2weeks is an effective alternative [676], although this approach frequently causes worry and concern to patients who have been satisfied by their response to the earlier method. The standard 3mg/kg 6-hourly dose of hydrocortisone used in the treatment of acute severe asthma is intended to achieve a plasma cortisol level of 100µg/dL or more [677]. For a 70-kg patient, this amounts to 200mg hydrocortisone 6-hourly, which is equipotent to 50mg of prednisolone 6-hourly or 200mg daily. The 16mg dexamethasone daily that is conventionally used as a starting dose for the palliative treatment of cerebral metastases is equivalent to about 100mg of prednisolone daily, and so on. When treating patients with steroids, it is usual practice to start therapy with a high dose and to

gradually reduce once a satisfactory therapeutic response has been achieved. In many conditions a so-called ‘maintenance dose’ is continued, i.e. the dose at which control of the disease proves acceptably balanced against undesirable side-effects. In asthma of sufficient chronicity to require systemic steroids despite optimal inhaled therapy, this dose is frequently about 10mg prednisolone daily.

*Timing of steroid dose*

It is recommended that, whenever possible, oral steroids should be given as a single dose in the morning [678], the only exception being twice-daily physiological replacement therapy in adrenal insufficiency. This method of administration has been shown to be as effective as the same total dose divided through the day [679]. There are also a number of theoretical advantages: first, a morning dose coincides with the maximal physiological output of ACTH and should therefore be less likely to cause adrenal suppression and, secondly, steroids tend to be less protein-bound during the daytime and therefore more active [680].

It may be advisable, whenever possible, to try to administer steroids on alternate days by doubling the usual maintenance daily dose [681]. This manoeuvre is intended to reduce pituitary–adrenal suppression and to diminish other steroid-related side-effects but is not always possible in terms of disease control and may lead to problems with compliance [681]. The relatively short-acting steroids such as prednisolone lend themselves to this regimen, which will prove ineffective if long-acting preparations such as dexamethasone are used [682]. Alternate-day prednisolone therapy does not always prove possible in patients with chronic asthma, who may experience increased wheezing on the ‘off’ day [683]. However, it is applicable in other conditions such as sarcoidosis. Patients who have been on daily steroid treatment for a long time

**Table 9.12** Equipotent doses of various systemic steroids for anti-inflammatory effect.

Drug	Equipotent anti-inflammatory dose (mg)
Cortisone acetate	25
Hydrocortisone	20
Deflazacort	6
Prednisolone	5
Methylprednisolone	4
Triamcinolone	4
Dexamethasone	0.75
Betamethasone	0.75

**Table 9.13** Equipotent anti-inflammatory doses of steroids: conversion factors.

	÷ 4			× 1.25	
	→	Prednisolone	Methylprednisolone	→	Prednisone
Hydrocortisone	←	or	or	←	or
	× 4	Prednisone	Triamcinolone	÷ 1.25	Prednisolone
	× 6.6			÷ 5	
Dexamethasone	→	Prednisolone		→	Methylprednisolone
or	←	or	Hydrocortisone	←	or
Betamethasone	÷ 6.6	Prednisone		× 5	Triamcinolone
	× 26.6			× 5.3	
Dexamethasone	→		Methylprednisolone	→	Dexamethasone
or	←	Hydrocortisone	or	←	or
Betamethasone	÷ 26.6		Triamcinolone	÷ 5.3	Betamethasone

may experience symptoms due to relative adrenal insufficiency on the 'off' day. This may be circumvented, if it is so wished, by introducing the change gradually, the dose on the intended 'on' day being steadily increased at the expense of dose on the 'off' day.

**Adverse effects of systemic steroids**

The general public are frequently aware, and not without good reason, that treatment with steroids is associated with unpleasant side-effects (Table 9.14). Those of which they are perhaps most aware are those that are medically least important but socially bothersome or distressing, such as a change in facial appearance and weight gain. The complete list of adverse effects is very long but fortunately some of these are either rare or their association only imperfectly established.

**Table 9.14** Adverse effects of steroids.

Cosmetic complaints
Facial fullness
Weight gain
Dependent oedema
Bruising
Atrophic skin
Striae
Acne
Bone complaints
Osteoporosis leading to fractures
Aseptic necrosis of the femoral head
Achilles tendon rupture
Dyspeptic symptoms
Peptic ulceration and complications
Ocular effects
Cataracts
Glaucoma
Benign intracranial hypertension
Mood change
Euphoria
Psychosis
Myopathy
Other metabolic and endocrine effects
Diabetes mellitus
Growth retardation
Salt and water retention
Hypokalaemic alkalosis
Hypothalamic–pituitary–adrenal axis suppression
Susceptibility to infection
Bacterial
Fungal (inc. candidiasis)
Viral
Adrenal insufficiency

For effects on pregnancy and lactation, see text.

The likelihood of side-effects from systemic steroid treatment depends on the size of the dose and the duration of treatment. Problems seldom occur with a short course of oral prednisolone, as used for asthma, started at a dose of about 30mg daily and continuing at this level or in reducing fashion for up to 2 weeks. Higher short-term dosage, usually in hospitalized patients, may be associated with untoward effects, as may maintenance doses taken for long periods as outpatient treatment. Adverse effects are also often more troublesome in the elderly. A community survey covering a population of 65786 subjects in the Nottingham area found that 0.5% were taking long-term (>3 months) steroids and that the steroids were being prescribed for respiratory conditions in 20% of cases (usually asthma/COPD), for polymyalgia rheumatica/temporal arteritis in 25% and for rheumatoid arthritis in 21% [684]. The prevalence of 0.5% rose to 1.7% in women aged 55 years or over.

The adverse effects of inhaled steroids are considered separately.

*Cosmetic complaints*

The most obvious of these to the patient is fullness of the face. The 'moon face' becomes evident to the physician after several weeks' treatment, usually with a dose of greater equivalence than 10mg of prednisolone daily, but may be noticed sooner by the patient and often persists to some extent, despite reduction of the dose to a lower maintenance level.

The patient also gains weight and should be warned to guard against the appetite-stimulating effects of steroids. This weight is typically gained centripetally, with the development of truncal obesity, although fluid retention due to mineralocorticoid effect plays a part and may produce dependent oedema in older patients. Weight gain may be associated with the appearance of striae. The older the patients, the more likely they are to complain of bruising. This is because elderly people bruise anyway and corticosteroids further increase capillary fragility, perhaps as a result of the atrophy of vascular supporting tissues. Cutaneous atrophy, which in extreme situations may produce shiny 'tissue-paper' thin and fragile skin, may be seen in elderly patients who have been taking maintenance steroids for months or years. Such a situation may result in the skin tearing with the least trauma, causing an unpleasant though superficial wound that may be slow to heal [685,686]. In the younger obese patient, cutaneous striae may appear on the trunk and proximal upper limbs, although these are rather uncommon and certainly less so than in primary Cushing's syndrome. Hirsutism is also less common in the iatrogenic form of Cushing's syndrome but tiresome acne may make an untimely reappearance in some adults.

### *Osteoporosis and other musculoskeletal disorders*

Treatment with glucocorticoids tends to produce a bone remodelling imbalance, both decreasing trabecular bone formation and increasing bone resorption, with resultant loss of bone density [687–689]. This leads to osteoporosis, which may be defined as a bone mineral density (BMD) score 2.5 standard deviations or more below the mean peak value in young (30–40 years) normal adults, osteopenia being said to be present at 1 standard deviation below the mean. The mechanisms are incompletely understood but it has been supposed that glucocorticoids primarily reduce new bone formation by inhibition of osteoblasts and that they also cause bone resorption, possibly by inducing secondary hyperparathyroidism as a result of impaired calcium absorption from the gut and renal tubules [688–690]. The result is a loss of up to 30% of trabecular bone in some cases, this being highest in the first 3–6 months of therapy. These effects often become clinically manifest in postmenopausal women and older men with the sudden onset of moderately severe and persistent back or girdle-type pain due to a collapsed dorsal vertebral body. Such compression fractures, which occur in about one-third of patients after 5–10 years of treatment [691], may be confirmed on spinal films or lateral chest radiographs. Chest pain may be due to a fractured rib caused by coughing and falls may result in femoral or other fractures. Whether or not intermittent courses of systemic steroids cause significant bone loss is unclear. It was estimated in 1993 that the annual cost of the consequences of osteoporosis to the community in England and Wales exceeded £500 million [684] so that it is regarded as an important public health problem.

The community survey covering a population of 65 786 subjects in the Nottingham area found that 0.5% were taking long-term (>3 months) steroids, that only 14% of such patients had been prescribed medication to treat or prevent osteoporosis and that only 10% of women over the age of 45 years on steroids in this group were taking hormone-replacement therapy [684]. Evidence of the efficacy of the various measures claimed to be effective for treating or preventing osteoporosis have been reviewed [688]. The encouragement of regular exercise, such as walking, and a dietary intake of 1500 mg calcium daily is recommended, with the addition of supplements as necessary in order to achieve this. Insoluble calcium salts such as carbonate have to be taken with food and are less well absorbed than soluble salts such as citrate; such supplements are more effective in preventing bone resorption if taken at bedtime. In older patients, heavy lifting should be avoided. Patients should be advised that both tobacco consumption and alcohol abuse are independent risk factors for the development of osteoporosis. Postmenopausal women are particularly at risk of osteoporosis

and treatment with estrogen replacement therapy is appropriate, compliance being enhanced by an explanation of the likely benefits and risks and, in appropriate cases, the use of a combined continuous estrogen–progestogen preparation in order to avoid uterine bleeding. Bisphosphonates, which may be regarded as ‘osteoclast poisons’, are an alternative and have also been shown to be effective in treating osteoporosis, for example cyclical etidronate 400 mg daily for 2 weeks followed by 500 mg supplemental calcium daily for 11 weeks or alendronate 10 mg daily taking care to follow instructions to avoid oesophagitis and ensure absorption. Oral vitamin D (800 iu daily) and calcium supplements are recommended in very elderly housebound or institutionalized patients, the effect of these various foregoing measures being to reduce the risk of fracture by about a half [692]. The active metabolite of vitamin D, calcitriol, and the related alfalcidol have been proposed as further alternatives, as has calcitonin.

There is a widespread assumption that such therapeutic or prophylactic interventions prevents corticosteroid-induced osteoporosis even though this is not certain. A 12-month, randomized, double blind, placebo-controlled trial involving 144 men and women taking at least 7.5 mg prednisolone or equivalent drug daily for at least 3 months, with ongoing treatment, has shown that cyclical etidronate and calcium prevents the loss of trochanteric and vertebral bone, on the basis of BMD assessment by dual-energy X-ray absorptiometry. New vertebral fractures were reduced by 40% in the treatment group at 1 year [693]. As high-dose systemic steroid treatment produces bone loss early, it is rational to introduce preventive interventions from the outset if it is expected that treatment will be prolonged [689]. It has been recommended that patients beginning long-term therapy with systemic steroids should ideally have the BMD of their lumbar spine measured at the onset. In young adults, those with bone densities at the lower end of, or below, the normal range should be offered preventive treatment, which should also be provided for elderly or postmenopausal patients [689].

Osteonecrosis refers to avascular necrosis of bone in which an impairment of the vascular supply to bone causes the death of osteocytes [694]. It may occur at any age, particularly in the third and fourth decades, and has a strong association with systemic steroid therapy, especially when high doses are used rather than small maintenance doses in the longer term. The mechanism is uncertain but it may be more common when steroids are used in conditions associated with vasculitis, such as systemic lupus erythematosus. Such aseptic necrosis affects the femoral head more frequently than other bones and collapse of the joint is often the consequence [695]. Patients may present with pain and limitation of movement in the

affected joint and in the case of femoral head involvement most require total hip replacement. It is fortunately rare and requires orthopaedic referral.

Non-traumatic Achilles tendon rupture may occur in patients taking systemic steroids. It can follow trivial exertion such as getting in or out of a car or simply walking on level ground. It produces local pain and swelling over the tendon and a discontinuity may be visible or palpable over the heel [696]. The affected gastrocnemius muscle may bulge proximally and bruising develops about the heel and foot. Degenerative changes occur in the Achilles tendon from the third decade onwards and it is assumed that these are made worse by steroid treatment, the condition usually occurring in patients taking long-term maintenance therapy [697]. The author has seen it occur bilaterally, with resultant total immobilization of a patient already severely limited by exertional dyspnoea. Management is orthopaedic, with heel raises, plaster of Paris, other forms of immobilization or open repair, should the patient be fit enough.

Two types of steroid myopathy are usually described. The more common chronic steroid myopathy occurs as a result of prolonged treatment with moderate doses and is characterized by the gradual onset of proximal limb muscle weakness, although respiratory muscles may also be affected [698,699]. This adverse effect is thought to be more troublesome with fluorinated steroids (triamcinolone, betamethasone, dexamethasone), which may selectively induce type IIb muscle fibre atrophy. The pathophysiology is unknown but a reduction in protein synthesis and the accumulation of glycogen are likely to be important. The condition reverses gradually on stopping the drug or with dosage reduction. An acute form of steroid myopathy is also described in which short-term treatment with high doses of steroid is thought to be causal. This form typically occurs with hydrocortisone in the course of treatment of respiratory failure with mechanical ventilation and is associated with diffuse weakness that includes the respiratory muscles [700,701]. It is unclear whether or not neuromuscular blocking agents contribute to this disorder, which appears to be related to the total dose of steroid. Degenerative changes may be shown on muscle biopsy and rhabdomyolysis may occur [698,702]. Both forms of myopathy occur in the absence of hypokalaemia and are unassociated with raised creatine kinase levels. There are occasional reports of muscle cramps occurring as a result of steroid therapy [700].

### *Dyspeptic symptoms*

It is common experience that patients taking corticosteroids orally may experience nausea and other upper gastrointestinal symptoms. It is also widely held that peptic ulceration may occur in such patients more frequently than would otherwise be the case, although this assumption

has been seriously questioned and no adequate prospective studies have been performed [704]. Retrospective studies using a variety of disease states requiring steroid treatment suggest a trend towards more peptic ulceration in steroid-treated groups, particularly in those receiving higher doses for longer periods of time [705,706]. A large case-control study in the USA showed that patients taking steroids doubled their chance of developing a peptic ulcer, although interestingly this risk was confined to patients who were taking concurrent non-steroidal anti-inflammatory drugs (NSAIDs). Patients who were taking steroids in the absence of NSAIDs had an incidence of peptic ulceration similar to the control population [707]. This leads to the conclusion that the simultaneous use of steroids and NSAIDs should be avoided if at all possible [708]. The beneficial effects of enteric-coated steroid tablets remains uncertain.

Complications of peptic ulceration, such as acute gastrointestinal haemorrhage or perforation, may occur with no particular antecedent symptoms, these being suppressed by the corticosteroid therapy itself. The situation may be further complicated by concurrent theophylline therapy, which may commonly cause nausea; furthermore, it is well recognized that peptic ulceration may occur in situations of stress due to any serious illness, respiratory or otherwise, and that it may occur during mechanical ventilation, whether steroids are used or not. Steroid-related upper gastrointestinal symptoms are frequently treated with  $H_2$ -receptor antagonists such as cimetidine or proton pump inhibitors such as lansoprazole. Such symptoms should ideally be investigated by endoscopy of the upper gastrointestinal tract. When peptic ulcers are found in patients who are taking steroids, there is no good evidence to suggest that they are less likely to heal or more likely to bleed or perforate than other peptic ulcers [709]. If cimetidine is used, it should not be forgotten that the half-life of oral theophylline may be doubled [710]. Pancreatitis may occur.

### *Ocular effects*

Cataracts are classified according to their location in the lens as nuclear, cortical or posterior subcapsular, the latter site being the most susceptible to metabolic insult, causing most visual loss and accounting for the majority of operative extractions, although with advancing age the other types increase in importance. The most common adverse ocular effect of systemic steroids is the formation of cataracts [711]. These are typically situated in the posterior part of the lens, immediately below the capsule and are usually bilateral [712]. Posterior subcapsular cataracts may be easily seen by the physician using an ordinary ophthalmoscope if it is held 15–20 cm from the patient's eye using a setting of +4 diopter (red or black number 4 on the wheel) and shows black against the red reflex and

moving opposite to the direction of the patient's gaze, as opposed to corneal opacities which move in the same direction [713]. Slit-lamp examination is more sensitive and is confirmatory. Cataracts in children are rare, but as with adults an association between the formation of posterior subcapsular cataract and prolonged systemic steroid therapy is recognized [714]. Although earlier studies showed no clear association, there is now good evidence that the use of inhaled steroids (see below) is indeed associated with the development of posterior subcapsular and nuclear cataracts in adults and that risk increases with larger dose and longer use [715]. The techniques used in a large community-based study of over 3000 subjects may actually have underestimated the true prevalence of cataract, which was three times higher in users of inhaled steroids [713]. No such association has yet been shown in children [716]. Raised intraocular pressure resulting in glaucoma has been described but is unusual. Rarely, benign intracranial hypertension occurs, sometimes following a reduction in steroid dose, young females being predominantly affected [717].

#### *Mood and neurological changes*

Corticosteroids have long been recognized to have a mild euphoric effect and this may be welcome. Unfortunately negative psychological changes with depression or anxiety may also sometimes be reported [718]. Occasionally, in large dosage, they may precipitate acute confusion and frank psychosis [719], much to the consternation of ward staff and patients alike. Such disturbances are fortunately uncommon and frequently no noticeable effect on psychological state occurs [720]. The control of epilepsy may deteriorate.

#### *Other metabolic and endocrine effects including growth*

Glucose intolerance is a well-recognized consequence of systemic steroid treatment [721], occurring either acutely during high-dose therapy, in which case insulin treatment may be required, or more insidiously where lower doses are concerned, in which case dietary regulation and oral hypoglycaemic therapy may suffice. The control of pre-existing diabetes invariably requires some adjustment.

Growth retardation [722] may occur in children, although the effect of the systemic steroid preparation itself is not always easy to separate from that of the disease for which the steroids are being prescribed [723–725]. Thus asthma in children may be associated with growth delay, often with a late onset of puberty, although in modern practice children with asthma usually attain a normal final height [726,727]. Discontinuance of therapy or a reduction in dose may allow growth to 'catch up' but this cannot be depended upon and it is accepted that the first priority is to control asthma effectively with

appropriate agents even if this entails the use of high doses. It has been concluded that slow growth in children is more likely to be caused by poor control of asthma than by treatment with inhaled steroids (see below) [728]. Hypothalamic–pituitary–adrenal axis suppression is discussed below.

Mineralocorticoid effects are a feature of the shorter-acting steroids and are exaggerated if the patient is also being ventilated mechanically. Sodium and water retention may precipitate or exacerbate heart failure and hypertension and high-dose steroid treatment may similarly produce significant potassium loss and a metabolic alkalosis.

#### *Increased susceptibility to infection*

Increased susceptibility to bacterial infection seldom seems to be a practical problem in patients other than those whose immune responses are separately suppressed by other factors, such as neoplastic disease and associated chemotherapy, in which case opportunistic infection is not uncommon. Certainly corticosteroids do suppress cell-mediated immune responses, and this has led to particular concern about their use in patients who may have had inadequately treated tuberculosis in the past. Such fears are not unjustified, although the probability of tuberculous reactivation seems to be low [729].

Relatively trivial fungal infection, such as oral candidiasis, is a well-known complication and the risk of serious systemic fungal infections is also increased, although such patients usually have other serious underlying disease and are otherwise immunocompromised.

Susceptibility to viral infection may also be increased and may become manifest by herpes-zoster infection, cold sores or cutaneous warts that sometimes defeat the best endeavours of the dermatologist.

#### *Effects on pregnancy and lactation*

Fertility is not necessarily reduced in patients taking systemic steroids. The occurrence of fetal abnormalities is also poorly documented and although common sense dictates the avoidance of systemic steroids if possible in the first trimester, pregnancy should not preclude their use in an urgent medical situation [730]. Animal experiments carried out nearly half a century ago produced a single report of an increased incidence of cleft palate in the offspring of rabbits treated with cortisone early in pregnancy [731]. Such an association has not been confirmed in pregnant women despite the use of systemic steroids for many years for a variety of disorders, nor is there good evidence of an increased incidence of other malformations or fetal harm [732,733]. Pregnant women who need systemic steroids can therefore be reassured and, in the case of asthma, usually accept the advice that the good health of

the fetus is best served by proper control of the mother's respiratory condition. The neonatal paediatrician needs to be aware that the mother has been taking steroids, although infantile adrenal suppression need not occur, possibly as a result of the protection of the fetus by placental inactivation of glucocorticoids. Doses of up to 40 mg of prednisolone or the equivalent may be taken daily by a lactating mother without hazard to the baby, especially if breast-feeding is delayed by 4 h after a single daily steroid dose [734].

### *Adrenal suppression and insufficiency*

The normal autoregulatory hypothalamic–pituitary–adrenal (HPA) axis is suppressed by the supraphysiological plasma levels of corticosteroids achieved when these agents are given systemically [735]. This results in reduced levels of corticotrophin-releasing hormone, produced by the hypothalamus, and ACTH, produced by the pituitary. In order to minimize HPA suppression, it is usual to give systemic steroids as a once-daily dose in the morning, since long-acting steroids and evening dosage regimens are more likely to produce HPA suppression [736]. HPA suppression may, in certain circumstances, result in the secondary failure of the adrenal glands to mount a response to various forms of 'stress', i.e. endogenous glucocorticoid output falls short of physiological requirements when exogenous steroids are withdrawn. Measurable HPA suppression may occur with high doses of inhaled steroids (see below) but is unlikely to be clinically important.

When short-course steroid therapy is used, for example in acute asthma, measurable HPA suppression may occur after the equivalent of 40 mg of prednisolone daily for 7 days or after 20–30 mg daily for up to 2 weeks [737,738]; however, this is only likely to present a potential problem for a few days after discontinuance and clinical difficulties are seldom encountered, so that it has become common practice to stop 2-week courses of 30 mg prednisolone daily (or equivalent) abruptly when this intervention is used in conditions such as asthma [737,739].

When longer-term treatment (>3 weeks) is used, the equivalent of 5 mg of prednisolone taken as a single morning dose need not cause HPA suppression [740], whereas supraphysiological doses (>7.5 mg prednisolone or equivalent) will. The data on such patients are not clear-cut but when long-term treatment with steroids is reduced, incremental dosage reductions should be relatively small and may be spread over the space of several months in order to allow the suppressed HPA axis to recover. Adrenal cortical recovery may take 12 months from the cessation of steroid therapy and during this period the patient may require exogenous steroids to cover periods of stress. A failure to meet this need may result in the development of symptoms of tiredness and

malaise, and in extreme cases hypotension and collapse with the features of Addisonian crisis. Such dramatic occurrences are rare but must be guarded against, as fatalities have occurred [741].

Various regimens of dosage reduction may be applied when a decision has been made to wean a patient off steroids [649,742]. Patients who have been given a trial of 40–60 mg prednisolone daily (or equivalent) for 1 month for conditions such as cryptogenic fibrosing alveolitis and who have failed to respond may be cut back to a dose of 15 mg daily in 2 weeks. Thereafter a 2-weekly reduction in the daily dose by 2.5 mg may be made until discontinuance. Patients who have been on steroids for longer periods of time for various conditions may need to be reduced more cautiously, particularly when it is unclear whether the disease for which the treatment was used has resolved or not. When a dose of 15 mg of prednisolone daily (or equivalent) has been achieved, further monthly decrements of 2.5 mg may be made down to 5 mg daily, after which slower decrements of 1 mg per month may be used to allow the HPA axis to recover. These tailing-off regimens may be implemented by using scored prednisolone 5-mg tablets (or enteric-coated 2.5-mg tablets) and 1-mg tablets. Clinicians should be aware that scored 25-mg prednisolone tablets are sometimes dispensed by pharmacists. These tailing-off regimens tend to be empirical and have to be tailored to the needs of individual patients.

It is recommended that patients who remain on systemic steroids for more than 3 weeks should carry a record of their dosages on a steroid card from the outset and those on long-term treatment may be advised to wear a 'medical-alert' bracelet or tag. Periods of moderate physical stress may be covered by temporary dose increases. Thus a patient taking a maintenance dose of 10 mg prednisolone daily for asthma who requires a cholecystectomy may be given 10 mg (or parenteral equivalent) preoperatively, followed by 50 mg hydrocortisone i.v. intraoperatively and 20 mg hydrocortisone i.v. 8-hourly on the first postoperative day, thereafter returning to their usual dose. Major surgical or other trauma in a patient taking 40 mg prednisolone may require treatment with hydrocortisone 50 mg 8-hourly i.v., reducing to the previous baseline dose after 2–3 days [743].

When doubt exists about whether the adrenals have regained their capability to respond to ACTH, a dynamic adrenal stimulation test is sometimes carried out, for example the short tetracosactrin (Synacthen) test in which an intravenous bolus dose of 250 µg of the ACTH analogue tetracosactrin is given. Hypersensitivity reactions, including anaphylaxis, have rarely been described with this test so that facilities for resuscitation should be available if it is used. For a normal result, the plasma cortisol prior to injection should be greater than 138 nmol/L (5 µg/dL) in a patient who has not received glucocorticoid for 12 h;



30 min after injection, the plasma cortisol should be greater than 500 nmol/L (18 µg/dL) and should have risen by at least 200 nmol/L (7 µg/dL). In practice this investigation is seldom necessary and indeed such tests of adrenal function are unfortunately not always good guides to the ability of the adrenals to respond to stress. A normal response to a short tetracosactrin test does not always guarantee normal adrenal function in the face of stress, although if the test is abnormal steroid cover for surgical procedures is certainly needed [742,743]. Single morning cortisol measurements alone cannot be relied upon as they show too much variability, even with strict standardization of collection time, and may be normal in 50% of patients with adrenal suppression due to episodic secretion [744].

At standard dosage, the systemic absorption of inhaled steroids (see below) is negligible, although at high doses evidence of adrenal suppression may be found. Although a potential hazard, in practical terms this seems to be of academic rather than clinical importance.

#### *Drug interactions with steroids*

Reduced therapeutic effects of corticosteroids may occur with the concomitant use of rifampicin, carbamazepine, phenytoin, phenobarbital (phenobarbitone), primidone and aminoglutethimide. A lack of awareness of such problems may result in a catastrophic loss of control when a rifampicin-based antituberculous regimen is started in patients with steroid-dependent asthma [745]. Steroids may enhance the hypokalaemic effect of diuretics. They tend to antagonize the effects of oral hypoglycaemic agents, hypotensive agents and diuretics.

#### *Avoidance of systemic steroid complications*

Physicians are generally well aware of the potential problems associated with corticosteroid therapy and make efforts to use the minimal effective dose, which varies in individual circumstances but which should, whenever possible, be gauged against some measured parameter of response according to the disease being treated. Such efforts are entirely rational, as adverse effects are related both to dose and duration of steroid therapy, which should be kept as short as reasonably possible.

When treatment is necessarily prolonged, long-acting fluorinated steroids should be avoided, since adverse metabolic effects may be more common and their greater potency makes fine dosage manipulation problematical. It may be possible to prescribe the short-acting corticosteroids used in maintenance therapy (prednisolone, methylprednisolone) on alternate days but at twice the equivalent daily dose [681]. This may produce a comparable therapeutic effect but tends to reduce both side-effects and the likelihood of HPA suppression. Patients with

asthma may experience worsening of their symptoms on the 'off' day, and those who have been on a stable daily maintenance dose for long periods may also be susceptible to adrenal insufficiency, often with weakness, joint pains and nausea on the 'off' day; thus transfer should be gradual by slowly increasing the dose on the 'on' day and reducing it on the 'off' day by a similar amount.

Whether oral steroids are used on a daily or alternate-day basis for maintenance therapy, they should be taken as a single morning dose since this may produce less HPA suppression and is as effective as divided doses.

#### **Inhaled steroids**

Early studies of inhaled steroids in the treatment of asthma were carried out in the 1950s using aerosolized agents such as hydrocortisone and dexamethasone in solution. These were disappointing, probably because of enzymatic inactivation, and no advantage over systemic preparations was demonstrated. The discovery that synthetic modifications to the basic steroid structure conferred topical anti-inflammatory (glucocorticoid) properties with little in the way of unwanted systemic effects was first put to use in dermatological practice with beclometasone (beclomethasone) dipropionate cream. The idea that a similar topical effect might result from the use of the aerosolized preparation was well demonstrated when beclometasone dipropionate became generally available as an MDI for the treatment of asthma in the UK in 1972. This and subsequent inhaled steroids have very high affinities for intracellular glucocorticoid receptors but are rapidly metabolized to biologically inactive compounds, with the result that they have a good topical anti-inflammatory effect on airways with relatively few adverse systemic effects. Any benefit from inhaled steroids in patients with COPD is likely to be small and of doubtful clinical significance, results from one international trial suggesting that abstinence from tobacco was likely to be more effective in reducing the rate of decline in FEV<sub>1</sub> than taking regular budesonide 400 µg twice daily, which had no significant effect on the overall rate of decline or indeed on symptom scores or the number of exacerbations [746].

#### *Advantages*

Inhaled steroids came to fill an important therapeutic gap in the treatment of asthma by reducing the symptoms of patients who were inadequately controlled on non-steroid therapy but whose symptoms were of insufficient severity to need systemic steroids. They also enabled some patients who might otherwise have required systemic steroids to remain off them and enabled those who did require systemic steroids to be maintained on a lower dose or to discontinue them altogether [74–750]. With the 'rediscovery'

that asthma is an inflammatory condition, there has been an increasing trend to use inhaled steroids at an earlier stage and it is now common practice to introduce them in asthma of sufficient nuisance to require dosage with  $\beta_2$  agonists more than once a day [658].

These advantages are achieved with few of those side-effects usually associated with systemic treatment (see above); furthermore at standard dosage, suppression of adrenal function does not occur and adrenal function returns in those patients in whom it is possible to discontinue previous systemic steroid treatment [751]. Patients should be warned that the onset of action is not immediate and that it may take a week or more to produce a beneficial effect. This conservative information reduces the chance of the abandonment of the preparation as ineffective. As with all inhalational devices, it is essential that the physician or a competent assistant demonstrates the technique for whichever delivery device is recommended and checks the patient's ability to carry out the necessary manoeuvre.

### Pharmacology

It is likely that the effective topical use of certain inhaled steroids results from the high surface activity achieved by esterification at the C-17 and/or C-21 positions and by the formation of C-16 and C-17 acetonide derivatives (Fig. 9.34). The molecular mechanisms are as described for systemic steroids above. Thus although the metered dose released from a delivery device is, for standard purposes, only measured in micrograms and although only about 10% of each dose reaches the lungs, nevertheless the topical potency of these inhaled steroids is such that a standard adult daily dose of 400  $\mu\text{g}$  beclometasone dipropionate is effective in asthma, to the extent of being equivalent in therapeutic efficacy to 5–12.5 mg of prednisolone [750,752,753].

### Mode of action

It is believed that the mode of action of inhaled topical steroids is broadly similar to that of their systemic

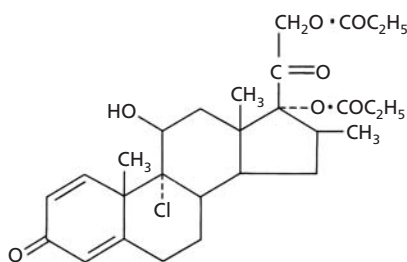
counterparts except that, for practical purposes, their actions at standard dosage are confined to the airways. By reducing airway inflammation, they diminish the airway hyperresponsiveness characteristic of asthma [658]. They have been shown to inhibit late allergic bronchoconstrictor reactions following an inhaled antigen challenge and, provided that several days' pretreatment is given, immediate reactions may also be inhibited [754,755]. They afford no immediate protection in exercise-induced asthma, although several weeks' pretreatment may have some protective effect in this respect [756].

### Absorption, metabolism and excretion

Up to 90% of each metered-dose inhalation may fail to reach the lungs, some being exhaled before deposition occurs but the bulk being deposited in the oropharynx, from where it is swallowed. In the case of beclometasone dipropionate, the small amount that reaches the lungs is rapidly absorbed into the blood [757]. The bulk of the drug is swallowed and is slowly absorbed, so that peak plasma levels occur 3–5 h after a dose [757,758]. It is likely that the small dose absorbed from the lungs is responsible for any potential systemic effects (such as adrenal suppression), since that fraction of the dose absorbed from the gut appears to be rapidly metabolized to inactive breakdown products during its first passage through the hepatic circulation [758,759]. These metabolites are for the most part excreted in bile and to a lesser extent in urine. The amount deposited in the mouth and subsequently swallowed is markedly reduced by the use of a large-volume spacer device attached to an MDI. A similar effect may be achieved by rinsing the mouth with water after using a dry powder delivery device.

### Method of administration

The original and most frequently used method of administration is pressurized MDI but there is a plethora of alternative dry powder delivery devices and spacers for the various preparations. It was at first recommended that inhaled steroids be taken in divided doses four times daily. As inhaled steroid treatment is essentially a preventive anti-inflammatory therapy, the patient receives no immediate signal of its efficacy, in contrast to  $\beta$  agonists in which a subjective response is usually rapid. This is disadvantageous with regard to patient compliance, so that treatments using less frequent dosage regimens were tested in order to increase the likelihood of the physician's advice being followed [760]. Twice-daily dosage regimens were shown to be as effective as the earlier four times daily regimens and are now standard [761,762]. This is the case for budesonide [763], beclometasone dipropionate [760,764] and fluticasone. It has been claimed that four times daily dosing may be more effective in severe asth-



**Fig. 9.34** Structure of beclometasone (beclomethasone) dipropionate: note dipropionate esterification in the C-17 and C-21 positions.

matics when high doses of inhaled steroid are used [765]. There is no convincing evidence that once-daily dosage regimens are as effective as the standard twice-daily approach [766,767].

#### *Dosage: standard or high*

Standard doses of inhaled topical steroids (equivalent to 400 µg of beclometasone dipropionate daily) have proved to be effective in the majority of patients with moderate asthma and early work with inhaled steroids showed no important improvement in the control of asthma with an increase in dosage of beclometasone from 400 to 800 µg daily [748], a finding that has been subsequently confirmed not only for beclometasone but also for budesonide [768,769]. Higher doses may be used with benefit in some patients with more severe asthma when the response to standard doses of inhaled steroid has been judged to be suboptimal [770]; studies that have examined the effects of higher doses on subsets of patients with more severe or chronic asthma have reported benefit with doses of beclometasone of up to 1000 or 1600 µg [771,772]. Similar claims have been made for high-dose budesonide (up to 1600 µg daily) compared with standard doses of beclometasone [773]. Needless to say, it may be misguided to prescribe higher-dose steroids before a check has been made to ensure that failure to respond to a lower dose was not due to poor inhaler technique [774]. An effort should also be made to demonstrate objective benefit if a high-dose regimen is to be continued. It should be remembered that the dose needed to maintain control may decrease [775], so that an attempt to reduce treatment may often be appropriate. All too frequently, patients may be left on an unnecessarily high dose of inhaled steroid in the longer term, a risk that may be increased by guidelines advocating initial treatment of asthma with high-dose inhaled steroids in order to gain rapid control, followed later by a step-down [776]. For most patients, the dose-response curve for airway efficacy becomes relatively flat at doses of inhaled steroid above 800–1000 µg daily [777], although the dose-response curve for systemic bioactivity and therefore any associated adverse effects becomes steep above this dose, particularly for steroids with greater systemic potency such as fluticasone propionate [778,779]. Some manufacturers have emphasized that their proprietary inhaled steroids may be inactivated by first-pass hepatic metabolism of the swallowed fraction of each metered dose, although it should not be forgotten that the dose which reaches the lungs is well absorbed directly into the systemic circulation and that this fraction assumes more importance with high-dose regimens. There is a risk that the uncritical use of high doses of inhaled steroid maximizes side-effects without increasing clinical benefit in many patients [780].

#### *Adverse effects*

The side-effects of inhaled steroids are relatively trivial and this, combined with their obvious therapeutic efficacy, has been the reason for their enormous success in the management of asthma.

Measures of HPA activity may be used as indicators of the systemic activity of topical steroids, being more sensitive in this regard than biochemical indices of bone metabolism [781]. HPA suppression equivalent to that encountered with maintenance alternate-day steroid therapy may be detected using such parameters [782]. These effects are minor and need not be regarded as indicating clinically significant impairment of adrenal function. When assessed by estimation of morning plasma cortisol or by 24-h urinary cortisol excretion, adrenal suppression in adults only occurs at doses of inhaled steroid exceeding the equivalent of about 1500 µg of beclometasone dipropionate daily [783–785]. The usual inhaled doses of other topical steroids, such as triamcinolone acetonide [786] and flunisolide [787], also seldom cause significant decreases in plasma cortisol levels.

From the standpoint of systemic activity, inhaled steroids should perhaps be used with more circumspection in children [782,788,789], although widespread and successful clinical use tends to belie such fears. Adrenal function was not found to be suppressed in children using either budesonide or fluticasone propionate at doses of 100–200 µg twice daily delivered by pressurized MDI via large-volume spacers, using overnight urinary cortisol as a marker [790]. It is possible that this result may be extrapolated to the budesonide dry powder device, bearing in mind that the respirable fraction from this is similar to that achieved with the pressurized device and large-volume spacer [790]. In general, in children doses of 400 µg beclometasone equivalent or less do not affect pituitary-adrenal function [658].

It should not be forgotten that patients who have received long-term treatment with systemic steroids only to be subsequently and successfully transferred to inhaled steroids may take about 12 months to recover normal responsiveness of their HPA axis and may therefore be susceptible to fatal secondary adrenal cortical insufficiency in any situations of stress that may occur during this period [791]. Although it has been suggested that patients taking inhaled steroids at doses equivalent to more than 1500 µg of beclometasone daily may need systemic steroids during prolonged stress [792], there is no evidence that such inhaled doses reduce a patient's capacity to produce endogenous cortisol in response to the stress of an attack of asthma [793]. The author is not aware of any published reports of adrenal crisis occurring as a result of the withdrawal of high-dose inhaled steroid therapy in either children or adults.

Whereas there is no doubt about the propensity of

systemic steroids to cause osteoporosis (see above), any links between inhaled steroids and altered bone metabolism are much more tenuous. Recent studies have been unable to reach consensus about whether steroids taken by the inhaled route have an effect on BMD, some showing a reduction in BMD [794], others not [795]. A recent cross-sectional study involving 81 patients found a reduction in lumbar spinal BMD in women equivalent to a reduction of about one-tenth of 1 standard deviation per 1000 µg/day inhaled steroid per year [794]. Such a seemingly small change would assume importance if any such relationship between reduced BMD and steroid usage was linear, since a number of studies have shown that the risk of vertebral fracture doubles for each standard deviation reduction in BMD [796]. No such relationship has so far been established.

The development of the technique of knemometry, which allows lower leg growth in children to be measured electronically with an accuracy of 0.2 mm, has demonstrated that inhaled steroids may indeed slow the rate of short-term growth [797,798]. This test appears to be a sensitive indicator of systemic activity since it has detected effects even when there has been no suppression of 24-h urinary cortisol; such changes have been shown with daily doses of 200–800 µg budesonide daily [799]. In another study, 400–800 µg beclometasone daily produced a greater effect on knemometry than fluticasone propionate 200 µg daily [800]. Although inhaled steroids may delay the onset of the prepubertal growth spurt in asthmatic children, there is good evidence that control of the asthma allows a subsequent 'catch-up' phase of growth to occur such that there is probably little difference in final adult height, which is likely to be compatible with that of their parents [801]. It is well known that asthma in children may be associated with growth delay, often with late onset of puberty, and it is accepted that the first priority is to control asthma effectively with appropriate agents even if this entails the use of high doses; indeed slow growth in children is more likely to be caused by poor control of asthma than by treatment with inhaled steroids [728,802]. In modern practice children with asthma who have been treated with inhaled steroids usually attain a normal final height [723,727,801].

A visible reminder that inhaled steroids are systemically absorbed is provided by the increased tendency of patients, particularly the elderly, to develop dermal thinning, striae and an increased tendency to bruise, especially when taking high doses [803,804].

Local side-effects of inhaled topical steroids include dysphonia and oropharyngeal candidiasis. Some degree of dysphonia has been reported in between one-third and one-half of patients taking inhaled steroids [805,806]. This may vary in intensity from a slight change in the quality of voice that is imperceptible to the observer and that the patient may not mention unless asked to obvious

hoarseness that regularly draws comment from social or casual contacts. Although at first attributed to candidiasis, visualization of the vocal cords in such patients has shown an adductor cord deformity in most cases [807]. It is now generally accepted that the dysphonia occurs as a result of a local steroid-induced myopathy affecting those intrinsic laryngeal muscles on which the steroid particles deposit during their passage through the oropharynx to the tracheobronchial tree. The frequency and severity of the complaint is related to the total daily inhaled steroid dose, tending to be more common with higher doses, although some patients may be badly affected in the lower dosage range [805]. Although a relatively minor nuisance to most patients, inhaled steroid-induced dysphonia may present a more serious problem to those who have to sing or who otherwise use their voices in their work. The dysphonia is reversible and disappears if the inhaled steroid is stopped [807]. The introduction of a spacer device (holding chamber) between the pressurized MDI and the patient's mouth undoubtedly reduces oropharyngeal deposition and therefore the incidence of candidiasis with inhaled steroids [808]. However, the use of these devices probably does not help to prevent dysphonia as they actually increase the proportion of the dose passing through the cords to the tracheobronchial tree [806,808]. There is evidence that some dry powder devices are less likely to cause dysphonia than pressurized MDIs, with or without spacers [809]. If this is the case, it may be that the anatomical position of the cords reduces laryngeal deposition of particles when the patient draws air through a resistance. Occasionally the inhaled steroid has to be reduced or temporarily discontinued altogether, provided that other medication is adjusted to allow for this. Unfortunately the problem often recurs.

Oropharyngeal candidiasis has been reported with inhaled steroid use, with widely varying frequencies of up to 77% [810]. However, such high figures are likely to be a consequence of the methodology of the study since *Candida albicans* may be recovered from the mouths and throats of 40–50% of control populations who are not taking predisposing medication [811]; it is presumably these patients, in whom the organism is established commensally before treatment, who are susceptible to develop the clinical syndrome of thrush. Although seemingly dose related when multiple inhalations from a lower-dose beclometasone pressurized MDI are used [748,772], the frequency of oropharyngeal candidiasis does not appear to increase in commensurate fashion when a higher dose is taken as a single inhalation using a 250 µg/puff MDI, implying that dosing frequency as well as total dose may affect the incidence [811]. The same may be true of budesonide [812]. There is no evidence that changing to a different steroid influences the risk. However, the delivery device is important and the use of large-volume plastic spacers with pressurized MDIs certainly diminishes the

risk of candidiasis by reducing oropharyngeal deposition from about 80% to about 20% [813,814]. The typical curd-like lesions on the tongue and oropharyngeal mucosa are easily recognized and treated with nystatin suspension (or pastilles) 100 000 units four times daily to be held in the mouth after food, continuing for 48 h after the lesions have resolved. Amphotericin 10 mg lozenges four to eight times daily for about 2 weeks may be used as an alternative. Such treatment is sometimes used empirically in the absence of obvious thrush if patients on inhaled steroids complain of soreness of the mouth. It is unusual for the inhaled steroid to have to be discontinued.

No long-term bronchial epithelial damage has been reported as a result of the use of inhaled steroids in conventional or high-dose form [815].

There have been occasional reports of inhaled steroids producing cough and wheeze in a few cases, with resultant patient intolerance [816]. Such difficulties, which in the author's experience are uncommon, could be a result of the propellant or dispersant rather than the steroid itself, in which case the use of an alternative pressurized MDI or dry powder device may overcome the problem [817,818].

### Individual inhaled steroid preparations

Although individual steroids have differing degrees of topical potency when tested on skin [819], the evidence that this provides one inhaled preparation with a clear therapeutic advantage over the next is slender, since at the recommended doses the different preparations available are approximately equivalent in terms of clinical efficacy. Failure of a patient to respond to one preparation is frequently due to poor compliance or technique. When this has led to patient disillusionment with a particular drug, a justifiable psychological ploy is to switch to another preparation and to ensure that the patient understands thoroughly how to use it properly.

#### *Beclometasone (beclomethasone) dipropionate*

Beclometasone dipropionate has a similar structure to dexamethasone except that it is halogenated, with a chlorine atom in the C-9 position and the C-16 methyl group in the  $\beta$  position (see Figs 9.33 & 9.34). The dipropionate derivative is formed by esterification of the hydroxyl groups in the C-17 and C-21 positions. Beclometasone is lipophilic, although less so than budesonide, flunisolide and fluticasone propionate, and the fraction absorbed from the gut is therefore susceptible to breakdown by P450 enzymes in the liver by first-pass metabolism. This is fortunate since it compensates for the ready systemic absorption of beclometasone and the other inhaled steroids from the mucosal surface of the lungs.

The standard adult dose by MDI is 200  $\mu$ g twice

daily (two 100  $\mu$ g puffs twice daily). 'High-dose' treatment usually comprises 500  $\mu$ g twice daily (two 250  $\mu$ g puffs twice daily) but doses of 1000  $\mu$ g twice daily may be used. Now that the product's patent has expired, a variety of standard and breath-actuated pressurized MDIs are available. The general principle is to use the lowest dose that controls the patient's symptoms adequately. This should mean that the vast majority of asthmatics in the community take the lower dosage range but that difficult cases may require the higher doses. These carry the risk of adverse systemic effects (see above), although to a lesser extent than an equivalent dose of oral steroid. Various dry powder preparations are available for those unable to operate pressurized MDIs (usually the very young and the elderly). A similar twice-daily regimen may be used, 400  $\mu$ g of dry powder being generally considered equivalent in effect to 200  $\mu$ g of the MDI preparation. Nasal aqueous sprays are available for the topical treatment of allergic rhinitis at a standard dose of 100  $\mu$ g twice daily to each nostril; these preparations are absorbed in similar fashion to inhaled steroids.

#### *Budesonide*

The structure of budesonide is shown in Fig. 9.35. It is non-halogenated (no chlorine or fluorine atom) and has acetone substitutions in the C-16 and C-17 positions. These substitutions increase its lipophilicity and pharmacological studies have shown that it has high topical potency with relatively low systemic activity [759,820]. As with fluticasone propionate and triamcinolone acetonide, the swallowed fraction of the inhaled dose undergoes a relatively high degree of first-pass metabolism in the liver (89%) so that systemic bioactivity is largely determined by the quantity of drug absorbed from the lung directly into the systemic circulation, thereby avoiding first-pass metabolism. The standard adult dose, as with beclometasone, is 200  $\mu$ g twice daily by pressurized MDI (*one* 200  $\mu$ g puff twice daily). Half this dose may be given in children using a 50- $\mu$ g MDI. 'High-dose' budesonide may be used up to 800  $\mu$ g twice daily. The same dose range may be delivered by a well-designed dry powder device. A formulation for nebulization is available (250–500  $\mu$ g/mL) but this is seldom indicated in adult practice. A nasal aerosol spray exists for the topical treatment of allergic rhinitis at a standard dose of 100  $\mu$ g twice daily to each nostril, reducing to once daily when control is achieved; these preparations are absorbed systemically in similar fashion to inhaled steroids.

#### *Fluticasone propionate*

Fluticasone propionate is a synthetic trifluorinated glucocorticoid, the molecular structure of which is shown in Fig. 9.36. It is highly lipophilic and therefore has very high

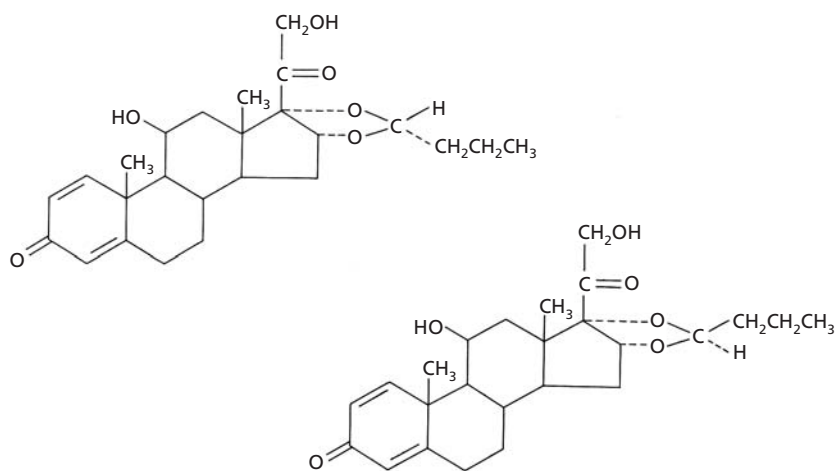


Fig. 9.35 Structures of the two epimers that comprise budesonide.

steroid receptor affinity, so that two puffs from a standard 50 µg/puff inhaler twice daily is, for practical purposes, equivalent to 200 µg twice daily of beclometasone or budesonide [821]. The 125-µg MDI may be considered equivalent dose for dose to the 250-µg beclometasone device. The greater potency weight for weight of fluticasone does not imply that asthma will be better controlled at optimal daily dosage. There is also a 250-µg pressurized MDI which has no equivalent beclometasone device. Fluticasone is licensed for dose regimens of up to 1 mg twice daily, which is equivalent to eight 250-µg doses of beclometasone twice daily, a fact that may not be appreciated in community prescribing. Fluticasone has a long plasma elimination half-life of about 14.5 h (cf. 2.3 h for budesonide). As with budesonide and triamcinolone acetonide, the swallowed fraction of the inhaled dose undergoes a high degree of first-pass metabolism in the liver (99%) so that systemic bioactivity is largely determined by the quantity of drug absorbed from the lung directly into the systemic circulation, thereby avoiding first-pass metabolism. The drug may be prescribed as pressurized MDI or dry powder. A nasal aqueous spray is available for the topical treatment of allergic rhinitis at a standard dose of 100 µg (two sprays) once or twice daily to each nostril;

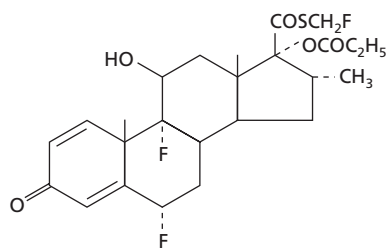


Fig. 9.36 Structure of fluticasone propionate.

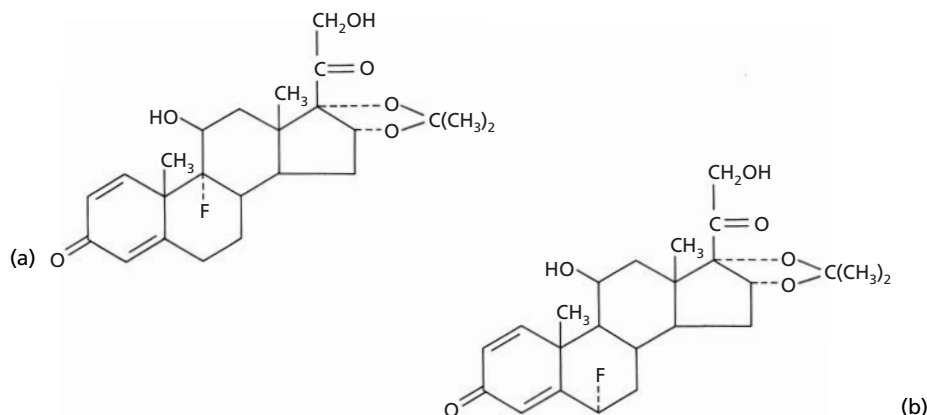
these preparations are absorbed in similar fashion to inhaled steroids.

#### Flunisolide

This preparation is available for the treatment of asthma as an MDI in the USA but not in the UK. Its structure differs from hydrocortisone in that it has a fluorine atom in the C-6 position and acetonide substitutions in the C-16 and C-17 positions (Fig. 9.37). It differs from triamcinolone only in the position of its fluorine atom. The dose is 500–1000 µg twice daily (two to four 250-µg puffs). Although absorption of this product is greater, as with budesonide first-pass hepatic metabolism is rapid with this compound [822]. A metered-dose nasal spray is available (also in the UK) for the treatment of allergic rhinitis, the usual dose being 50 µg (two sprays) to each nostril twice daily, topical glucocorticoids having been shown to be effective in blocking the nasal response to antigen challenge [823].

#### Triamcinolone acetonide

This compound (Fig. 9.37) is available for inhalation in the USA as an MDI but not in the UK. As with fluticasone propionate and budesonide, the swallowed fraction of the inhaled dose undergoes a relatively high degree of first-pass metabolism in the liver so that systemic bioactivity is largely determined by the quantity of drug absorbed from the lung directly into the systemic circulation, thereby avoiding first-pass metabolism. The dose per puff is 200 µg, although a spacer device allows only 100 µg to reach the patient. The standard dose is eight inhalations daily given in divided doses at least twice daily. Up to 16 doses daily may be used in 'high-dose' therapy. A nasal aqueous spray is available for the topical treatment of allergic rhinitis at a standard dose of 110 µg (two sprays)



**Fig. 9.37** Structure of (a) triamcinolone acetonide (note acetonide group attached to C-16 and C-17 positions) and (b) flunisolide (differs only in position of fluorine atom).

once daily to each nostril, reducing to one spray when control has been achieved; these preparations are absorbed in similar fashion to inhaled steroids.

### Delivery devices for inhaled medication

It is beyond the scope of this chapter to describe the large number of devices commercially available for the delivery of inhaled bronchodilators and anti-inflammatory drugs. The two main categories are pressurized MDIs and dry powder devices [437]. The first category has been refined with the introduction of breath-actuated devices that do away with the need to coordinate finger and diaphragm and may be used in place of the standard 'press and breath' inhalers. Many of the 'press and breath' inhalers may be used with large-volume spacer devices designed to reduce oropharyngeal impaction and to generally reduce the need for coordination [824]. There are also many different dry powder devices, ranging from simple 'capsule in chamber' arrangements and blister packs or strips to cunningly engineered twist-loading turbine devices. Some manufacturers produce attachments for their devices in order to assist the patient who has difficulties actuating or loading the inhaler because of a weak grip. Suffice to say that no one inhaler device reigns supreme. Many patients are able to manage the original 'press and breath' devices adequately. Other patients may cope better with a device that requires simple suction. It is a matter for the doctor or nurse to first familiarize themselves with the alternatives and to be prepared to spend time teaching whichever technique the individual patient seems most comfortable with and best able to manage [437,825].

Jet nebulizers are the delivery mechanism of choice for bronchodilators in acute severe asthma affecting all age groups, and have the added advantage that they may be driven by oxygen. The jet of driving gas draws the solution to be nebulized up a fine-bore tube using the venturi principle. The solution is then fragmented into small droplets by impact with a baffle, the remaining solution

falling back into the reservoir of the nebulizer to repeat the cycle until all is used up. The mass and volume distribution of particles produced by different nebulizers varies according to the characteristics of the jet nebulizer, the compressor, the rate of flow of driving gas and the volume of fill [437].

### Chlorofluorocarbons (freons) and the Montreal Protocol

Under the terms of an international agreement known as the Montreal Protocol, 140 countries agreed to phase out their entire use of chlorofluorocarbons (CFCs) in order to diminish damage to the earth's stratospheric ozone layer. One effect of this agreement has been the gradual replacement of CFC propellants in pressurized MDIs with hydrofluoroalkane (HFA) alternatives; rather than chlorine these contain fluorine, which does not deplete the ozone layer. It is probable that the transition will be completed within the first 5 years or so of the twenty-first century. The first salbutamol HFA formulation has somewhat different physical characteristics and the patient may notice these in terms of the impact of the spray and the slightly different taste, but the formulations may be substituted dose for dose. However, there are preliminary data indicating that some HFA steroid formulations have markedly different characteristics, with a smaller particle size resulting in a greater fractional deposition of steroid in the lungs with less being swallowed, to the extent that it may be desirable to step *down* the dose of inhaled steroid when the change is made from CFC to HFA in order to achieve the same bronchial effect. Thus one proprietary beclomethasone product will have approximately the same clinical effect for half the dose [826]. Such changes may reduce the importance of first-pass metabolism in the liver and increase the importance of direct systemic absorption from the lungs. The trend is therefore likely to be one of dose reduction, depending on the physical characteristics of individual delivery devices as they become available, and it may help to focus the medical profession on the opportunity to reduce inhaled steroid treatment.



## Respiratory stimulants

Many drugs are known to stimulate ventilation in humans but few have found a place in therapeutics, largely because of their high incidence of toxic side-effects, a prime example being strychnine. A description of some drugs that have found, or may yet find, a useful clinical role follows.

### Analeptic drugs: doxapram

Three analeptic drugs were available for intravenous administration at the time of the last edition of this book: doxapram, nikethamide and ethamivan. Of these, only doxapram remains commercially available in the UK and USA. The principal, if limited, role of this drug is in the short-term management of acute ventilatory failure, usually in patients with chronic bronchitis and emphysema, as an addition to the more usual interventions such as bronchodilators and controlled oxygen therapy. The clinical situation in which this drug is applied is where the seriously hypoxic patient is starting to become obtunded and is displaying increasing evidence of alveolar hypoventilation, with a rising  $P_{aCO_2}$  and shallow irregular breathing. The use of a respiratory stimulant in these circumstances may rouse the patient's conscious level, enabling better clearance of respiratory secretions and improving minute ventilation [827,828]. Analeptic drugs are of no value in the treatment of an alert and anxious patient who is already fighting for breath, and may indeed be harmful in such circumstances, possibly resulting in increased metabolic production of carbon dioxide, without usefully adding to an already seemingly maximal ventilatory drive. Beneficial effects from the use of respiratory stimulants cannot be relied upon and if it is judged that mechanical ventilation (either nasal/face mask or by endotracheal intubation) is indicated, then this form of treatment is probably best prepared for without delay. If for some reason mechanical ventilation is thought to be contraindicated, if it is not immediately available for reasons of limited resource or if there is doubt about whether it will be necessary, then doxapram may be worth a trial [829]. Doxapram has also been used to treat respiratory depression following general anaesthesia [830].

### Mode of action, administration and pharmacokinetics

Analeptics are CNS stimulants, although at therapeutic doses doxapram acts on carotid body chemoreceptors [831]. Tidal volume and respiratory rate have been shown to be increased in healthy volunteers and ventilatory response to hypoxia and hypercarbia are heightened [831,832].

All analeptic drugs have to be given intravenously and

the duration of their action following injection is short, seldom exceeding 10 min. Nikethamide and ethamivan used to be given by slow bolus injection, whereas doxapram is normally given by infusion in the setting of acute respiratory failure due to chronic bronchitis and emphysema. There are no good data about whether repeated intravenous injection or continuous infusion is best, but the latter is usually preferred.

All these agents are rapidly metabolized and excretion of inactive metabolites is largely renal. Only a small proportion of doxapram is excreted unchanged in the urine, metabolism being largely hepatic [833].

### Dosage

Doxapram hydrochloride is available as a 2 mg/mL solution in 5% glucose contained in a 500-mL infusion bottle. An initial dose of 5 mg/min has been recommended, reducing according to response to a maintenance dose of 1–3 mg/min. Therapy should be controlled by blood gas and pH analysis. Limitation of the total dose to about 600 mg is advised. Nikethamide was given at a dose of 500 µg by slow intravenous injection, to be repeated at 30-min intervals according to response.

### Adverse effects

Analeptic drugs have a narrow therapeutic index, their effects extending from the desirable increased sense of wakefulness to undesirable CNS stimulation, including agitation, restlessness and in the worst case major convulsions; thus dose control must be careful and these drugs are contraindicated in epilepsy. Clearly a grand mal seizure in an already seriously hypoxic and hypercapnic patient with a depressed respiratory rate may deliver the *coup de grâce* and should be avoided at all costs; indeed it is for this reason that nikethamide and ethamivan are no longer recommended. Analeptics may also have a pressor and dysrhythmic effect as a result of increased epinephrine (adrenaline) release, so that hypertension and known coronary artery disease are relative contraindications.

### Progestogens: medroxyprogesterone acetate

An association between high levels of endogenous progesterone production in pregnancy and increasing ventilation has long been recognized [834] and can be demonstrated in terms of both increased minute ventilation and mouth occlusion pressure [835]. Similar respiratory stimulation may be induced by the administration of synthetic progesterone analogues such as medroxyprogesterone acetate. Minute ventilation rises as a result of an increased tidal volume and in normal subjects has been shown to result in a mean fall in  $P_{aCO_2}$  of about 0.7 kPa (5 mmHg) within

approximately 2 days [836]. It has been supposed that progesterone has a central action, crossing the blood-brain barrier and stimulating the brainstem respiratory centres, although this is uncertain [836]. Some workers have also found that progesterone may increase ventilatory responses to both hypoxia and hypercarbia [837–839].

There were early reports of medroxyprogesterone acetate having been used with evident clinical success in the treatment of patients with what was then thought to be hypercapnia due to primary alveolar hypoventilation occurring in association with obesity and hypersomnolence (previously known as pickwickian syndrome) [840,841]. Clinical improvement, in terms of reduced daytime somnolence and diminished heart failure, was also reported in some obese patients with what later became recognized as obstructive sleep apnoea syndrome; however, there was no significant diminution of episodes of potentially serious nocturnal arterial hypoxaemia or cardiac dysrhythmias in this study [842]. Subsequent experience with medroxyprogesterone in obstructive sleep apnoea syndrome was disappointing [843], this being predictable in view of the mechanical nature of the obstruction, which is now usually successfully overcome with continuous positive airway pressure or other measures (see Chapter 47).

A number of small studies have been carried out to assess the effect of medroxyprogesterone in patients with respiratory failure due to COPD. One such study examined the effect in 17 patients who were in chronic but stable respiratory failure with a mean  $FEV_1$  of 1.2 L,  $Pao_2$  6.6 kPa (50 mmHg) and  $Paco_2$  6.9 kPa (52 mmHg). A mean fall in  $Paco_2$  of about 1 kPa with a mean rise in  $Pao_2$  of about 0.7 kPa at 4 weeks was found in 10 of the patients [844]. Three other studies in patients with hypercapnic COPD have also shown mean falls in  $Paco_2$  with medroxyprogesterone, usually of about 1 kPa over the space of 1–4 weeks [845–847]. These other studies also reported modest improvements in oxygenation although, not surprisingly, this was not necessarily maintained at night [845]. It may be possible to predict which of this category of patients will respond by seeing whether they are capable of voluntarily lowering their  $Paco_2$  by deliberately trying to overbreathe [844].

Medroxyprogesterone acetate is well absorbed following oral administration, doses used having varied between 20 mg three times daily and 50 mg twice daily. Preparations available include 10 mg and scored 100 mg tablets (which are used for menstrual irregularities and the hormonal treatment of metastatic breast, endometrial and other hormone-sensitive cancers). The drug is mainly metabolized in the liver but significant amounts are excreted unchanged in the urine.

Adverse effects are uncommon but may include male

impotence and alopecia, fluid retention, weight gain and menstrual irregularities correctable with testosterone or cessation of the drug. There is a theoretical risk of thromboembolic disorders.

There is no good evidence to support the general or long-term use of this drug as a respiratory stimulant and whether there might be a case for its occasional shorter-term use during the stabilization of hypercapnic patients with diminished respiratory drive is still open to debate.

### Protriptyline

Protriptyline is a tricyclic antidepressant that has relatively little sedative effect. It is not a true respiratory stimulant in that it appears to have no effect on waking ventilation in normal subjects [848], although small doses appear to affect the pattern of breathing during sleep, tending to reduce the time spent in the rapid eye movement (REM) phase [849]. This effect is probably relevant to the benefit that has been recorded following its use in some patients with obstructive sleep apnoea syndrome [849,850]. Its mode of action is uncertain but it may modify upper airway motor activity via an effect on the brainstem reticular system, so that upper airway resistance is reduced [851]. There is some evidence to suggest that the centrally acting selective serotonin reuptake inhibitor fluoxetine also decreases the proportion of REM sleep and that some patients with obstructive sleep apnoea syndrome may similarly derive benefit, with fewer adverse effects than protriptyline [852]. Small studies in which it has been used in patients with hypercapnic respiratory failure due to COPD have shown increases in mean  $Pao_2$  and reduced nocturnal desaturation [853,854], although no improvement was found in daytime arterial oxygen concentration in a placebo-controlled double-blind trial of 10 mg protriptyline daily [855]. It may be given as a single dose 1 h before retiring, starting at 5 mg and gradually increasing to 20 mg according to response. Its usefulness may be limited by atropine-like side-effects, including dry mouth, constipation and urinary hesitancy. As with other tricyclics cardiac dysrhythmias may occur.

As with medroxyprogesterone, there is no good evidence to support the general or long-term use of this drug solely as a respiratory stimulant and whether there might be a case for its occasional shorter-term use during the stabilization of hypercapnic patients with diminished respiratory drive and in the more medium term for improving sleep quality is open to debate [853].

### Acetazolamide

Acetazolamide is a sulphonamide that reversibly inhibits the enzyme carbonic anhydrase. The primary site of action of the drug is the kidneys, where it inhibits renal tubular

hydrogen ion excretion, increasing urinary bicarbonate and decreasing urinary chloride concentrations [856]. Such changes reduce the extracellular fluid bicarbonate concentration, producing a metabolic acidosis with resultant stimulation of both medullary and peripheral chemoreceptors. These actions may prove clinically useful in patients with COPD, who may develop hypoventilation to compensate for a diuretic- or steroid-induced metabolic alkalosis. A double-blind placebo-controlled study assessing the effect of acetazolamide 250 mg twice daily over 1 week in a group of 53 hypoxaemic patients with COPD found that it produced a small fall in daytime  $P_{aCO_2}$ , a small increase in daytime  $P_{aO_2}$  and increased ventilatory responses to both hypercapnia and hypoxia [857]. There is also some evidence that the drug reduces periods of apnoea and arousals in central sleep apnoea [858,859].

Acetazolamide may also be used by mountaineers and trekkers as a means of helping to prevent acute mountain sickness by counteracting the hypoventilation that may develop following overbreathing caused by an excessively rapid ascent to high altitudes [860,861], hypoxaemia being particularly exaggerated during REM sleep at night [862].

The usual dose is 250 mg orally twice daily or 500 mg as two sustained-release capsules once daily; 250 mg 1 h before bedtime has been used in central sleep apnoea [859].

Side-effects include a mild diuretic effect with a predisposition to hypokalaemia. Paraesthesiae are also common. Sulphonamide adverse effects may occur and these can include agranulocytosis, so that blood counts are recommended if treatment is to be prolonged. Diclofenamide (dichlorophenamide) is an alternative carbonic anhydrase inhibitor available in the USA [863].

### Other drugs with respiratory stimulant properties

#### *Theophyllines*

Theophyllines are widely used for their bronchodilator properties and have been discussed fully in this context in an earlier section of this chapter. There has also been some interest in the ability of theophylline to stimulate respiration centrally and improve the contractility of the diaphragm and reduce its fatigue [547,864,865]. The clinical significance of these physiological observations in adults has been questioned [866], although in paediatric practice apnoeic episodes have been reduced in premature infants by theophylline administration [867].

Some but not all studies in normal subjects have found that intravenous aminophylline or therapeutic oral doses of theophylline increase minute ventilation, presumably as a result of a central effect [868]. It is doubtful whether any such respiratory stimulant effect is likely to be of clinical

significance in patients with COPD and the rationale for prescribing this group of drugs is to make use of their bronchodilator properties.

#### *Almitrine bimesylate*

Almitrine is a respiratory stimulant chemically related to the antihelminthic drug piperazine rather than to doxapram and other analeptic drugs. It has the apparent advantages of both oral administration and a long duration of action. The mode of action of this drug has yet to be fully defined but unlike other respiratory stimulants it acts peripherally on carotid and aortic body chemoreceptors with no effect on the central medullary respiratory centres [869,870]. There is little change in resting ventilation in normal subjects but the ventilatory response to hypoxia is greatly enhanced [871,872], that to hypercarbia being heightened to a lesser extent. In addition to increasing ventilatory responses [873,874], almitrine also improves ventilation-perfusion matching in patients with chronic bronchitis and emphysema, although it is unclear whether this is the result of a pulmonary vasoconstrictor effect [875–877]. The summation of these effects tends to increase  $P_{aO_2}$  and reduce  $P_{aCO_2}$  in such patients.

Almitrine is rapidly absorbed following oral administration. It is metabolized in the liver to largely inactive metabolites, the majority being excreted in bile and less than 5% in urine [878]. The plasma half-life after a single dose is 2–3 h but with increasing duration of therapy becomes gradually prolonged to well over 2 weeks, presumably as a result of its binding to tissues with subsequent slow release [879,880].

The indications for almitrine are still under investigation and whether it has a place in the treatment of hypoxic patients with COPD remains *sub judice*. Readers may wish to draw their own conclusions when considering that this drug has been under investigation for over 25 years and is still without a licence for general clinical use. A small early study suggested that as well as improving blood gas tensions during wakefulness, the frequency and severity of episodes of nocturnal hypoxaemia tended to be reduced [881], while other work suggested that a treated group of chronic bronchitics required fewer hospital admissions during the period of study. It was noticed in these early studies that some patients complained of worsening dyspnoea [879], paraesthesiae and peripheral neuropathy having been reported in other studies [882,883].

A larger prospective study examined the effect of almitrine 50–100 mg twice daily compared with placebo in over 700 patients with stable hypoxic COPD for up to 1 year in order to determine whether the drug had a role as a long-term treatment in this group, just as long-term oxygen therapy had been previously investigated in similar groups [884]. There was no survival advantage but the mean  $P_{aO_2}$  in the actively treated group improved by

about 1 kPa, with a smaller fall in  $P_{aCO_2}$  [884]. The treated group also had fewer hospital admissions, a reduction in secondary polycythaemia, a small rise in  $FEV_1$  but no change in 6-min walking distance [884]. About one-third of patients in the treatment group failed to respond. Improvement in these measured parameters was offset by a troublesome side-effect profile, with malaise, gastrointestinal upsets, loss of weight, increased dyspnoea and peripheral neuropathy; there was also a 40% withdrawal from the active limb of the trial compared with 25% with placebo [884]. These difficulties correlated with raised blood levels of the drug, resulting from its tendency to accumulate with prolonged use, so that a later UK study attempted to address this by adopting a regimen of 25–50 mg twice daily (1 mg/kg daily) for 2 months followed by a 1-month 'rest period' [885]. Small changes in arterial gas tensions were found similar to those of the earlier larger study, but there was no change in 6-min walking distance. The fall-out rate for the active treatment limb was 28% compared with 20% for placebo. Increased dyspnoea, gastrointestinal disturbance and paraesthesiae were equally cited, although no patient was thought to develop clinical peripheral neuropathy [885]. A study designed to evaluate the effect of short-term oral almitrine in addition to usual measures in patients admitted to hospital with acute-on-chronic respiratory failure due to COPD failed to show any benefit [886]. It is not known whether the addition of almitrine to long-term oxygen therapy in patients with COPD confers any benefit [880].

Small studies intended to examine the effect of almitrine on nocturnal oxygen saturation in patients with COPD have shown that just as this drug increases baseline  $P_{aO_2}$  during the day, so baseline  $S_{aO_2}$  is similarly increased at night [881]. In the short term, almitrine 1.5 mg/kg daily was found to be more effective in increasing nocturnal  $S_{aO_2}$  than 100 mg medroxyprogesterone in a similar group of patients with COPD [839].

There is no clearly defined role for almitrine in the management of central sleep apnoea [887,888].

## Cytotoxic drugs used in respiratory medicine

Cytotoxic drugs may be used in respiratory medicine both in the management of non-neoplastic disease in which there is some disturbance of immune regulation and in neoplastic disease. Non-neoplastic disease is more usually treated using corticosteroid therapy alone, other cytotoxic/immunosuppressive drugs being held as second-line treatment following the failure of steroids or are added for their steroid-sparing effect. There are exceptions to this general rule, such as Wegener's granulomatosis, other vasculitides and Goodpasture's syndrome. The drugs most commonly used in such non-neoplastic diseases are, in descending order of frequency, cyclophos-

phamide, azathioprine and chlorambucil, the use of cyclosporin being largely confined to transplant work.

Many cytotoxic drugs have been used in the treatment of intrathoracic neoplastic disease. The most notable successes have been scored in certain intrathoracic germ cell tumours, in lymphomas (especially Hodgkin's disease) and, to a much lesser extent, in small-cell lung cancer. The appropriate use of cytotoxic drugs in non-small-cell lung cancer remains controversial and continues to be examined, there being a need for randomized clinical trials to establish optimal management for this common group of diseases. These trials will have to be large in order to demonstrate anticipated improvements in median survival in the order of a few percentage points; although this appears to be a small difference, it might nevertheless make a significant impact on a common cancer, provided that a satisfactory quality of life could be maintained [889]. Such trials are still possible in the UK, where the scepticism of respiratory physicians for the value of chemotherapy in non-small-cell lung cancer has prevented its general use, in contrast to many centres throughout the world where its application would be considered the norm, almost irrespective of stage of presentation [890]. Such regimens usually make use of combinations of drugs, the detailed management of which is a matter for the specialist. The majority of regimens for non-small-cell lung cancer are based on cisplatin, the most active probably being mitomycin/vinblastine/cisplatin (MVP) and mitomycin/ifosfamide/cisplatin (MIC) [889]. Treatment of germ cell tumours is discussed in Chapter 49, lymphoma in Chapter 42 and small-cell lung cancer and non-small-cell lung cancer in Chapter 41.

This section deals with the individual properties of some of those cytotoxic drugs found to be most useful in respiratory medicine.

### *Cyclophosphamide*

Cyclophosphamide, like chlorambucil, is an alkylating agent of the nitrogen mustard type. Although mainly used as an antineoplastic drug, it is also useful as an immunosuppressive agent, being effective in autoimmune diseases where antibody is a major factor. Its principal uses in respiratory medicine include the treatment of small-cell lung cancer (see Chapter 41), Wegener's granulomatosis [891,892] (see Chapter 40) and Goodpasture's syndrome (see Chapter 38). It has also been used in a wide variety of other disorders, mainly in a supportive role with steroids, including cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) (see Chapter 31) [893,894]; other eosinophilic vasculitides, such as polyarteritis nodosa, Churg–Strauss syndrome and microscopic polyangiitis (see Chapter 40) [895–897]; rheumatoid vasculitis and Beçhet's syndrome (although clear-cut evidence of benefit is insubstantial) [898,899]; and pulmonary involvement

in a variety of collagen vascular disorders, such as polymyositis/dermatomyositis (see Chapter 53) [900]. Cyclophosphamide has been used in the past in the treatment of angioimmunoblastic lymphadenopathy (a type of T-cell lymphoma) [901] but the prognosis remains poor and it is not clear whether any real benefit accrues from its use. There is some evidence to suggest that pulse therapy with two 1-g doses of cyclophosphamide intravenously on consecutive days followed by three 1-g doses of methylprednisolone daily for 3 days might improve survival after moderate to severe paraquat poisoning [902,903].

#### *Mode of action*

The mode of action of cyclophosphamide is complex. An active hepatic metabolite, phosphoramidate mustard, alkylates or binds with many biologically important proteins and with DNA and RNA, so that the genetic processes of replication and transcription are impeded. Its antineoplastic activity is thought to arise from the formation of cross-linkages between strands of DNA and RNA and from the resulting inhibition of protein synthesis. Its immunosuppressive activity appears to be dose dependent and probably extends to both cell-mediated and humoral functions. Bone marrow suppression diminishes the numbers of circulatory neutrophils and the capacity of these and other cells to become involved in inflammatory immune processes is reduced. Antibody responses may also be reduced by the suppression of B lymphocytes, of which fewer are found in lymphoid follicles [904].

#### *Administration, distribution, metabolism and excretion*

Cyclophosphamide is well absorbed orally and may also be given intravenously. It is widely distributed and is converted in the liver to active metabolites including phosphoramidate mustard. Degradation also takes place in the liver and the drug is not recommended in patients with a plasma bilirubin greater than  $17\text{ }\mu\text{mol/L}$  ( $1.0\text{ mg/dL}$ ) or if the serum transaminase or alkaline phosphatase are more than twice the upper limit of normal. The plasma half-life of the parent drug is about 6 h. As excretion is renal (about one-quarter as unchanged drug and the remainder in the form of metabolites) the plasma half-life is prolonged in renal insufficiency and cyclophosphamide is not recommended in patients with a plasma creatinine greater than  $120\text{ }\mu\text{mol/L}$  ( $1.5\text{ mg/dL}$ ).

#### *Dosage*

Dosage varies according to clinical circumstances and usually depends on the combination chemotherapy protocol followed. An antineoplastic oral dose is usually  $2\text{--}6\text{ mg/kg}$  daily in divided doses depending on the composition of the combination chemotherapy regimen, whereas the dose for immunosuppression might be  $1\text{--}2\text{ mg/kg}$

daily. When the drug is used intravenously in neoplastic disease, a low-dose regimen might use  $2\text{--}6\text{ mg/kg}$  as a single dose weekly, a medium-dose regimen  $10\text{--}15\text{ mg/kg}$  similarly and a higher-dose regimen  $10\text{--}40\text{ mg/kg}$  as a single dose at  $10\text{--}20$  day intervals. When cyclophosphamide therapy is initiated at relatively high doses, the white cell count should be checked on alternate days, the aim being to prevent it from falling below  $3\times 10^9/\text{L}$ . Once a more stable maintenance dose has been achieved, white cell counts may be made weekly and then every 2 or 3 weeks, so long as treatment is continued.

#### *Adverse effects and precautions*

Cyclophosphamide, in common with other cytotoxic drugs, may produce many side-effects [905,906]. Nausea and vomiting occur commonly with higher doses and are treated symptomatically with agents such as prochlorperazine, domperidone or a specific 5-hydroxytryptamine ( $5\text{-HT}_3$ ) antagonist such as ondansetron, these proving very effective antiemetic drugs in cancer chemotherapy [907]. Mucosal ulceration may occur.

Myelosuppression is unavoidable and indeed the white cell count is commonly used to gauge the effectiveness of treatment and as a means of regulating the dose. Once the white count begins to fall in response to treatment, it may continue to do so for 7–14 days and recovery may take about 3 weeks. The reduced white cell count increases the risk of infection, which may be minimized by avoiding reductions in the neutrophil count to below  $1\times 10^9/\text{L}$  and in the total white cell count to below  $3\times 10^9/\text{L}$ . One way to achieve this is to temporarily withhold cyclophosphamide if the total white cell count drops below  $4\times 10^9/\text{L}$  (or if the platelet count dips below  $100\times 10^9/\text{L}$ ). Patients should be warned of the risk of infection and to report such symptoms promptly, as well as bleeding or bruising should these occur. It is now possible to treat severe neutropenia with parenteral recombinant human granulocyte colony-stimulating factor, thereby reducing the incidence of associated sepsis, although there is as yet no evidence that it improves overall survival.

Alopecia is inevitable following high-dose treatment and may develop over about 3 weeks. Hair usually regrows if the drug is stopped. This problem is diminished at lower doses and may not occur on maintenance therapy of  $2\text{ mg/kg}$  daily, although this cannot be guaranteed.

Chemical cystitis may occur with high-dose treatment or following long-term low-dose therapy. It is caused by a metabolite of cyclophosphamide called acrolein, which is toxic to the epithelium of the urinary tract. This cystitis may be haemorrhagic, particularly following high doses, and may result in bladder contracture and fibrosis or even fatality if the drug is not stopped. When high-dose therapy is necessary it is essential to keep the patient well hydrated in order to reduce the likelihood of this complication. Mesna, which reacts specifically with acrolein, may

be given parenterally initially and subsequently orally as a prophylactic against urothelial toxicity when cyclophosphamide is used at high dosage (>2 g intravenously) or in those patients with a previous history of urothelial toxicity from cyclophosphamide. Cystitis complicating cyclophosphamide therapy usually resolves within a few days of drug withdrawal.

Pulmonary fibrosis may occur during treatment with cyclophosphamide as with other cytotoxic agents and also with radiotherapy so that it may be difficult to apportion blame. This adverse effect is probably related to the cumulative dose and may occur after the drug has been discontinued [908]. Treatment with steroids has been advocated but no convincing evidence of benefit exists.

It is recognized that cytotoxic drugs may themselves have a carcinogenic effect. Leukaemia, usually acute, and lymphomas may occur with greater than expected frequency for several years following the administration of cyclophosphamide, as may urinary tract neoplasms, usually carcinoma of the bladder [909,910]. Such complications are generally a feature of long-term chemotherapy. Meta-analysis of early non-small-cell lung cancer trials that made use of long-term oral alkylating agents such as cyclophosphamide in single-drug form showed a survival disadvantage [911].

As with all cytotoxic therapy, the drug should only be used in pregnancy after very careful consideration of the considerable risks to the fetus versus benefit to the patient; adequate contraceptive precautions should be taken if either partner is taking the drug. The use of cyclophosphamide in younger patients is associated with infertility that is usually reversible.

### *Ifosfamide*

Ifosfamide is an alkylating agent of the nitrogen mustard type, related to cyclophosphamide but with a different and larger spectrum of activity and a different toxicity profile. It is used as an antineoplastic drug and has activity in non-small-cell lung cancer, for which its parent drug cyclophosphamide is relatively ineffective. In this role it is generally given as combination chemotherapy with cisplatin and another agent, for example mitomycin/ifosfamide/cisplatin.

#### *Mode of action*

This is similar to cyclophosphamide. Ifosfamide interacts with DNA, cross-linking resulting in inhibition of protein synthesis.

#### *Administration, distribution, metabolism and excretion*

Ifosfamide is formulated for intravenous administration. It is highly lipid soluble and widely distributed. It is made up as an 8% solution for infusion or as a more dilute solu-

tion for bolus injection. Ifosfamide is a prodrug that has no cytotoxic activity until activated in the liver by microsomal enzymes, so that local tissue damage is unlikely if the drug extravasates. The drug is primarily excreted as its metabolites via the kidneys.

#### *Dosage*

Dosage varies according to clinical circumstances and usually depends on the combination chemotherapy protocol followed. Doses of 5 g/m<sup>2</sup> over 24 h every 21 days or 1.5 g/m<sup>2</sup> as single daily doses for 5 days repeated every 21 days have been used as single agents in small-cell lung cancer.

#### *Adverse effects and precautions*

These are similar to cyclophosphamide. Chemical cystitis is the main dose-limiting adverse effect and is caused by the metabolite acrolein, which is toxic to the epithelium of the urinary tract. This cystitis may be haemorrhagic, particularly following high doses, and may result in bladder contracture and fibrosis. When high-dose therapy is necessary it is essential to keep the patient well hydrated in order to reduce the likelihood of this complication. Mesna, which reacts specifically with acrolein, is given routinely with ifosfamide, preferably orally. Cystitis usually resolves within a few days of drug withdrawal.

Myelosuppression occurs, although to a lesser extent than with its parent alkylating agent cyclophosphamide, the white cell count usually reaching a nadir 5–10 days after commencement of therapy and recovering within 3 weeks. Patients should be warned of the risk of infection and to report such symptoms promptly, as well as bleeding or bruising should these occur. Infrequent encephalopathic symptoms have been described, in which circumstance the drug must be stopped. Ifosfamide is contraindicated if the serum creatinine is greater than 120 µmol/L (1.5 mg/dL), if the bilirubin is greater than 17 µmol/L (1 mg/dL) or if the transaminases or alkaline phosphatase are greater than 2.5 times the upper limit of normal. As with all cytotoxic therapy, the drug should only be used in pregnancy after very careful consideration of the considerable risks to the fetus versus benefit to the patient; adequate contraceptive precautions should be taken if either partner is taking the drug.

### *Azathioprine*

Azathioprine, a cytotoxic immunosuppressant, is a purine analogue with similar actions to 6-mercaptopurine, to which it is metabolized. It has been used largely to treat diseases whose pathogenesis is thought to involve disordered immune function. Although it may be used alone, it is more usual for it to be used in conjunction with systemic corticosteroids such as prednisolone. It complements

cyclosporin in immunosuppressive therapy following solid organ transplantation. Reports of its efficacy are often based on retrospective data and individual case reports rather than on controlled prospective studies. It has been used in Wegener's granulomatosis, usually when cyclophosphamide has had to be discontinued because of unacceptable side-effects such as haemorrhagic cystitis [891,912]. It has also been used to treat other vasculitides [897], such as Churg–Strauss syndrome if a response to corticosteroids has not been achieved [913], and cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) in similar circumstances [893,914]. Azathioprine may also be used with steroids, either in a supporting role (when response to steroids is inadequate) or commonly in a steroid-sparing role (when the steroid dose required for control is unacceptably high) for the treatment of cryptogenic fibrosing alveolitis [914] and sometimes in those forms of fibrosing alveolitis associated with rheumatoid disease, systemic lupus erythematosus, dermatomyositis and polymyositis [915,916] (see Chapter 53). The drug has also been used to support steroids in the treatment of idiopathic pulmonary haemosiderosis [917,918] (see Chapter 51).

#### *Mode of action*

The mechanisms by which azathioprine acts as an immunosuppressant are poorly understood. It is recognized that the drug is a purine antagonist and its effects on intracellular metabolism may result in the inhibition of nucleic acid synthesis, preventing the proliferation of cells involved in the immune response. Its activities include the suppression of bone marrow, with depletion of circulating polymorphs and monocytes and diminution of the numbers of macrophages in the lungs and other tissues. At therapeutic dosage, T- and B-lymphocyte function and antibody production are impaired, and one of its more important clinical uses, as an immunosuppressant in transplant recipients, results from its ability to inhibit the recognition of transplanted material by the suppression of antibody responses due to immunologically competent lymphoid cells.

#### *Administration, metabolism and excretion*

Azathioprine is well absorbed from the gastrointestinal tract after oral administration, following which it is metabolized to its active form, 6-mercaptopurine. This enters cells and undergoes conversion into the active moieties, which are purine thioanalogues. Further metabolism is largely hepatic and is mediated by xanthine oxidase (see below). Excretion, chiefly of metabolites, is mainly renal and dosage reduction may be necessary in renal insufficiency. An intravenous preparation is also available but the oral route is preferred.

#### *Dosage*

The usual maintenance dose range in respiratory disease is 1–3 mg/kg daily orally, although even smaller doses occasionally suffice. A therapeutic response may take 2 weeks to 1 month to become evident. The blood count, including platelets, should be monitored at least weekly for the first 2 months or more frequently if high doses are used and thereafter monthly or at least every 3 months. The dose may be titrated against the white cell count and the treatment stopped if this falls below  $3 \times 10^9/L$  until sufficient recovery has occurred. For immunosuppression following organ transplantation an induction dose of 5 mg/kg orally or intravenously may be given on the first day, followed by a maintenance dose of 1–4 mg/kg daily orally or according to the protocol adopted. Cyclosporin (see below) is a usual co-immunosuppressant but if the use of this is limited by renal insufficiency, the addition of prednisolone (0.2 mg/kg daily) to azathioprine may be required. Doses of azathioprine at the lower end of the recommended ranges are advised if the drug has to be used in the presence of renal or hepatic insufficiency.

Allopurinol, a xanthine oxidase inhibitor, blocks the hepatic degradation of the active metabolite of azathioprine (6-mercaptopurine) so that toxicity is likely if these two drugs are used together, unless the dose of azathioprine is reduced. Such combined use is best avoided if possible.

#### *Adverse effects and precautions*

As with all cytotoxic drugs, its use is limited by toxic side-effects. The most important of these is myelosuppression so that careful monitoring of peripheral blood counts is necessary. For general purposes these are recommended at least weekly for the first 8 weeks then monthly or at least every 3 months thereafter. All cell series may be depressed, but leucopenia and thrombocytopenia occur more commonly and are dose limiting. A few patients have a rare enzymatic deficiency that predisposes them to myelosuppression by azathioprine. Occasionally, megaloblastic erythropoiesis and macrocytosis may occur [919].

Secondary infection, often with opportunistic organisms, may occur as a result of immunosuppression (see Chapter 52), especially if the white cell count is allowed to fall too far. Patients should be warned of the risk of infection and asked to report such symptoms promptly, as well as bleeding or bruising should these occur. Gastrointestinal side-effects include mucosal ulceration, nausea, vomiting and diarrhoea. Such adverse effects may be avoided to some extent by taking the drug with food in divided doses, but sometimes temporary dose reductions or cessation of therapy are required. More seriously, azathioprine may cause hepatotoxicity in an apparently idiosyncratic manner, liver function tests showing both



hepatic and cholestatic features [920]. This may necessitate withdrawal of the drug but is usually reversible. Pancreatitis may also occur but is rare. Idiosyncratic hypersensitivity reactions may occur with azathioprine [921] and become manifest with one or more of the following: fever, rigors, erythematous rash, myalgia, arthralgia, malaise, nausea, vomiting, diarrhoea, dizziness and hypotension. Azathioprine should be stopped in this context, following which recovery is the rule.

As with other cytotoxic drugs, interstitial pneumonitis that may result in pulmonary fibrosis has been described but is rare [922]. Diffuse bilateral pulmonary infiltration may occur and it may be necessary to exclude opportunistic infection. Recovery of impaired lung function following discontinuance of the drug cannot be guaranteed. There are a number of reports of neoplastic disease occurring in patients following treatment with azathioprine and other antineoplastic or immunosuppressive drugs [923]. As with all cytotoxic therapy, the drug should only be used in pregnancy after very careful consideration of risks versus benefit and adequate contraceptive precautions should be taken if either partner is taking the drug.

### *Cyclosporin*

Cyclosporin (ciclosporin) is a potent immunosuppressant cyclic peptide metabolite that revolutionized the field of organ transplantation [924]. It is extracted from the fungus *Tolypocadium inflatum* and although used chiefly in solid organ and bone marrow transplant work, to prevent and treat allograft rejection, it is also used in the short-term treatment of severe atopic eczema that has become resistant to conventional therapy and for various other inflammatory/immune dermatological, rheumatological and renal indications [925]. It has been the subject of small experimental trials in a variety of other inflammatory or autoimmune disorders involving the lungs, including severe steroid-dependent asthma [926], cryptogenic fibrosing alveolitis [927] and sarcoidosis [928,929]. It has virtually no myelotoxicity but its main dose-limiting adverse effects are related to severe nephrotoxicity and it has a very low toxic–therapeutic ratio.

### *Mode of action*

The precise mechanism of its action is unknown, although it is thought to interfere with the synthesis of lymphokines with resultant inhibitory effects on the activation of T lymphocytes [924]. It does not depress haematopoiesis, nor does it affect the function of phagocytic cells.

### *Administration, metabolism and excretion*

Bioavailability differs between individual oral formulations of cyclosporin so that care should be taken in pre-

scribing and dispensing the same preparation. Before the availability of a microemulsion formulation, the absorption of cyclosporin from the gut exhibited wide interpatient variation. It is fat soluble and highly bound to lipoproteins and erythrocytes. There are several separate hepatic metabolic pathways and the principal route of excretion is biliary, with little urinary excretion so that renal impairment does not alter its elimination. The terminal half-life is about 6 h in healthy subjects, increasing to about 20 h in severe liver disease.

### *Drug interactions*

Many drugs interact with cyclosporin, so that where there is any doubt a formulary or the manufacturer's summary of product characteristics should be consulted. Some drugs, such as macrolide antibiotics, reduce cyclosporin metabolism and therefore increase the risk of toxicity, as do some calcium channel blockers, including nifedipine and diltiazem, and some azole antifungal drugs, including ketoconazole and itraconazole. On the other hand, liver enzyme-inducing drugs increase its metabolism, lowering blood levels and therefore increasing the risk of rejection or failure of treatment. These include phenytoin, carbamazepine, phenobarbital and rifampicin. Drugs that are themselves potentially nephrotoxic may increase the nephrotoxicity of cyclosporin, examples being NSAIDs (which also increase the risk of hepatotoxicity), aminoglycosides, ciprofloxacin and amphotericin. Clinical gout and hyperuricaemia are problematical because of the potential nephrotoxicity of NSAIDs and because colchicine may increase cyclosporin levels as may allopurinol, so that blood level measurements and dose adjustment may become necessary. Angiotensin-converting enzyme inhibitors and potassium-sparing diuretics both increase the risk of hyperkalaemia and the diet should not be high in potassium. The risks of rhabdomyolysis may be increased if hypercholesterolaemia is treated with certain HMG-CoA reductase inhibitors. Nifedipine may increase the risk of gingival hypertrophy. Grapefruit or grapefruit juice should be avoided for 1 h before the dose as it increases plasma cyclosporin concentration.

### *Dosage*

For induction of immunosuppression in solid organ transplantation 10–15 mg/kg may be given orally preoperatively in two divided doses, followed by 10–15 mg/kg daily for the first week or two postoperatively, also as two divided doses, thereafter adjusting down to a maintenance dose of 2–6 mg/kg daily as two divided doses. Cyclosporin may be given as an intravenous infusion postoperatively until the patient can swallow, the relative bioavailability of oral to intravenous being 1:3. Doses of cyclosporin are reduced when other immunosuppressants

such as azathioprine or systemic steroids are used as well, many transplant centres using combined regimens with the object of keeping the dose of cyclosporin low in order to reduce the likelihood of renal damage. Dosages of cyclosporin are adjusted by monitoring renal function and by assaying cyclosporin trough levels in whole blood (taken just before a due dose) to be sure that they fall within the therapeutic range [930]. Different assay techniques are available and each laboratory should establish its own therapeutic and toxic concentration ranges, based on local practice. These levels have to be measured frequently in the early post-transplant stage. Lower trough levels of cyclosporin may be accepted after the first 6 months of therapy without increased risk of rejection. The serum creatinine and urea have to be measured very frequently in the first month after transplantation, then every week or two for the first year and thereafter monthly, depending on the stability of the situation.

For non-transplant situations, lower doses of cyclosporin that do not normally exceed 5 mg/kg daily are used.

#### *Adverse effects and precautions*

Many of the adverse effects are dose dependent so that the lowest possible dose should always be used. Renal function has to be monitored closely and dose adjustments made accordingly. Increases in the serum creatinine and urea in the first few weeks of treatment are generally dose dependent and reversible on dose reduction. Nephrotoxicity is minimal at doses of less than 2.5 mg/kg daily but higher doses or long-term administration may lead to structural changes in the kidneys, involving both vasculature and tubules, and may progress to interstitial fibrosis. Hypertension may also occur so that blood pressure should be monitored and appropriate hypotensive medication started if needed.

Other unwanted effects include nausea and vomiting and hepatotoxicity so doses may need reducing if liver enzymes or bilirubin climb. Occasional biochemical disturbances may occur, including hyperkalaemia, hyperuricaemia (sometimes with clinical gout, see above), hypercholesterolaemia (rhabdomyolysis may be more likely with HMG-CoA reductase inhibitors) and hypomagnesaemia. Patients may develop a rather hirsute appearance, with hypertrichosis, weight gain and oedema leading to problems with compliance. Gingival hypertrophy may occur. Myalgia, cramps, paraesthesiae and peripheral neuropathy are described, as are convulsions particularly in the presence of high blood levels of cyclosporin. As with any immunosuppressive therapy, patients are liable to develop opportunistic infections. There is an increased incidence of lymphoma (especially non-Hodgkin) and other malignancies, as seen with conventional immunosuppressants such as azathioprine. The

prescriber needs to be on guard against the possibility of drug interactions (see above).

#### *Chlorambucil*

Chlorambucil is an antineoplastic and immunosuppressive agent derived from mustard and belongs to the nitrogen mustard group of alkylating agents (like cyclophosphamide). It has been used mainly in the treatment of Hodgkin's disease, non-Hodgkin lymphomas, chronic lymphocytic leukaemia and Waldenström's macroglobulinaemia. It is occasionally used as an immunosuppressant although, as it is toxic, usually only when the patient is unresponsive to steroids or intolerant of them.

Like cyclophosphamide and azathioprine, it has been used in steroid-resistant Churg–Strauss syndrome [931]. It has been used to treat vasculitides such as Wegener's granulomatosis but has been superseded by cyclophosphamide or azathioprine. Another use of chlorambucil is as an alternative to cyclophosphamide and azathioprine in certain collagen vascular conditions, such as mixed connective tissue disease which combines the clinical features of scleroderma, systemic lupus erythematosus and polymyositis [932].

#### *Mode of action*

Active metabolites of chlorambucil alkylate or bind to many intracellular structures including nucleic acids. Cross-links are established between DNA and RNA so that DNA replication and RNA transcription are impeded. The mechanism by which immunosuppression occurs is unclear but it is likely to be related, at least in part, to the suppressive effect of the drug on bone marrow activity.

#### *Administration, metabolism and dosage*

Chlorambucil is taken orally and is well absorbed from the gastrointestinal tract. Metabolism is hepatic, the major metabolite being phenylacetic acid mustard. Excretion is renal but less than 1% of a dose appears in the urine other than as metabolites.

The usual dose when used as an immunosuppressant is 100–200 µg/kg as a single daily dose. The blood count, including platelets, should be checked at least weekly at first, aiming to keep the white cell count above  $3 \times 10^9/L$  and the platelet count above  $100 \times 10^9/L$  [932].

#### *Adverse effects*

As with other cytotoxic drugs, the most important side-effect is myelosuppression. Depression of all cell lines may occur, the white cell count being particularly affected. After a single high dose of chlorambucil, the white cell and

platelet counts reach a trough at 7–10 days and recovery may take 2–3 weeks. Similarly, when the drug is being taken on a daily basis, the count may continue to fall for some days after the last dose. Very high doses may cause irreversible marrow suppression. Resultant immunosuppression, particularly in the presence of neutropenia, may lead to opportunistic secondary infection.

Less serious but nevertheless distressing gastrointestinal symptoms may occur, including mucosal ulceration, nausea, vomiting and diarrhoea. As with other immunosuppressants, chlorambucil may cause chromosomal damage and carries the risk of secondary neoplastic complications, particularly leukaemia [933,934]. This may be related to the duration of therapy. Interstitial pneumonitis can occur and may lead to pulmonary fibrosis [935,936]. This adverse effect may be dose related and response to discontinuance of the drug and corticosteroid therapy is uncertain but has been reported. Infertility due to azoospermia or amenorrhoea can occur, as is the case with cyclophosphamide. All cytotoxic drugs must be considered to be potentially teratogenic, carrying the risk of fetal damage. Other rare side-effects include aseptic cystitis, neurotoxicity including peripheral neuropathy and seizures, hepatotoxicity, and widespread rashes progressing to Stevens–Johnson syndrome.

### *Doxorubicin*

Doxorubicin (often denoted by 'A' for Adriamycin in multidrug mnemonics) is a cytotoxic anthracycline antibiotic, being produced by a species of *Streptomyces*. It is used widely in combination chemotherapy for the treatment of various malignancies, including acute leukaemias, lymphomas and small-cell lung cancer. Small-cell lung cancer may be treated with a variety of regimens some of which contain doxorubicin, for example cyclophosphamide/doxorubicin/vincristine ('CAV' see below). A liposomal formulation of doxorubicin for intravenous use has been licensed for treating Kaposi's sarcoma in patients with AIDS.

The mode of action of doxorubicin, while not fully understood, seems to involve its concentration in cell nuclei where it binds to and disrupts the structure of DNA. It also forms free-radicals and may have direct effects on the integrity of lipid membranes, these actions possibly accounting for its toxic and dose-limiting effects on normal cells.

### *Administration, metabolism, excretion and dosage*

The drug is given as a bolus over 2–3 min, being injected into the tubing of a freely running intravenous infusion. Doxorubicin is rapidly metabolized by the liver to produce an active substance, adriamycinol. Over 70% of excretion is biliary, either as unchanged doxorubicin or as

adriamycinol. Less than 10% of excretion is renal; nevertheless such excretion may colour the urine red for up to 48 h, a phenomenon about which the patient should be forewarned. Liver disease increases the likelihood of toxicity and if the agent has to be given in the presence of hepatic dysfunction, the dosage should be reduced.

Dosage is conventionally calculated according to body surface area, a usual dose being 60–75 mg/m<sup>2</sup> every 3 weeks. However, when used in combination chemotherapy the dose may need to be reduced to 30–40 mg/m<sup>2</sup>, for example cyclophosphamide 600 mg/m<sup>2</sup>, doxorubicin 40 mg/m<sup>2</sup> and vincristine 1 mg/m<sup>2</sup> to a maximum 2 mg repeated every 21 days for a maximum of six cycles in 'CAV' which is commonly used in the treatment of small-cell lung cancer. The total dose should be limited to about 400 mg/m<sup>2</sup> in order to reduce the chance of cardiotoxicity [937].

### *Adverse effects*

Adverse effects include myelosuppression, the white count reaching its nadir about 10–14 days after a dose and taking up to 3 weeks to recover. Doxorubicin is particularly noted for its potential toxicity to heart muscle and its propensity to cause serious tissue necrosis should it be allowed to extravasate from an intravenous injection site. Cardiotoxicity is a dose-related side-effect. Acute effects include the production of various cardiac dysrhythmias or rarely myocarditis. Cumulative cardiotoxicity is much more common and produces a cardiomyopathy, ultimately resulting in myocardial fibrosis that may precipitate heart failure [937]. Its use should therefore be avoided in patients with pre-existing heart disease. Heart failure due to cardiomyopathy may occur without warning several weeks after discontinuation of therapy. These effects are more likely to become clinically significant if mediastinal radiation has been given, the patient has pre-existing coronary artery or hypertensive heart disease, or alkylating agents (e.g. cyclophosphamide, ifosfamide, chlorambucil or lomustine) are used concurrently. Cardiotoxicity may be limited by using a 'dosage ceiling' (see above). A reduction in the height of the QRS complex on the ECG is said to be indicative of toxicity and a relative contraindication to continued treatment with this agent.

Tissue necrosis may occur with other cytotoxic agents such as cyclophosphamide, but is particularly severe if doxorubicin finds its way into extravascular tissues. The extent to which tissue is damaged is probably a consequence of the high degree to which the drug is bound [938]. Such accidents should be guarded against with extreme care by ensuring that the injection is given by fast-running infusion into a clearly patent intravenous line.

Other side-effects include buccal ulceration, nausea and vomiting, diarrhoea and alopecia (which is virtually

inevitable, although hair may regrow when treatment ceases). Radiotherapy following doxorubicin may produce an intense radiation pneumonitis, with strikingly demarcated borders marking the edge of the radiation field.

### **Mitomycin**

Mitomycin is another cytotoxic antibiotic used in combination chemotherapy in the treatment of a variety of solid tumours, including breast and upper gastrointestinal tract cancers. It is also under investigation in the management of advanced non-small-cell lung cancer in combinations such as mitomycin/ifosfamide/cisplatin (MIC) and mitomycin/vinblastine/cisplatin (MVP) [939,940]. Mitomycin becomes activated in tissues, forming an alkylating agent that both disrupts and interferes with the synthesis of DNA.

#### *Administration, metabolism, excretion and dosage*

Mitomycin is given by intravenous infusion and must be administered with great care in order to avoid extravasation (see p. 289). The chief site of metabolism is the liver and about 10% is excreted unchanged in the urine. Doses of 6–10 mg/m<sup>2</sup> may be used in 4-weekly combination chemotherapy schedules for non-small-cell lung cancer. Failure to respond within two cycles of treatment would be reason for abandonment of such a course.

#### *Adverse effects*

The principal side-effect is myelotoxicity. The nadir tends to be later than with other drugs used for treating cancer, occurring at about 4 weeks. Myelotoxicity with this drug tends to be cumulative with repeated courses, the platelets and white cells being particularly affected. The drug should not be repeated before the white cell count has recovered to  $3 \times 10^9$ /L and the platelets to  $90 \times 10^9$ /L. The drug is also nephrotoxic so that renal function should be monitored. Pulmonary toxicity is a rare but well-described side-effect of mitomycin. Although it may reverse with corticosteroids, progressive lung fibrosis may occur [941]. Nausea and vomiting may occur. Extravascular leakage may cause tissue necrosis.

### **Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine)**

Vincristine, vinblastine and vindesine are antineoplastic agents derived from the periwinkle plant. Vinorelbine is a more recent semisynthetic vinca alkaloid. They are very similar in their properties and structure, differing mainly with respect to their principal dose-limiting side-effects, that of vincristine being peripheral neuropathy and that of vinblastine, vindesine and vinorelbine being myelosup-

pression. Vinorelbine may cause both these side-effects but, like vinblastine, its dose is mainly limited by myelosuppression. They are used in combination with other oncolytic drugs to treat a wide variety of malignancies, including leukaemias, lymphomas and various solid tumours. Vincristine is included in many combination chemotherapy regimens used for treating small-cell lung cancer, for example cyclophosphamide/doxorubicin/vincristine (CAV). The use of vinblastine and vinorelbine continues to be investigated as part of platinum-based combination chemotherapy in the management of inoperable non-small-cell lung cancer. The mode of action of these drugs appears to involve their attachment to intracellular proteins such as tubulin that are concerned with the facilitation of microtubule formation in the mitotic spindle of the dividing cell.

#### *Administration, metabolism, excretion and dosage*

Vinca alkaloids are administered as slow intravenous boluses or short infusions, care being taken not to allow extravasation (see p. 289). Metabolism occurs in the liver and up to 90% of a dose is excreted in bile, mainly in the form of breakdown products. Reduction in dosage is necessary in hepatic but not renal insufficiency. A vinca alkaloid is often included as one component of a 3-weekly cycle of combination chemotherapy in lung cancer. Vincristine is included in many combination chemotherapy regimens used for treating small-cell lung cancer, for example cyclophosphamide 600 mg/m<sup>2</sup>, doxorubicin 40 mg/m<sup>2</sup> and vincristine 1 mg/m<sup>2</sup> to a maximum 2 mg repeated every 21 days for a maximum of six cycles. Vinblastine, vindesine and vinorelbine may be included in platinum-based regimens (see cisplatin), such as mitomycin/vinblastine/cisplatin, vindesine/cisplatin and vinorelbine/cisplatin, currently under investigation in the management of non-small-cell lung cancer.

A usual dose of vincristine in small-cell lung cancer is 1.4 mg/m<sup>2</sup> (up to a usual maximum dose of 2 mg in adults), which is reduced or stopped in the presence of a significant neurological deficit (see below). The dose of vinblastine may be increased incrementally from 3.7 mg/m<sup>2</sup>, according to the white cell count. Vindesine has been used in combination chemotherapy at weekly doses of 2.5 mg/m<sup>2</sup> and vinorelbine at 30 mg/m<sup>2</sup>. Dosing is regulated according to the white cell and platelet counts, which have to be monitored closely. An oral formulation of vinorelbine is under investigation.

#### *Adverse effects*

The most important side-effect of vincristine is peripheral neuropathy [942], neurotoxicity being uncommon with vinblastine. Impaired neuronal function may result from both demyelination and axonal degeneration; mild neuro-

toxicity is to be expected with therapeutic doses of vincristine. Early symptoms, which include paraesthesiae and peripheral sensory loss, are common as is the loss of previously present tendon reflexes at the ankles. Further treatment may lead to difficulties with fine movements of the fingers and wrist and foot drop, with resultant disturbances of gait. More serious paresis may occur in severe cases. Autonomic neuropathy may also occur and may cause constipation, intestinal ileus and urinary retention. Cranial nerve palsies have been described but are rare. Neurotoxicity is dose dependent and occurs more readily in the elderly. It is usual practice to reduce the dose of vincristine by half with early neurological symptoms and signs (unusual before 4–6 mg) and to stop it altogether if the problem progresses or if significant weakness or ileus develops (unusual before 10–12 mg) [943]. Functional recovery is usual if the drug is stopped at an early stage but recovery from more serious deficits may be both delayed and incomplete.

Myelosuppression is the major dose-limiting effect of vinblastine, vindesine and vinorelbine, with which neurotoxicity is unusual. The neutrophils are principally affected and reach a trough up to 10 days after a dose, recovery occurring within 3 weeks.

Other adverse effects are shared and include severe tissue necrosis if the drug is allowed to extravasate during an intravenous infusion. The same precautions should be followed as for doxorubicin (see p. 289). Nausea, buccal mucosal ulceration, rashes and reversible alopecia may occur. Cardiotoxicity, lung fibrosis and inappropriate ADH secretion are also recorded but are rare [944].

### *Lomustine*

Lomustine is an antineoplastic alkylating agent of the nitrosourea type that has been used in combination chemotherapy to treat small-cell lung cancer and other usually solid tumours. It is taken orally. Lomustine and its metabolic products appear to act, in broad terms, by causing the inhibition of nucleic acid function and more specifically of DNA synthesis.

#### *Administration, distribution, metabolism and dosage*

Lomustine is well absorbed orally. It is lipid soluble and its active metabolites cross the blood–brain barrier and penetrate the CNS, enabling the drug to be used in the treatment of brain tumours. It is rapidly metabolized by the liver and primarily excreted as metabolites by the kidneys [945].

The usual dose range is 100–130 mg/m<sup>2</sup> given as a single dose no more frequently than every 6–8 weeks. The dose should not be repeated until the white cell count recovers to  $4 \times 10^9$ /L and the platelet count to  $100 \times 10^9$ /L. Haematological toxicity may be cumulative, with increasingly low white cell and platelet counts following

repeated dosage. Lower doses may be used in combination chemotherapy and individual monographs should be consulted for further guidance.

#### *Adverse effects*

The major adverse effect is myelosuppression, which differs from that produced by other antineoplastic agents in that it is both delayed and sustained, so that white cell and platelet counts may not reach a trough until 4–6 weeks after the dose. This has important implications for dosage scheduling (see above). Nausea and vomiting are to be expected and usually begin within 4–6 h, taking a day or two to settle, although anorexia may last longer. Treatment is symptomatic with agents such as prochlorperazine, domperidone or a specific 5-HT<sub>3</sub> antagonist such as ondansetron. Unusual adverse effects include stomatitis, buccal ulceration, renal insufficiency, pulmonary fibrosis and alopecia.

### *Etoposide*

Etoposide is a semisynthetic antineoplastic derivative of podophyllotoxin, an active component of the naturally occurring substance podophyllin, long used topically in the treatment of warts and obtained from the root of the mandrake plant. It is one of the most active single agents in small-cell lung cancer but is usually given as part of a course of combination chemotherapy [946].

It is regarded as a 'broad-spectrum' cytotoxic agent and is also used to treat lymphomas, metastatic germ-cell tumours and acute leukaemias [947–949]. The use of etoposide as a single oral agent in patients with small-cell lung cancer with moderate or poor prognosis, in order to reduce the intensity of chemotherapy, has been found to produce inferior results to conventional intravenous combination chemotherapy [890,950]. The intracellular mode of action of etoposide is complex and poorly understood. It appears to inhibit DNA synthesis at the premitotic stage of cell division [951].

#### *Administration, metabolism, excretion and dosage*

Etoposide is usually given intravenously as part of 21-day cycles of combination chemotherapy but may be taken orally. The number of cycles is variable but six is often considered optimal, provided the patient is responding. The dose varies according to the myelosuppressive characteristics of the other drugs in the regimen but dosages of 80–120 mg/m<sup>2</sup> intravenously for three consecutive days are not uncommon, the agent being infused slowly over 30–60 min since more rapid administration may produce hypotensive reactions. The regimen may be repeated after 3 weeks if the white count is not less than  $4 \times 10^9$ /L and the platelet count not less than  $100 \times 10^9$ /L. Oral dosage

follows the same general pattern except that the doses are usually doubled because absorption is incomplete. Metabolism is hepatic, excretion being via the kidneys both in unchanged form and as metabolites.

#### *Adverse effects*

The principal dose-limiting adverse effect is myelosuppression, chiefly affecting the white cell and platelet counts, so that the drug is conventionally given on three to five consecutive days in 21-day cycles in order to allow the marrow to recover. The white cell count reaches a trough at about 2 weeks. More prolonged oral courses of etoposide in combination with cisplatin intravenously produce significant myelosuppression, with no advantage over conventional chemotherapeutic regimens in small-cell lung cancer. Nausea and vomiting occurs in about half of all patients treated and diarrhoea and buccal ulceration may also arise. Alopecia may also occur but is reversible. Other side-effects are rare and include wheezing and anaphylaxis.

#### *Cisplatin and carboplatin*

The discovery that compounds of platinum impaired cellular division was made serendipitously in the 1960s when a study looking into the effects of electrical fields on cellular growth reported that *E. coli* failed to divide in an apparatus when the current passed through platinum electrodes. This effect was found to be due to the production of *cis*-diamminedichloroplatinum or 'cisplatin' [952]. Cisplatin, and its later analogue carboplatin, are both platinum complexes that are thought to exert their cytotoxic effects by forming cross-linkages within and between DNA strands, as is the case with alkylating agents [953,954]. Both have been used in the combination chemotherapy of a variety of solid tumours, such as small-cell lung cancer and metastatic testicular, germ cell and ovarian cancers.

#### *Administration, metabolism, excretion and dosage*

Both cisplatin and carboplatin are given intravenously. Non-enzymatic conversion to inactive metabolites occurs and platinum is heavily bound by tissue and protein. Excretion is renal. One or other drug is usually given as part of a course of combination chemotherapy, being commonly combined with etoposide in the treatment of small-cell lung cancer (cisplatin/etoposide and carboplatin/etoposide). These compounds have also been included in trials of multidrug therapy in locally advanced non-small-cell lung cancer, for example mitomycin/vinblastine/cisplatin (MVP), mitomycin/ifosfamide/cisplatin (MIC), cyclophosphamide/doxorubicin/cis-

platin (CAP), or in combination with docetaxel, gemcitabine or vinorelbine, the general view being that platinum-based regimens are superior to other types of chemotherapy in advanced non-small-cell lung cancers [955]. Pre-dose estimations of creatinine clearance and blood urea are necessary before cisplatin administration, and the drug is best avoided if the serum creatinine is above  $100\mu\text{mol/L}$  ( $1.5\text{mg/dL}$ ), the blood urea higher than  $9\text{mmol/L}$  ( $55\text{mg/dL}$ ) or the creatinine clearance reduced by more than 25%. Even so, adequate hydration is recommended by priming the patient with 1–2 L of intravenous fluid in the 8–12 h before the dose of cisplatin in order to initiate a diuresis, and by giving the drug in a further 2 L of dextrose/saline over the next 6–8 h; 40 g mannitol may be added to this to maintain the diuresis. Concomitant use of other potentially nephrotoxic drugs is best avoided if possible. The drug is commonly given at a dose of  $50\text{mg/m}^2$  in multidrug regimens and is usually repeated after 3–4 weeks for about four cycles according to response. Leucopenia and thrombocytopenia may occur and the dose should not be repeated before the white cell count has recovered to  $4\times 10^9/\text{L}$  and the platelet count to  $100\times 10^9/\text{L}$ .

Heavy hydration is unnecessary with carboplatin but myelosuppression with leucopenia and thrombocytopenia should be expected, reaching a nadir by about 3 weeks, so that administration should not be repeated more than every 4 weeks. The dose ratio of carboplatin to cisplatin is about 4:1. Doses of  $300\text{mg/m}^2$  have been used in combination with etoposide. The dose has to be reduced in the presence of renal insufficiency.

#### *Adverse effects*

Cisplatin is potentially highly toxic [956], carboplatin being less so and therefore more manageable but more expensive. The principal dose-limiting side-effect of cisplatin is nephrotoxicity, resulting from renal tubular necrosis. This effect may be guarded against by avoiding cisplatin in patients with pre-existing renal insufficiency and by maintaining adequate hydration. Nausea and vomiting are to be expected and may be prevented by a rigorous antiemetic regimen using high-dose glucocorticoids (dexamethasone or methylprednisolone) and a  $5\text{-HT}_3$  antagonist (ondansetron or granisetron) or other agents [957,958]. Myelotoxicity occurs and requires regular blood count monitoring as with other agents. Neurotoxicity includes a dose-dependent sensory peripheral neuropathy, with paraesthesiae, numbness and impaired proprioception. Auditory loss with tinnitus may occasionally occur. The sensory peripheral neuropathy may progress after the drug has been stopped and recovery may be slow. Hypomagnesaemia may also arise.

Carboplatin causes less nausea and vomiting [959], and clinically significant nephrotoxicity and neurotoxicity appear to be uncommon [960], so that carboplatin may be useful in those who have renal insufficiency or who cannot tolerate the high fluid load required for cisplatin administration (see above). However, myelosuppression occurs more frequently with carboplatin, the platelets being particularly susceptible [960].

### *Methotrexate*

Methotrexate is classed as an antimetabolite, its mode of action being to competitively inhibit the enzyme dihydrofolate reductase. This prevents the formation of reduced folate, which is necessary in the synthesis of purines and pyrimidines and without which DNA synthesis is interrupted [961]. Methotrexate has been used as an antineoplastic agent in the treatment of leukaemias, non-Hodgkin lymphomas and various solid tumours including small-cell lung cancer. Its ability to interrupt the rapid turnover of cells is illustrated by its use in severe psoriasis. It also possesses some immunosuppressive properties that have led to its increasing use in refractory rheumatoid arthritis.

### *Administration, metabolism, excretion and dose*

Methotrexate may be administered intravenously or orally. Absorption following an oral dose is somewhat variable and in antineoplastic treatment intravenous administration is more usual. Intrathecal administration may be used in the treatment of leukaemia. Methotrexate may accumulate in ascitic or pleural fluid, which acts as a pool from which the drug may be subsequently released with enhancement of its toxicity. Its use in such situations is therefore best avoided altogether or followed, after an interval of 24 h, by four 6-hourly doses of oral calcium folinate 15 mg, which opposes its effect. Metabolism is both hepatic and intracellular. Excretion is primarily via the kidneys and renal insufficiency is a relative contraindication to its use as is severe hepatic impairment.

The dose for antineoplastic use is 15–50 mg/m<sup>2</sup> once or twice per week, or at a dose not exceeding 30 mg/m<sup>2</sup> daily for 5 days followed by a 'rest period' of at least 2 weeks in order to allow the bone marrow to recover. The dosage used will be influenced by the choice and dose of any other agents that may be used concurrently in combination chemotherapy.

### *Adverse effects*

The most notable side-effects of methotrexate are myelosuppression, particularly leucopenia and thrombocytopenia, and mucosal inflammation and ulceration

particularly affecting the gastrointestinal tract and resulting in painful buccal ulceration, severe diarrhoea and, in extreme cases, intestinal perforation. These and other serious side-effects can be treated with intravenous folinic acid (given as calcium folinate, see above), which antagonizes the effects of methotrexate. Less common side-effects include drug-related pneumonitis [962], which may appear with alarming rapidity, and pulmonary fibrosis, pleuritis and hepatic toxicity, all of which tend to occur with prolonged use, sometimes resulting in requests for assistance from worried rheumatological colleagues. Rashes, alopecia and infertility may also occur. High-dose therapy (used in experimental protocols) may cause renal tubular precipitation of drug products, and such rigorous treatment is invariably followed by 'folinic acid rescue' [961].

### *Gemcitabine*

Gemcitabine is an antimetabolite and is a fluorinated nucleoside analogue of cytarabine, having a broad spectrum of activity against a number of solid tumour types. It undergoes intracellular metabolism and its triphosphate metabolite is incorporated into DNA, replacing the natural nucleotide with resultant inhibition of DNA synthesis by a process known as chain termination. Gemcitabine is undergoing evaluation as single-drug therapy for patients with locally advanced (stage III) or metastatic (stage IV) non-small-cell lung cancer. There are some data to suggest that a 'partial response', defined as an apparent decrease in tumour size of at least 50%, may occur in 20% of patients but there is a lack of controlled trials to compare symptom control with this agent versus palliative radiotherapy and supportive care [963].

### *Administration, metabolism, excretion and dosage*

Gemcitabine has to be administered intravenously. The recommended dose for monotherapy in non-small-cell lung cancer is 1000 mg/m<sup>2</sup> given by infusion over 30 min once weekly for three consecutive weeks, followed by a 1-week rest period. This monthly cycle may then be repeated. It undergoes metabolism in various tissues including the liver and kidneys and its metabolites are excreted in the urine.

### *Adverse effects and precautions*

The drug is relatively well tolerated and can usually be administered in an outpatient setting. Nausea and vomiting may occur in a minority of patients but usually respond to standard antiemetics, such as prochlorperazine or metoclopramide, without a requirement for more potent 5-HT<sub>3</sub> antagonists. Blood counts should be



monitored every 2 weeks during treatment as myelosuppression may occur and is the predominant toxicity. It is as well to omit treatment or reduce the dose if the neutrophil count has reached  $1 \times 10^9/L$  or the platelet count  $100 \times 10^9/L$ . Biochemical abnormalities include mild elevations of hepatic transaminases, mild proteinuria and haematuria, although these urinary abnormalities are not usually associated with a rise in serum creatinine or urea. It is recommended that periodic checks of liver and renal function should be carried out. Macular rashes are not uncommon and need not lead to discontinuation of the drug. Patients may experience mild self-limiting influenzal-type symptoms during treatment. Dependent oedema may also occur. Hair loss is uncommon. The use of gemcitabine should not be combined with radical radiotherapy as severe radiation-induced pneumonitis and oesophagitis may complicate this intervention.

#### *Taxanes: paclitaxel and docetaxel*

The taxanes are a relatively new group comprising paclitaxel, extracted from the bark of the Pacific yew (*Taxus brevifolia*), and docetaxel from the needles of the common European yew (*Taxus baccata*), long known to have poisonous leaves, seeds and bark, its destructive properties also being of historical interest as the source of the longbow staves of medieval archers. Both compounds interrupt microtubule formation in the mitotic spindle of the dividing cell by promoting the polymerization of the intracellular protein tubulin. Both drugs have clinical activity against a broad spectrum of solid tumours, including non-small-cell lung cancer, breast and ovarian cancer. Paclitaxel currently has a UK licence permitting its use in non-small cell lung cancer.

#### *Administration, metabolism, excretion and dosage*

Paclitaxel is given by slow intravenous infusion following premedication (see below). The optimal rate of infusion (1, 3 or 24 h) has been the subject of study and debate. Paclitaxel and docetaxel undergo hepatic metabolism by cytochrome P450 enzymes, so that care should be taken to avoid interactions. Although they are excreted predominantly in the bile, nevertheless dose modifications are recommended in renal insufficiency and the drugs are better not given if the bilirubin level is raised and the dose reduced in the presence of moderately raised transaminases. Conventional doses of paclitaxel in non-small-cell lung cancer trials are usually  $135\text{--}225\text{ mg/m}^2$  and the drug has been combined with other agents such as carboplatin and cisplatin in 3-weekly cycles [964]. Docetaxol is usually given at a dose of  $100\text{ mg/m}^2$  by intravenous infusion over 1 h every 3 weeks. This compound too is the subject of ongoing comparative trials with cisplatin and non-

platinum-based drugs in advanced non-small-cell lung cancer [965].

#### *Adverse effects and precautions*

Neutropenia is the principal dose-limiting side-effect of both paclitaxel and docetaxel. With paclitaxel it usually occurs in the second week after treatment, the marrow recovering by the end of the third. Hypersensitivity reactions are also problematical and have to be guarded against [966]. Hypersensitivity reactions occurred in over one-quarter of patients in early trials of paclitaxel and may have been caused by a castor oil-based vehicle. These included urticarial rashes, wheezing and hypotension within a few minutes of dosing, so that premedication with a corticosteroid (e.g. dexamethasone 20 mg orally 6–12 h before), an antihistamine (e.g. chlorphenamine [chlorpheniramine] 10 mg i.v. 30–60 min before) and an  $H_2$  antagonist (e.g. cimetidine 300 mg i.v. 30–60 min before) is necessary, this protocol having substantially reduced the incidence of major hypersensitivity reactions. Electrocardiographic abnormalities may include sinus bradycardia, conduction defects and dysrhythmias that are seldom symptomatic. Mucocytosis may also occur with high doses. A predominantly sensory peripheral neuropathy with 'stocking and glove' numbness and paraesthesiae may occur with multiple courses at conventional dose levels (cf. vincristine, cisplatin) and is a major toxicity in paclitaxel/cisplatin regimens, a problem that may be reduced by the substitution of carboplatin. Transient myalgia and scintillating scotomas have also been reported.

Docetaxel may also cause hypersensitivity reactions and peripheral neuropathy. In addition, it may cause fluid retention with troublesome dependent oedema. It is recommended that a 5-day course of dexamethasone, 8 mg twice daily starting the day before docetaxel, is given to avoid hypersensitivity and fluid retention problems. Both drugs may cause nausea, vomiting and reversible alopecia.

#### *Procarbazine*

Procarbazine is an antineoplastic alkylating agent and mild monoamine oxidase inhibitor. It is a standard agent in the multidrug treatment of Hodgkin's disease, for example mustine/vincristine/procarbazine/prednisolone (MOPP). The precise mode of action is unknown but it is thought to inhibit the synthesis of RNA, DNA and other cellular protein constituents.

#### *Administration, metabolism, excretion and dosage*

Procarbazine is administered orally and is well absorbed from the gut. It is rapidly metabolized in the liver, the active metabolites crossing the blood–brain barrier. It is

excreted in the form of metabolites almost entirely by the kidneys.

Dosage varies according to the drug combination used, being 2–4 mg/kg daily (to the nearest 50 mg tablet) for the first week, increasing to 4–6 mg/kg daily until a response or until dose-limiting myelosuppression occurs, in which case treatment is stopped until recovery and may then be resumed at a lower dose such as 1–2 mg/kg daily.

### Adverse effects

The side-effects most frequently encountered are anorexia,

nausea, vomiting and myelosuppression. Both leucopenia and thrombocytopenia may occur, so that the blood count must be monitored and the drug temporarily discontinued if the white cell count drops to  $3 \times 10^9/L$  or the platelet count to  $100 \times 10^9/L$ . Neural effects may occur but are uncommon. They include peripheral neuropathy and central effects, such as depression of consciousness and psychotic behaviour. Other side-effects including hepatic impairment, rashes and interstitial pneumonitis have been described [967]. A disulfiram-like reaction may occur with alcohol.

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# SMOKING

IAN A. CAMPBELL

Half of all regular cigarette smokers will eventually be killed by their habit [1]. In 1995 in developed countries some 2 million deaths could be attributed to tobacco, in developing countries 1 million. Within 30 years these figures are likely to increase to 3 and 7 million respectively [2]. Smoking increases the absolute number of deaths from lung cancer, cancer of other respiratory sites, chronic bronchitis/emphysema and cor pulmonale. Deaths from ischaemic heart disease and cerebrovascular disease are advanced by smoking without an increase in the absolute number [3]. Stopping smoking, even in middle age, reduces the risk of dying from smoking-related disease [1] and reduces disability [4]. Since the initial reports by Doll and Hill [5–7] and Wynder and Graham [8] the Royal College of Physicians and the US Surgeon General, among others, have reported further on the harm caused by smoking and on the benefits of giving up the habit [4,9–14]. Yet in the UK 29% of adult males and 28% of females still smoke regularly and there is some evidence that smoking among children is increasing [15,16].

Smoking usually begins for psychosocial reasons, such as parental smoking, curiosity, peer pressure, rebelliousness and assertion of independence [17]. Once it becomes regular the pharmacological properties of nicotine are a major influence on the persistence of the habit [18], which appears to become advantageous to mood and/or life response [19]. Russell [20] described cigarette smoking as 'probably the most addictive and dependence-producing form of object-specific self-gratification known to man'. London drug users rated tobacco as their most needed drug, more than heroin, methadone, amphetamine, cannabis, LSD or alcohol [21]. Yet the manufacture and sale of cigarettes remain universally legal and advertising is permitted in all but a handful of countries.

## Harm to smokers

### Respiratory system

#### Lung cancer

Lung cancer is the most notorious of the diseases caused by smoking. Compared with non-smokers, death from lung cancer is 8–25 times more common among cigarette smokers [1], with a clear dose–response relationship [1,22]. As smoking has increased among women so have their death rates from lung cancer [23–25], leading to a situation in some areas where lung cancer has overtaken breast cancer as a cause of death [26]. In the USA between the 1960s and the 1980s, lung cancer death rates per 100 000 increased among current cigarette smokers from 26 to 155 in women and from 187 to 341 in men, the markedly steep increase of rates in women reflecting the change in smoking habits in women after the Second World War. Rates among non-smokers were stable [14]. Smoking and asbestos exposure are synergistic in producing bronchial carcinoma in humans. A smoker exposed heavily to asbestos runs nine times the risk of developing lung cancer compared with a smoker who is not exposed to asbestos and 92 times the risk of a non-exposed non-smoker [27,28].

Pipe and cigar smokers have an increased risk of lung cancer compared with non-smokers but are at less risk than cigarette smokers [29,30]. Carcinoma of the upper respiratory tract is increased up to 50-fold among cigarette smokers [1], particularly laryngeal carcinoma. In former cigarette smokers mortality declines with time [4]. Those who change from cigarette smoking to pipe or cigar smoking can lower risk but not by as much as does stopping smoking altogether [31]. Changing to lower-nicotine cigarettes is unlikely to reduce risk much because smokers continue to inhale or even inhale more to compensate [32–36]. Such compensation to maintain nicotine intake means that tar intake can only be substantially reduced by using a cigarette with a very low

tar/nicotine ratio/or, better still, by not smoking at all [37].

### **Chronic bronchitis and emphysema**

Mortality from chronic bronchitis and emphysema shows a relation to cigarette smoking almost as strong as that for lung cancer. Among those smoking 25 or more cigarettes daily mortality is over 20 times higher than in non-smokers [1]. Chronic bronchitis is related much more strongly to smoking than to atmospheric pollution [38]. Fletcher and Peto [39] showed that smoking was associated with irreversible obstructive changes in the airways in some subjects but not in others. Once smoking stopped, the rate of fall of forced expiratory volume in 1 s (FEV<sub>1</sub>) with age reverted to the normal rate. Cough, phlegm and wheeze are directly related to the number of cigarettes smoked daily and improve after cessation of smoking [40,41]. Giving up smoking reduces mortality from chronic bronchitis and emphysema [1]. Tar yield is related to sputum volume [42], whilst reduction in exercise tolerance is aggravated by the high levels of carboxyhaemoglobin [43]. Physical fitness and lung function in healthy middle-aged men were substantially lower in Norwegian smokers compared with non-smokers. Fitness and FEV<sub>1</sub> declined by twice as much in smokers compared with non-smokers in the 7 years of the study. Stopping smoking during the period halved the rates of decline, whilst starting smoking increased them [44]. These findings for lung function were confirmed in a study of Japanese-American men in Honolulu [45]. In the Lung Health Study in the USA, cessation of smoking has again been shown to reduce the age-related decline in FEV<sub>1</sub> in middle-aged smokers with mild airways obstruction, whilst regular use of an inhaled anticholinergic bronchodilator did not influence the long-term decline of FEV<sub>1</sub> [46].

### **Cardiovascular system**

It would be parochial not to describe the importance of smoking as a cause of morbidity and mortality in ischaemic heart disease, cerebrovascular disease and peripheral vascular disease. A cigarette smoker has two to three times the risk of heart attack compared with a non-smoker and a 30–60% greater chance of death from heart attack, whilst heavy smokers aged 45 years or younger have 10–15 times the risk of fatal heart attack [29,47–50]. Three-quarters of smokers who have heart attacks under the age of 50 would not have done so had they not smoked [51]. Patients with angiographically proven coronary artery disease who continue to smoke have a 50% greater risk of dying within 5 years than those who stop [52]. Pipe and cigar smokers are also at risk compared with non-smokers [53].

In men and women the risk of stroke and subarachnoid haemorrhage is increased two- or three-fold by smoking; the heavier the smoking, the greater the risk [1,24,54–57]. In New Zealand it was estimated that just over one-third of strokes could be attributed to smoking, much the same as were attributed to hypertension. The presence of both risk factors increased the risk of stroke by almost 20 times over that of a non-smoker [58]. Over 90% of patients with peripheral vascular disease are smokers, these individuals finding themselves unable to give up smoking even after multiple amputations [59].

Stopping smoking after a heart attack is by far the most important factor in preventing further morbidity and mortality, improving prognosis more than do  $\beta$ -blockers [60–62]. The risk declines over 15 years to that of a non-smoker [63]. Continuing to smoke reduces the beneficial effects of anti-anginal therapy [64]. Men who give up smoking before a heart attack occurs reduce their risk of a first myocardial infarction over the next 5 years to that of a non-smoker, although for heavy smokers ( $\geq 20$  cigarettes daily) the risk takes 15–20 years to decline [65,66]. In women the risk declines quicker than in men, approaching that of a non-smoker 3 years after quitting [67]. Changing to cigarettes with lower tar yields is not an effective means of reducing the risk of myocardial infarction [68].

Stopping smoking reduces the risk of stroke in middle-aged men by a factor of four, benefit occurring rapidly within the first 5 years overall but never being complete in former heavy smokers ( $\geq 20$  cigarettes daily). Benefit was most marked in those who also had hypertension. Switching to pipe or cigar smoking reduced the risk very little [69]. Much the same has been found in women in relation to cerebral thrombosis/haemorrhage, although cessation reduces the risk of subarachnoid haemorrhage in women even more than it does in men [70]. In peripheral vascular disease outcome is influenced less by vasodilator drugs than by smoking cessation [71].

### **Gastrointestinal system**

Oesophageal carcinoma is highly related to smoking, death from this condition being eight times as common in smokers as in non-smokers, with a clear dose-response relationship [1]. The association with pancreatic cancer, although significant, is not as strong and the same applies to stomach cancer [1]. Smoking increases susceptibility to peptic ulcer, impairs healing, and increases the risk and rapidity of recurrence and of perforation [72]; the effect of treatment with histamine H<sub>2</sub> antagonists is reduced if a patient continues to smoke [73,74]. Patients with Crohn's disease are more likely to be smokers, whilst in ulcerative colitis there appears to be an association with non-smoking [75,76].

### Genitourinary system

Men who smoke run two to three times the chance of developing bladder cancer; in women the association is positive but not as strong [77]. Smoking also increases the risk of renal cancer [78].

Carcinoma of cervix is up to four times more common in smokers than non-smokers [79], and although some of this apparent risk is likely to be due to confounding factors, there is a direct relationship [78,80]. Fertility in women is decreased by smoking [81], whilst the menopause occurs 2–3 years earlier in smokers [82].

Men who smoke have increased morphological abnormalities of their sperm [83] and fertilizing potential is reduced [84].

### Miscellaneous systems

Smoking is thought to contribute to cataract, possibly as a result of deposition in the lens of the cadmium from tobacco [85].

Bone density is reduced sufficiently by smoking to increase the risk of postmenopausal fracture [86,87].

Premature facial wrinkling is increased by smoking [88], as is palmoplantar pustulosis [89].

### Mechanisms of harm

Cigarette smoke contains many toxic compounds, including polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines and radioactive polonium as well as radon, all of which are potent carcinogens and mutagens in animals. Presumably the increased incidence of lung and other cancers in humans are related to one or more of these substances [90]. Cigarette smoke causes release of elastolytic enzymes from lung neutrophils and macrophages, nitrogen oxides contained in the smoke cause emphysema in animals, and oxidants in smoke reduce the levels of  $\alpha_1$ -antitrypsin in human and animal lungs [91]. Hopkin and Steel [92] found consistent and significant variation in the response of lymphocytes from different individuals to the cytotoxic effect of cigarette smoke condensate *in vitro*. Polymorphs from patients with emphysema were more sensitive to the cytotoxic effects of cigarette smoke condensate than those from age- and smoking-matched control subjects [93]. The implications for emphysema and carcinoma are clear. Endogenous nitric oxide is important in defending the respiratory tract against infection and in counteracting bronchoconstriction and vasoconstriction. Cigarette smoking reduces exhaled nitric oxide concentration, a reduction likely to contribute to the increased risk of chronic respiratory disease in smokers [94].

Pulmonary epithelial permeability is greater in symptomless cigarette smokers compared with non-smokers and this permeability is correlated with carboxyhaemo-

globin concentration [95] but not plasma nicotine concentration [96]. Besides the implications for bronchitis and emphysema, the increase in epithelial permeability is likely to contribute to the genesis of lung cancer by permitting easier ingress of the chemical and physical carcinogens in tobacco smoke.

Increase in permeability of systemic blood vessel walls to lipids has been suggested as contributing to the cardiovascular risks of smoking [90]. Smoking increases atherosclerosis and a tendency to thrombosis [97]. However, smoking seems related to myocardial infarction independently of its effect on atherosclerosis; in 4000 patients with ischaemic heart disease, myocardial infarction was more common in smokers than in non-smokers with a comparable degree of occlusive disease on the coronary angiogram [98]. This may be related to the loss of oxygen-carrying capacity of the blood due to raised carboxyhaemoglobin levels and to the effect of nicotine in causing increased catecholamines, platelet stickiness and platelet aggregation [90].

### Harm to non-smokers

Passive (or forced) smoking can have deleterious effects on health. In many situations the passive smoker has no choice in the matter, an infringement of rights that in most other instances would be illegal.

Maternal smoking increases the combined mortality in fetal and neonatal life by 28%, and reduces birthweight by 170 g to 320 g [99,100]. It is thought that there is hypoxic damage to the fetus as a result of placental insufficiency caused by nicotine-induced vasoconstriction and by high carboxyhaemoglobin concentrations in fetal and maternal blood [101]. Interestingly, reduced birthweight is also correlated with paternal smoking even after controlling for the mother's habits [102]. Smoking by parents is the most important risk factor for inducing sudden infant death syndrome (cot death). Maternal smoking is more important than paternal, with a fivefold risk if both smoke [103–105]. In the first year of life, children of smoking parents have twice the risk of pneumonia and bronchitis and twice the risk of admission to hospital because of respiratory illness [106–108].

Lung function in children is impaired by maternal smoking, the damage possibly occurring *in utero* as well as in infancy/childhood [109,110]. There is a link between smoking in the home and coughs and snoring in young children [111,112], as well as with acute attacks of asthma and the prevalence of asthma [113–115]. Allowing for associated social and biological factors, smoking in pregnancy leads to retarded reading, mathematical and general ability [116], as well as an increased risk of cancer in childhood [117]. Exposure to environmental tobacco smoke during childhood and adolescence leads to increased risk of lung cancer in adulthood [118].



Exposure to tobacco smoke can cause cough and breathlessness in non-smoking patients with chronic bronchitis and emphysema and can induce attacks of asthma [4]. In 1980, White and Froeb [119] found evidence of small airways disease in non-smokers who were chronically exposed to tobacco smoke. Non-smokers exposed to tobacco smoke in their workplaces had more cough, phlegm, shortness of breath, eye irritation, 'chest colds' and lost days from work due to 'chest colds' [120], with significant effects on lung function [121]. Passive smoking at home and at work is associated with breathlessness, cough, sputum, asthma and allergic rhinitis [122]. Patients with asthma experienced symptoms, had increased airway irritability and showed a fall in FEV<sub>1</sub> when exposed to environmental tobacco smoke for 1 h [123].

In 1981, in both Greece and Japan, passive smoking by wives was reported to increase their risk of lung cancer [124,125]. Since then the weight of evidence has been such that five independent expert groups have concluded that passive smoking causes lung cancer in non-smokers, increasing the risk by 10–30%. In the UK, at least 300 deaths every year from lung cancer in non-smokers can be attributed to the effects of passive smoking [126].

Passive inhalation of cigarette smoke can worsen angina [127]. Death from ischaemic heart disease is significantly higher for non-smoking spouses who live with smokers compared with those not exposed to passive smoking in the home [128,129]. Wells [130] reviewed the evidence linking passive smoking to ischaemic heart disease and concluded that passive smoking increased the coronary death rate among people who never smoked by 20–27%, a finding supported by a later meta-analysis [131].

## Stopping smoking

Much has been achieved in the last 25 years, but the aim must be a further reduction and eventual complete eradication of the smoking habit. Education of health professionals, the general population, civil servants, politicians and governments is a key step. In itself education should reduce smoking but it is also important as a prerequisite to more effective restrictive and legislative steps. An educated population will understand and respect restrictions [132]. Politicians must be persuaded not only that smoking is harmful to both active and passive smokers but also that, given enough educational preparation, smokers will recognize that cigarette tax is not reason enough to change their vote. After a period of education the Norwegian Tobacco Act of 1975 banned all advertising of tobacco products, required all packets to be labelled with a symbol and text pointing out their health dangers, prohibited sales to those under 16 years old and allowed the Ministry of Health and Social Affairs to issue regulations concerning content, weight, filters, etc. of tobacco

products. Further legislation has been accepted in Norway, i.e. only non-smokers are offered new jobs in the asbestos industry and smoking is not allowed in such work premises. Between 1975 and 1980 smoking fell markedly in men and among young people of both sexes, whilst the increase among Norwegian women was halted. In 1980 the Government increased the price of cigarettes by 30%, with accompanying publicity about the underlying medical reasons for this move; simultaneously the Norwegian Council on Smoking and Health ran an advertising campaign emphasizing the financial savings if a person stopped smoking.

Smoking in children is related to whether their parents smoke and, to a lesser extent, peer pressure, which itself is dependent on parental habits. Thus moves to reduce smoking in adults will reduce smoking in children. Increasing the real price of cigarettes by relentless tax rises is a most effective means of reducing smoking in adults [133]. Atkinson and Townsend [134] proposed a policy for the UK which they calculated would reduce smoking by 40%, reduce morbidity, increase longevity but would not increase net cost to the exchequer.

The importance of banning advertising of cigarettes and other tobacco products has been demonstrated not only in Norway but also in New Zealand, Finland and Canada; consumption falls among children and adults but advertising and publishing industries are not disadvantaged. The ethics of advertising a product that is so dangerous to health should continually be questioned in public. Over 70% of the UK population are now non-smokers and they should press for their right to breathe clean air. Evidence of damage from passive smoking was sufficient to persuade Australian and Swedish courts to award compensation to harmed passive smokers and to relatives of deceased passive smokers. Courts in the UK and the USA are likely to respond similarly. Employers and organizations fear this consequence, a fear that should be exploited when they resist health and nuisance arguments for smoke-free environments. Smoking should not be permitted on healthcare premises except in very special circumstances and then only in private. In the current purchaser-provider situation in the UK National Health Service, purchasers (health authorities and GPs) should require smoking to be banned from all but specially designated areas in healthcare premises and should include such a policy and measures to monitor its effectiveness in contracts with providers, e.g. hospitals. Ultimately, staff and visitors should not be allowed to smoke in healthcare premises, and patients only in very exceptional circumstances.

## Smoking cessation in general practice

With simple advice to stop smoking and with a warning of possible later follow-up, GPs can motivate more of their



patients to stop smoking and some 5% will still be abstinent 1 year later [135]. On average any GP could thereby achieve 25 long-term successes each year. If every GP in the UK were to do this, then initially more than half a million people would stop smoking. Health risks are the most frequent reason for quitting; of successful ex-smokers who gave illness as a reason for stopping, 54% said that they had done so on a doctor's advice. In 1967, only 20% of smokers reported that their doctor had advised them to stop or cut down [21]. Disappointingly, in a survey in 1982 Inman [136] found that only 15% of GPs encouraged the smokers among their patients to stop. It will be interesting to see whether these figures have changed during the 1990s, with the introduction of government incentives to GPs to encourage their patients to stop smoking. A GP's advice increases the proportion intending to stop and the proportion who try to stop, rather than increasing actual success rates among those intending or trying to stop [135].

In Oxford, a further study showed an 11% quit rate at 1 year in a control group, 15% in a group given advice plus a booklet, 17% in a group where the patient's expired carbon monoxide level was measured at the time of giving advice plus booklet, and 13% in a group where an offer of a visit from a health visitor replaced the carbon monoxide measurement as part of the strategy. Claims of abstinence were verified by urinary cotinine measurements. The combined result of the active groups was significantly better than the control group, but there was no difference between the active treatments nor between any one treatment and control [137].

In Sydney, Richmond *et al.* [138] gave intensive advice to patients who agreed to join a smoking cessation programme and compared this with a control group where the patient was asked to participate in a study of 'smoking and health'. At the initial encounter the control subjects completed a questionnaire, had blood taken for carboxyhaemoglobin estimation and had their FEV<sub>1</sub> measured. A follow-up appointment in 6 months was arranged. The active group received advice and a booklet in addition to the questionnaire and carboxyhaemoglobin and FEV<sub>1</sub> measurements, and were given five follow-up appointments over the next 6 months. Advice was repeated at each follow-up visit. At 3 years, 2% in the control group were abstinent compared with 23% in the active group ( $P < 0.01$ ), using salivary cotinine to validate claims of cessation. However, in another study in New South Wales neither simple advice nor a structured behavioural change programme resulted in a statistically significant increase in the number of patients stopping smoking, 5% in the structured group remaining abstinent for 12 months compared with 1% in the simple advice group or control group [139].

In the USA, physicians advised 2707 patients to stop smoking and then referred them for further help from a

nurse. The nurses either provided a two-page pamphlet or one of three nurse-assisted interventions: (i) giving advice on how to stop; (ii) group cessation; or (iii) combination of (i) and (ii). At 12 months the group given nurse-assisted interventions did better than the group given a pamphlet only (7% vs. 3.9% validated cessation) [140].

Following the promising results of nicotine chewing gum in the setting of smoking withdrawal clinics, Russell *et al.* [141] tried it in general practice. At 1 year they obtained a validated success rate of 8% in a group receiving nicotine gum plus advice, compared with 4% in a group receiving advice plus a leaflet and warning of follow-up and 4% in a group that just completed a questionnaire. The design of the study did not include a group receiving placebo chewing gum. Jamrozik *et al.* [142] did compare nicotine gum with placebo in 199 of the 429 patients who had failed to give up smoking in their earlier study and who then agreed 'to try an anti-smoking chewing gum' as an aid to stop smoking. Validated success rates at 6 months were 10% vs. 8% in this motivated but nevertheless 'hard case' population. Nicotine gum has been compared with placebo (confectionery gum) in South Wales in smokers routinely consulting their GP. The GP's usual advice to stop smoking was given to both groups and to an advice only group. At postal follow-up at 1 year, claims of sustained abstinence for at least the last 6 months were then verified by measurement of expired air carbon monoxide levels. The nicotine gum resulted in 3.1% success, placebo gum 2.2% and doctor's advice only 1.3%, differences that were not statistically significant [143]. In a further British study Marshall and Raw [144] compared intensive follow-up in 200 patients who wished to stop smoking and who agreed to try nicotine gum as an adjunct. At 1 year they recorded 15% and 14% success rates.

In Sydney 450 smoking patients were allocated to structural behavioural change plus nicotine gum or structural behavioural change without nicotine gum or GP advice with nicotine gum. Continuous abstinence from the end of 1 week to 1 year (validated) was 9% for the groups undergoing structural behavioural change and 6% for the other group [145]. The clear and significant benefit from nicotine gum when used in specialized smoking cessation clinics is not evident when it is used in general practice [146].

Transdermal nicotine was used in general practice in Switzerland and, in middle-aged, dependent smokers seen monthly for 3 months, was shown to produce better results than placebo patches. Further studies led to the conclusion that transdermal nicotine would work in motivated smokers (20 or more cigarettes daily) when used in specialized smoking cessation settings, but emphasized the need to provide adequate support and counselling if success rates as good or better than the 26% reported by the Transdermal Nicotine Study Group were to be achieved [147]. In a general practice study in Oxfordshire,

treatment with transdermal nicotine in addition to advice and support from practice nurses resulted in 10% continuous abstinence at 1 year in the active group compared with 7% in the placebo group ( $P < 0.05$ ) [148]. Early abstinence from smoking was the strongest predictor of sustained cessation [149]. In another study, extending over 30 general practices in 15 English counties, Stapleton *et al.* [150] compared nicotine and placebo patches in patients who all received brief advice from the GP plus a booklet, both groups receiving brief support and follow-up at regular intervals throughout the year. Validated continuous abstinence rates at 1 year were 9.6% for the nicotine group and 4.8% for the placebo ( $P < 0.01$ ). The patch enhanced cessation during the first week and reduced relapse during the second week. The majority of eventual successes had stopped smoking during the first week. Adverse effects were limited to moderate to severe local irritation or itching of the patch site in about 15% of the patients.

### Smoking cessation in hospital patients

Patients attending hospital with smoking-related diseases who nevertheless continue to smoke up to the time of their attendance must, by definition, be a 'hard-core' population. They are suffering from symptoms and conditions which, in all probability nowadays, they know are related to cigarette smoking and yet they have not stopped before coming to the hospital. They must be a different group from patients encountered in general practice and from smokers in the general population who are recruited or seek help from smoking cessation schemes.

At a London chest clinic, simple advice by the physician, resulted in an abstinence rate over 6 months of 18–23%, although these claims were not validated objectively [151]. In another study, patients with airways obstruction who were advised by a chest physician to reduce or stop smoking were more likely to do so than those not so advised. In the same study, it was shown that the wearing of a white coat by a clinical psychologist who interviewed the patients after they had seen the chest physician increased the numbers claiming to have stopped or reduced their smoking [152]. For patients recovering from myocardial infarction, firm advice from a physician, repeated by junior staff and nurses and reinforced by written advice, special follow-up clinics and home follow-up by community nurses, resulted in 63% claiming abstinence at 1 year. Over 85% of these patients stopped while in hospital, the remainder during follow-up. Abstinence was not verified but even allowing for a 30% rate of false claims the calculated success rate of 40–45% is good. In the control group who received conventional advice without follow-up only 27.5% claimed abstinence [153]. Strong, uncompromising advice to patients attending a post-myocardial infarction clinic resulted in 42% verified abstinence rates, although

in this study the period of abstinence was not stated [154].

In the large multicentre trial run by the British Thoracic Society, nicotine chewing gum was used as an adjunct to physician's advice but it proved no more effective than placebo gum or an advisory booklet or the advice alone; at the end of 1 year 10% of these patients with smoking-related diseases had successfully stopped smoking for at least the previous 6 months. Chewing gum clearly aided abstinence for 1 and 3 months but there was no difference between active and placebo gums [155]. Men did better than women (12.5% vs. 5.3% success), success rate increased with age in both sexes and people with heart disease did better than those with any other diagnosis. If the most important other person to the patient was a non-smoker then success was more likely, whilst single or married men did better than separated or divorced men. Confidence in ability to stop was a predictor of success in men but not women. Cigarette consumption, social class, concern about weight gain and perceived benefit of stopping smoking did not relate to success. Patients cited worry or anxiety as things that made them want to smoke after they had stopped and those who stated that they still craved or found it difficult to do without cigarettes were more likely to relapse [156].

This trial was criticized for lack of early support after the initial advice from the physician. That such support might increase success rates in patients was suggested by the study from Sweden in which nicotine gum plus group therapy gave a validated success rate of 29% at 1 year compared with 16% for placebo gum plus group therapy. One-third of the subjects were self-referrals to the clinic or hospital, whilst two-thirds were referred by physicians [157]. In two further multicentre trials in the UK in outpatients with smoking-related diseases, the British Thoracic Society compared physician's advice alone with advice backed up by a signed agreement to try to stop smoking by a target date, two visits from a health visitor in the first 6 weeks and encouraging follow-up letters from the physician (five in the first 6 months). The design of the trials allowed assessment of the follow-up letters, the health visitor and the signed agreement as separate parts of the package. It was hoped that out of the trials would emerge an effective, simple strategy that would prove superior to a doctor's advice alone and would also be within the human and financial resources of hospitals and chest clinics. The results indicated that physician advice alone would persuade 5% of outpatients with a smoking-related disease to stop smoking and that subsequent postal encouragement would increase the cessation rate by more than half as much again. The signed agreement and visits by health visitors did not affect outcome. Thus a simple method based on advice followed by postal encouragement to stop smoking has been shown to be more effective in hospital outpatients than advice alone. Even these

modest increases in cessation rates are worthwhile if they have the potential to be applied on a large scale [158].

In a chest clinic in South Wales, cigarette-smoking patients referred just for chest radiography were allocated at random to a control group (radiography only) or to an active group who had radiography and were given a pocket-sized, 13-page advisory booklet on smoking. At 1 year, claims of abstinence were verified with measurements of expired air carbon monoxide levels and demonstrated 6.5% success with the booklet compared with 2.7% in the controls ( $P=0.09$ ). If this effect could be shown to be real rather than due to chance, then the application of such a strategy on a wide scale would result in significant numbers giving up smoking at very little cost, perhaps as little as £10 per successful ex-smoker [159].

A study at two clinics in Ann Arbor Veterans Administration Medical Center (Michigan, USA) compared a leaflet on smoking with a self-help booklet plus a 20–30 min session from a trained counsellor and with the latter strategy plus individually tailored follow-up treatments by telephone and post. At 6 months, success, as determined by those who claimed not to have smoked for at least 1 month prior to answering and with measurement of urinary cotinine to verify their claims, was 6% in the active treatment groups compared with 1% in the control group [160].

The work by Hjalmarson [157] has been taken further in a hospital in South Wales, where a medical secretary with good interpersonal skills has been used as a smoking cessation counsellor to reinforce the physician's advice to stop smoking. In addition to intensive early support from the counsellor (three sessions in the first month and further sessions at 2 months and 3 months), patients were randomized to nicotine or placebo chewing gum. At 1 year, the validated sustained abstinence rate was 20%, with no difference between nicotine and placebo [161]. The same design was used in a further study of patients attending hospital (inpatients and outpatients) with smoking-related diseases, but instead of gum transdermal nicotine was compared with placebo patches; at the end of the year 21% in the active group and 14% in the placebo group said that they had not smoked throughout the period from week 12 to week 52 and measurements of expired air carbon monoxide levels at 12, 26 and 52 weeks confirmed these claims [162]. Although this difference was not significant at the 5% level, it does indicate that a further study large enough to answer this question should be conducted, such a study ideally including a third group receiving just support and advice. These two studies showed that success rates two to four times greater than those obtained in the studies by the British Thoracic Society [155,158] and comparable to the results achieved in Sweden [157] could be obtained using relatively unsophisticated staff under routine health service conditions. The counsellor continues to achieve 20% sustained suc-

cess at 1 year, a service which, in terms of cost per life-year saved, is more cost-effective than  $\beta$ -blockade for mild to moderate hypertension [163].

### Smoking cessation in other clinical settings

Family planning clinics and antenatal clinics provide good opportunities for influencing the smoking habits of women. In San Francisco, Coates *et al.* [164] showed that 3–5 min of advice from the doctor or midwife did better than just posters plus a video shown in the waiting room, cotinine-verified success rates at 1 year being 0.1% for the control group, 2.4% for posters plus video, and 3.7% for the doctor's or midwife's advice.

At an antenatal clinic staffed by family practitioners in Toledo City, pregnant women were just advised by the physician in the usual way to stop smoking or were provided with the American Lung Association's *Freedom from Smoking for You and Your Baby* booklet or were shown an educational videotape about smoking in pregnancy. Smoking status was assessed objectively 2–3 weeks prior to delivery when abstinence rates ranged from 4 to 9% with no significant difference between the three interventions [165]. A similar study by Messimer *et al.* [166] had shown 5–15% cessation rates, the differences between these two studies appearing to be due to the fact that the populations were markedly different, with more people in the study by Messimer *et al.* being married, more in employment and fewer from ethnic minorities.

### Smoking cessation clinics

Traditionally, smoking cessation clinics have offered treatment to self-selected clients and emphasized group therapy and educational approaches. In a review of the results of several studies in such clinics, Raw [167] found similar long-term success rates of between 15 and 20%. Success rates of up to 80% could be achieved in the first month but most clients relapsed in the next 3–4 months. He found no evidence that tranquillizers helped people to stop smoking; results of hypnosis were mostly anecdotal, with controlled investigations and biochemical verification of abstinence sadly lacking. No specific effect could be demonstrated for electrical aversion therapy, whilst other aversion therapies in the form of rapid smoking or blowing warm, smoky air into the faces of smokers gave success rates of around 60% at 6 months but, as Raw concluded, 'it is difficult to be sure whether the aversive components or the inevitable, non-specific, therapeutic variables in these experimental situations are more important'. More recently, the antidepressant amfebutamone (bupropion) has been shown to increase the point-prevalence cessation rate at 1 year in smokers without current depression [168]. Nicotine chewing gum was first shown to be effective in studies conducted in smoking

cessation clinics. In London, at the Maudsley Hospital's smokers' clinic, 31% of patients treated with nicotine chewing gum and usual supportive treatment abstained from smoking for 1 year compared with 14% in the placebo gum group ( $P < 0.05$ ) [169]. When transdermal nicotine is used within the setting of a smoking cessation clinic and in populations of healthy smokers who volunteer to attend, it too produces an improvement over placebo patches [170–172]. Nicotine by inhaler or nasal spray has been studied in smokers' clinics based in hospitals. At the Maudsley Hospital, validated continuous abstinence rates throughout a year were achieved by 26% of the patients assigned to nicotine nasal spray plus usual supportive group treatment, whilst with placebo the abstinence rate was 10% ( $P < 0.01$ ) [173]. In Reykjavik, the use of nicotine nasal spray increased abstinence rates up to 6 months but not to 1 year [174]. In these studies the majority of the patients experienced local irritant effects but only a small minority ( $< 1\%$ ) discontinued the spray because of adverse effects.

In Copenhagen, volunteers recruited by newspaper advertisements received either 3 months of nicotine inhaler or placebo inhaler in the context of minimal levels of advice and support. Continuous abstinence rates (verified) after 1 year were 15% for the active inhaler and 5% for the placebo ( $P < 0.02$ ) [175]. In Sweden, Hjalmarson *et al.* [176] obtained 27% continuous abstinence with nicotine inhaler and 15% with placebo in a mixed population of patients (one-third) and newspaper-recruited volunteers (two-thirds).

The best smoking cessation clinics are labour intensive and produce good results, but the majority are labour intensive and produce mediocre or poor results [177]. Chapman [178] has cogently argued the case for their abandonment, pointing out that they reached 0.5% or less of the smokers in the UK who wanted to stop and were not cost-effective. To be effective on a population basis and to be cost-effective, smoking cessation programmes and techniques must be capable of being inexpensively incorporated into a delivery system that involves significant numbers of smokers, including patients who smoke. Humerfelt *et al.* [179] have recently shown how this can be done with postal methods applied to young Norwegian men at increased risk for smoking-related lung disease.

### Mass media methods

In 1975, two UK television programmes on smoking increased the numbers of smokers trying to give up by 27%. By virtue of this extra motivation the programmes produced a useful effect on long-term abstinence [180]. After a television programme on the health hazards of smoking, two-thirds of those requesting a postal smoking cessation kit were sent the kit, whilst one-third were

chosen at random as controls and did not receive the kit. Validated cessation at 1 year was 9% in recipients of the kit compared with 7% in the control group ( $P < 0.05$ ) [181]. Leaflets on the reasons for stopping smoking increased abstinence rates at 1 year by 30% among responders to a newspaper advertisement (F. Ledwith, personal communication, 1982). Radio and newspapers were used to advertise the 'Quit and Win' contest in Wales in 1990 in which the reported sustained quit rate at 1 year was 30% (unvalidated). The estimated cost for each year of life saved by the contest was £42 [182]. Reid [183] calculates that mass campaigns involving television are probably cost-effective; the cost per year of life saved would be in the region of £6–12, about the same as brief advice from a GP. He argues that media publicity not only reduces smoking but also creates a climate of opinion in favour of effective measures such as fiscal policy.

Continued efforts on all the aspects covered in the preceding sections will be necessary to renew the downward trend shown in Fig. 10.1, a trend which should give some satisfaction not only to those who have obtained and published the evidence for the dangers of smoking and the benefits of stopping but also to those who have campaigned for society and government to reduce smoking.

### Safer cigarettes

No cigarette is safe. Progressive reduction of tar yields over the last 20 years has contributed to the reduction of deaths from lung cancer at all ages among men and to

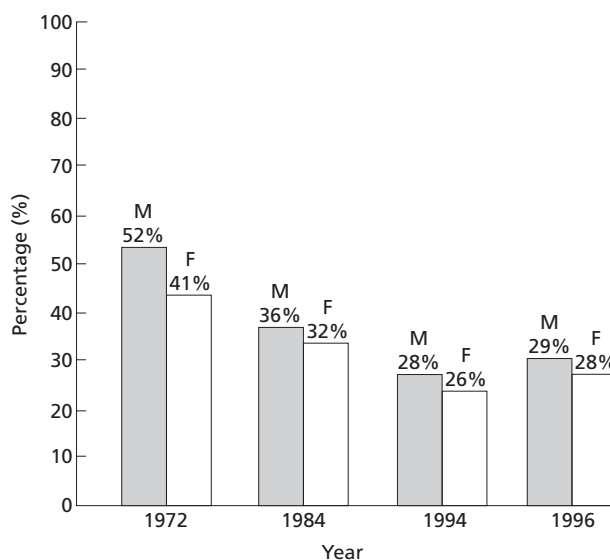


Fig. 10.1 Smoking prevalence in the UK, 1972–96 (16 years-old and over), (General Household Surveys 1972, 1984, 1994, and 1996.)

deaths under 65 years among women. If nicotine is reduced to an unduly low level, compensatory smoking occurs, with increase in hazard from the increased smoke, tar and carbon monoxide inhaled. The introduction of synthetic tobacco substitutes in cigarettes to replace some of the natural tobacco was not successful in 1977 when the substitutes were based on modified cellulose [184]. Experience with glycerol particle cigarettes does not suggest that they are likely to be any more successful as substitutes [185].

### **Smoking and weight**

The evidence for an inverse relation between cigarette smoking and body weight is convincing. Smokers tend to weigh 2–5 kg less than non-smokers of comparable age and height and many studies have shown that smokers who quit gain a similar amount [156,186]. Animal studies suggest that nicotine is responsible for the effects of smoking on weight; in humans it has been established that cigarette smoking increases 24-h energy expenditure by approximately 10% and that this effect is mediated by nicotine [187]. In modern society smoking is widely perceived as an effective strategy of weight control, especially by women. It should be made clear, especially to adolescents and adults, that smoking is an unhealthy way to control weight. In the meantime further studies should seek a more precise understanding of the mechanisms of smoking-related weight loss, and strategies of weight control for smokers who try to give up should be developed.

### **Smoking in the workplace**

Many employers have recognized the importance of controlling smoking in the workplace, not only because this practice reduces disease and days off sick among their workforce but also because it reduces the likelihood that non-smokers in their workforce might acquire a condition induced by passive smoking and seek compensation. Being unable to smoke at work contributes to a reduction in smoking prevalence in workforces, with prevalence declining at about twice the rate found in the general community [188]. Minimal smoking intervention programmes based on the use of videotapes produced long-term abstinence rates of under 10% in four companies in the UK. The addition of four, short consultations with the occupational health nurse, coupled with the use of nicotine chewing gum, resulted in 16% sustained cessation at 1 year in the intervention group compared with only 2% in the control group [189]. The organizations ASH and QUIT now offer advice and help to employers who wish to reduce smoking in the workplace.

### **Children and smoking**

Children are more likely to become smokers if their parents smoke [190]; pressure from peers is also important. At age 15, 26% of boys and 30% of girls in the UK are regular smokers. The number of children aged between 11 and 15 who reported smoking at least one cigarette per week rose from 10% in 1993 to 12% in 1994. In this age range, 70% of those who were regular smokers smoked more than 20 cigarettes a week and 25% smoked at least 10 cigarettes daily [16]. In the UK very few people take up smoking after the age of 18 years. Besides the influence of parents and peers, children are influenced towards smoking by the availability of cigarettes, advertising and the portrayal of smoking in films, magazines and literature. Cigarette prices also have an effect. Taking up smoking is associated with early onset of cough, production of phlegm and shortness of breath on exertion in children and adolescents. Studies detailing the deleterious effect of smoking in children and adolescents are summarized by Charlton [17], who also underlines the fact that children who smoke become addicted to nicotine quickly and at an early age. Of the methods that she suggests for preventing and reducing smoking in children and adolescents, by far the most important is government action to ban cigarette advertising, increase the price of cigarettes and create a smoke-free norm. The study by Porter [191] has established that measures reducing the exposure of an uncommitted adolescent to peer-group smoking decreases the chances of tobacco dependence in adulthood.

### **Smoking and the developing world**

Worldwide deaths from cigarettes are expected to increase from 3 million currently to about 10 million by the year 2020 [192,193]. Patterns of smoking are different in developing and developed countries: in the developing countries over 50% of men smoke whilst only 10% or less of women smoke, compared with developed countries where 25–30% of both men and women smoke. As in developed countries, smoking starts among young people and for much the same reasons. Consumption of tobacco is increasing in eastern Europe and Asia, the latter continent accounting for about half the world's cigarette consumption. As the market for tobacco shrinks in the developed nations, the multinational tobacco companies are targeting the developing countries. The human and economic burden of medical and health costs, coupled with lost productivity, loss of the use of land that could be used to grow food and loss of the foreign exchange paid in importing cigarettes will all impose severe penalties on the developing nations.

Medical and paramedical professionals from the developed world have a responsibility to influence medical

opinion in developing countries and via this means alert governments to the problems that increased smoking will cause. The World Health Organization and international non-governmental agencies should have a programme on influencing smoking in developing countries. Governments should be encouraged to develop national tobacco control policies, which would include bans on tobacco promotion, discouraging smoking in children and adolescents and the creation of national non-smoking norms.

Taxing tobacco in developing countries will have as strong an impact as it has done (and can continue to do) in developed countries.

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# AIR POLLUTION

ANTHONY SEATON

Two great social revolutions have been the main contributors to anthropogenic air pollution. The first of these was the Industrial Revolution, which started in Britain and western Europe in the eighteenth century and resulted in the growth of cities to house the workers in the new factories. The fuel of the Industrial Revolution, in both the factories and the houses, was coal and the buildings of the towns and cities became black with the sooty smoke. Throughout the first half of the nineteenth century the major conurbations of western Europe were noted for their winter-time smoky fogs, or smogs, during which it was commonplace in these cities not to be able to see across the street. It is important to realize that this epoch of rapid industrialization is still continuing in other parts of the world and that uncontrolled burning of coal and other fuels may constitute one of many threats to health in developing countries.

The second important contributor to air pollution has been the revolution in mobility, characterized by increasing ownership of cars and use of motor vehicles for transportation of goods. This rapid change has occurred as a consequence of greater general prosperity and of the ready availability of cheap fuel. Prosperity is relative and even in many poorer countries there has been a massive increase in the use of cars and lorries wherever the economy has improved, to the extent that some of the worst traffic pollution in the world now occurs in cities such as Calcutta and Cairo. This has resulted in a change in the type of pollution in places where coal burning has been reduced and traffic has increased, so that the smoke may contain less black matter and sulphur dioxide but more nitrogen oxides and other chemicals. The increased output of these substances has also led to greater secondary pollution by the photochemical production of ozone.

It has been a characteristic of cities since their populations started to increase in the Industrial Revolution that the poorer people have lived in the more polluted parts, downwind and close to the sources of the smoke. Those who could afford to bought their houses upwind of, and

distant from, such areas. It is perhaps because of this, and because of the other accompanying social disadvantages that led to poorer health among the less well-off, that it took the medical profession so long to recognize the harmful effects of air pollution on health. It was not until the 1950s that a succession of major air pollution episodes, most notably in the Meuse valley in Belgium and in London, were seen to be associated with excess numbers of deaths and hospitalizations from respiratory and cardiac disease. Investigation of the effects of the severe London smog of 1952 showed that during the week of the episode some 4000 excess deaths occurred in the city (Fig. 11.1) and this resulted in the first serious scientific studies of air pollution and its effects on health [1]. The evidence was so compelling that the British Parliament (which of course has its seat in the very place where the smogs were at their worst) enacted legislation, the Clean Air Act 1956, that aimed to control the burning of smoky fuel in towns and cities. The benefits of this legislation rapidly became apparent with the abolition of winter smogs, and it was widely believed that the problem of air pollution had been solved.

Over the past two decades it has slowly become apparent that the problem of air pollution still exists. Ecologists have drawn attention to the effects of exported pollution in the acidification of rivers and lakes in other countries, with damaging consequences on trees and aquatic life. This has occurred as a result of concentrating electricity generation in rural areas, in large coal-burning power stations with tall stacks, an economical and rational means of reducing urban pollution but one with consequences that were unforeseen at the time of their building. Others have drawn attention to the damaging effects of urban pollution on the fabric of buildings and to the economic costs involved. With respect to worldwide effects on health, the increasing combustion of fossil fuels and the consequent increase in carbon dioxide concentration in the air is likely to be a major contributor to global temperature rise, with possible secondary effects on rainfall in arid areas, rise in sea level and the distribution of diseases. Moreover, the

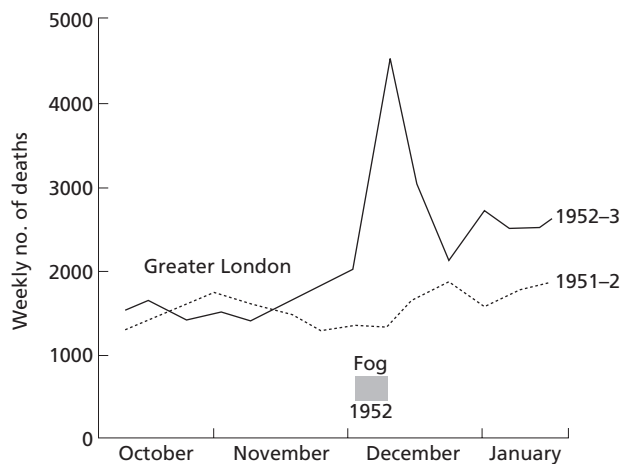


Fig. 11.1 Daily mortality in London in December 1952 compared with the previous year. During the week-long episode 4000 excess deaths occurred.

release of certain chemicals that destroy stratospheric ozone has increased access of ultraviolet rays to ground level and may be contributing to the increase in skin neoplasms among fair-skinned people. This generally increased awareness of the effects of the anthropogenic use of energy on the environment has been accompanied by a resurgent interest in possible more direct effects of the current types and concentrations of air pollution on health, and epidemiological studies have shown that this problem has not gone away. Finally, it has been recognized that the indoor, domestic environment may also contribute to ill-health, particularly by the production of oxides of nitrogen by gas appliances. This chapter considers the main outdoor and indoor pollutants, their sources and their effects on the respiratory system.

## Main pollutants

### Particles

The popular concept of airborne pollution is soot, more of a nuisance than a threat to health. Indeed, the original and still most widely used method of measuring particulate air pollution is drawing the air through a filter paper and measuring the blackness of the stain produced, the black smoke method. However, even in the 1960s, pioneering studies showed that the particles were of an enormous size range and contained vast numbers smaller than  $1\mu\text{m}$  in diameter [2]. It was also shown that the particles were strongly acidic, reaching a pH of as low as 2. The current standard method for characterizing particles uses an instrument with an orifice that selects those below about  $10\mu\text{m}$  in aerodynamic diameter, these being most likely to reach and be deposited in the lung acinus (the so-called  $\text{PM}_{10}$ ). The deposition of such particles is shown in Fig. 11.2; deposition at alveolar level in terms of proportion of

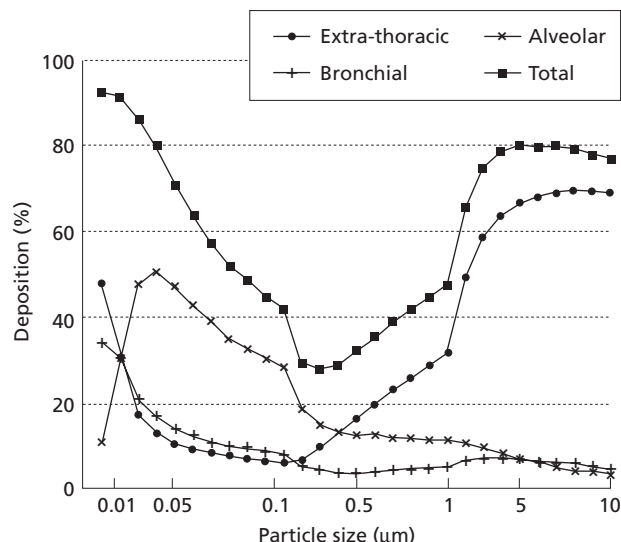
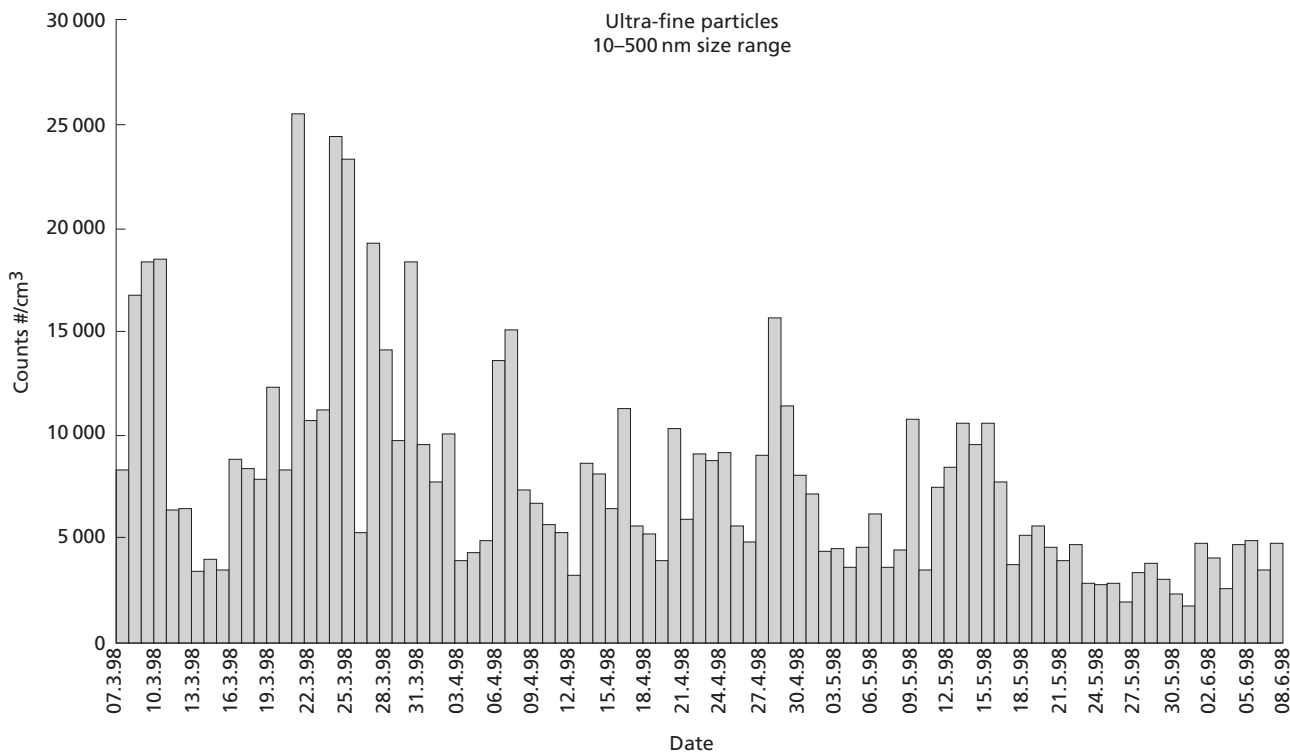


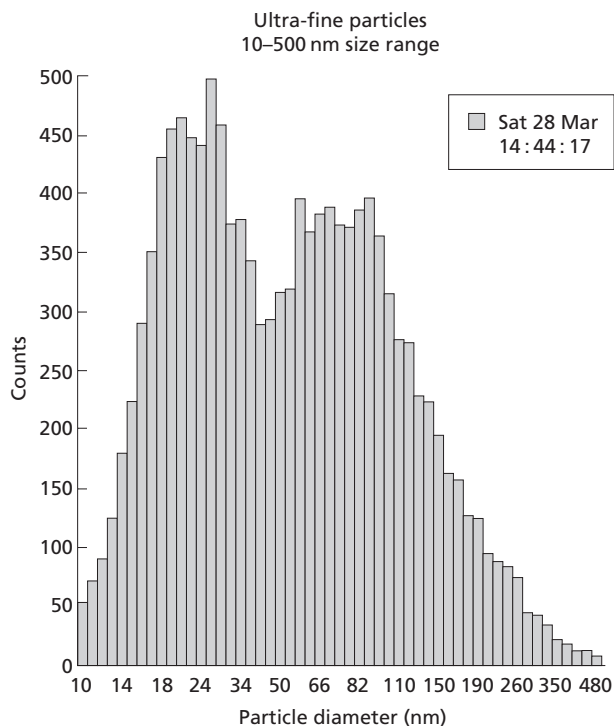
Fig. 11.2 Deposition of particles in the lung in relation to particle size. (From Department of Health Committee on the Medical Effects of Air Pollution [3] with permission.)

particles increases progressively as diameter decreases, reaching a peak at around  $30\text{nm}$ . In terms of numbers of particles, therefore, the greatest deposition is in the range below  $0.5\mu\text{m}$ ; however, since larger particles are heavier, in terms of mass deposition is greatest above this size. This fact is crucial to understanding the toxicity of particles. Both methods of measurement, black smoke and  $\text{PM}_{10}$ , use the same gravimetric units ( $\mu\text{g}/\text{m}^3$ ) but there is no very close relationship between them because of the variable composition of particles, some sources such as diesel exhaust producing less black particles than others such as coal burning. Recent studies have confirmed that urban airborne particulate pollution contains billions of small particles in every cubic meter of air, even when the total mass is only a few micrograms [4] (Fig. 11.3). The finest of these, around  $20\text{--}30\text{nm}$  diameter, are generated by combustion and are short-lived, aggregating into larger particles resembling bunches of grapes and thus maintaining a high surface area, with an average diameter around  $100\text{nm}$ ; these two separate peak concentrations can be seen in Fig. 11.4.

The adoption of  $\text{PM}_{10}$  as a standard measure of urban air pollution has recently been recognized as problematical. The usual measuring instrument is called a tapered element oscillating microbalance (TEOM). This gives a continual read-out and operates at a temperature of  $60^\circ\text{C}$  in order to remove water. This also drives off other volatile components, thus underestimating the weight found by other filter-weighing methods. This may not be significant if the volatiles are non-toxic but at present this (though possible) is not known. More importantly,  $\text{PM}_{10}$  includes a disproportionate contribution from coarser resuspended particles in the  $1\text{--}10\mu\text{m}$  range. These are very unlikely to



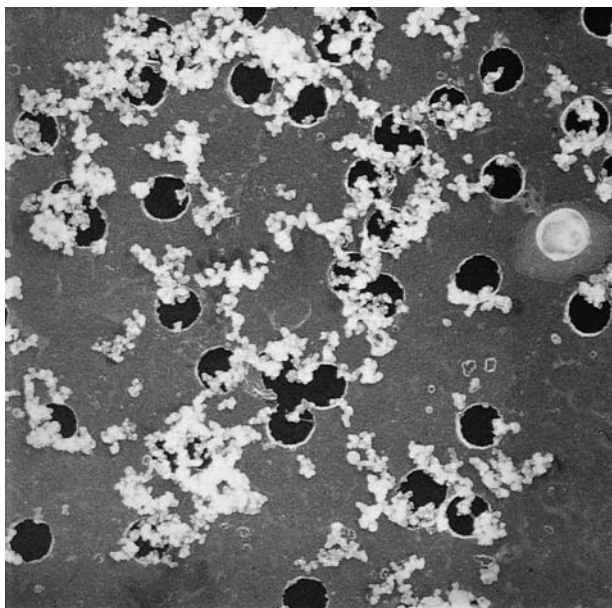
**Fig. 11.3** Average daily counts of particles less than 500 nm in diameter in Aberdeen, a relatively unpolluted city, over 3 months. Mean counts range between 3000 and 25 000/mL (i.e. up to 25 billion/m<sup>3</sup>).



**Fig. 11.4** Typical size-number distribution of airborne particles below 500 nm measured in Aberdeen showing peaks at about 30 and 100 nm diameter.

be toxic at the low concentrations found in urban air but may seriously distort measurements made in dry, dusty parts of the world. There is thus a move towards measuring particles less than 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ) but here the proportionate loss from evaporation in the TEOM is likely to be even greater. At present the best metric for measuring particulate air pollution is not clear, but is likely to depend on a better understanding of the toxicity of the different size fractions within  $\text{PM}_{10}$  (see below).

The chemical composition of airborne particles relates to their size. Larger ones, above about 2.5  $\mu\text{m}$  in aerodynamic diameter, include mineral particles produced by abrasion of rocks and wind dispersion of soil, and salt from sea spray. Carbon particles produced by combustion processes are found in all size ranges; in the smallest sub-micrometre range they may have complex shapes and large surface areas, with the potential to carry adsorbed chemicals deep into the lung (Fig. 11.5). The smallest particles are produced by condensation of gases arising from combustion and comprise predominantly ammonium sulphate and nitrate. The composition of particulate clouds also clearly relates to the source of the pollution, and it is important to remember that  $\text{PM}_{10}$  measured in different places is often very different chemically. However, in cities the main sources are combustion, either in vehicle engines or from oil burning in houses and factories. The petrol engine fitted with a catalytic converter makes a relatively



**Fig. 11.5** Electron micrograph of diesel particles collected on filter. The pores in the filter are approximately  $0.2\mu\text{m}$  in diameter and the particles are primarily aggregates of much smaller ones with high surface area. (Courtesy of Professor Roy Richards.)

small contribution, the main source currently being diesel combustion. In other places, large industrial complexes such as power stations, chemical or steel works may act as important point sources of particulate pollution, while natural sources such as forest fires, volcanoes and dust storms make the major contribution in some parts of the world.

### Sulphur dioxide

Sulphur dioxide is also produced mainly by combustion of fossil fuels, principally coal and oil, and naturally by volcanic activity. It is oxidized at a rate of about 1–10% per hour in the atmosphere to sulphur trioxide, which is then hydrolysed to sulphuric acid. As an urban pollutant it is now only important in places where coal is still widely burned, and concentrations have declined rapidly in most western cities since the 1960s. Concentration of power generation in large rural plants has meant that the main sites of sulphur dioxide pollution are now in the countryside, downwind of the source, when winter temperature inversions bring the plume to ground level. This method of solving urban pollution problems by creating a new problem of long-distance acidification of soil and water has already been mentioned.

### Oxides of nitrogen

While the major worldwide sources of nitrogen dioxide are volcanoes, thunderstorms and bacteria, the most

important sources from the point of view of human health, because of their local concentration, are fuel combustion in vehicles and industrial processes. In this respect, in contrast with particles and sulphur dioxide, gas burning is also important and domestic use of gas for cooking and heating is often the main source of exposure of individuals to nitrogen dioxide. Cigarette smoke is another important source. In most cases the combustion processes produce nitric oxide but this is rapidly oxidized in the air by ozone to nitrogen dioxide. As discussed later, oxides of nitrogen then take part in further chemical reactions in the air that result in the regeneration of ozone, so the production of these gases may have not only immediate local effects but also later more distant effects.

### Carbon monoxide

Carbon monoxide is produced by the incomplete combustion of carbon-containing matter, mainly in vehicles, industrial and domestic energy production and use, and incineration. It is the most widely produced air pollutant and is particularly significant indoors, where faulty flues in domestic heating systems and escape of the gas from industrial furnaces are responsible for many deaths each year. It is also an important component of the gas phase of tobacco smoke, and this makes the greatest contribution to the blood levels of smokers and an important contribution to those of people forced to inhale side-stream smoke. In the urban environment, the highest concentrations are found in relation to heavy traffic, in still conditions and in tunnels.

### Ozone

Ozone is a natural constituent of the air, existing in equilibrium with oxygen. In the stratosphere it filters out ultraviolet light and therefore from the human point of view serves a useful function. In the lower atmosphere the naturally low concentrations are the result of photochemical reactions involving volatile organic compounds produced by plants, together with intrusions of the gas from the upper atmosphere caused by meteorological events such as thunderstorms. As an air pollutant, it is not produced directly by any human activities but arises secondarily from the action of sunlight on nitrogen dioxide and on volatile organic compounds released into the air by vehicles and industrial and domestic processes. The essential reactions are (i) the photochemical reduction of nitrogen dioxide to nitric oxide and an oxygen radical, (ii) the combination of this radical with oxygen to form ozone and (iii) the reduction of ozone by nitric oxide to reform nitrogen dioxide and oxygen. Thus, in steady-state conditions there is an equilibrium between oxygen, ozone and nitrogen dioxide. The introduction of large quantities of nitrogen dioxide or volatile organic compounds into the system

moves this equilibrium towards the greater production of ozone.

These photochemical reactions are obviously dependent on the presence and intensity of sunlight, and therefore ozone is a more important pollutant in sunnier southern than northern climates. The reactions also take time and thus ozone tends to be produced at some distance from the site of production of the primary pollutants. It is therefore likely to occur in highest concentration some miles downwind of the urban centre. Indeed, the generation of primary pollutant in cities usually causes a local fall in ozone as the gas is used up in oxidizing nitric oxide. Ozone concentrations thus tend to be highest in the countryside and suburban areas. The gas also drifts over long distances and may cause pollution episodes across national boundaries. In the UK, the highest concentrations are measured in the south and west and the lowest in Scotland (Fig. 11.6). Atmospheric photochemistry is a complex

subject and many other reactions take place simultaneously, producing such substances as aldehydes, hydrogen peroxide, peroxyacetyl nitrates and nitric acid, many of which are respiratory irritants. Low concentrations of these and many other chemicals can be found in the air. The blue haze visible over distant mountains and when looking down towards earth from an aeroplane is due to refraction of light by ultra-fine condensation particles produced by these photochemical reactions [6].

### Carcinogens

The main carcinogens that may be found in ambient air are benzene, 1,3-butadiene and several of the polycyclic aromatic hydrocarbons (PAHs) including benzo[a]pyrene, benz[a]anthracene and dibenz[a,h]anthracene; all are genotoxic carcinogens. Benzene and butadiene are produced mainly by vehicle engines, as a result of combustion

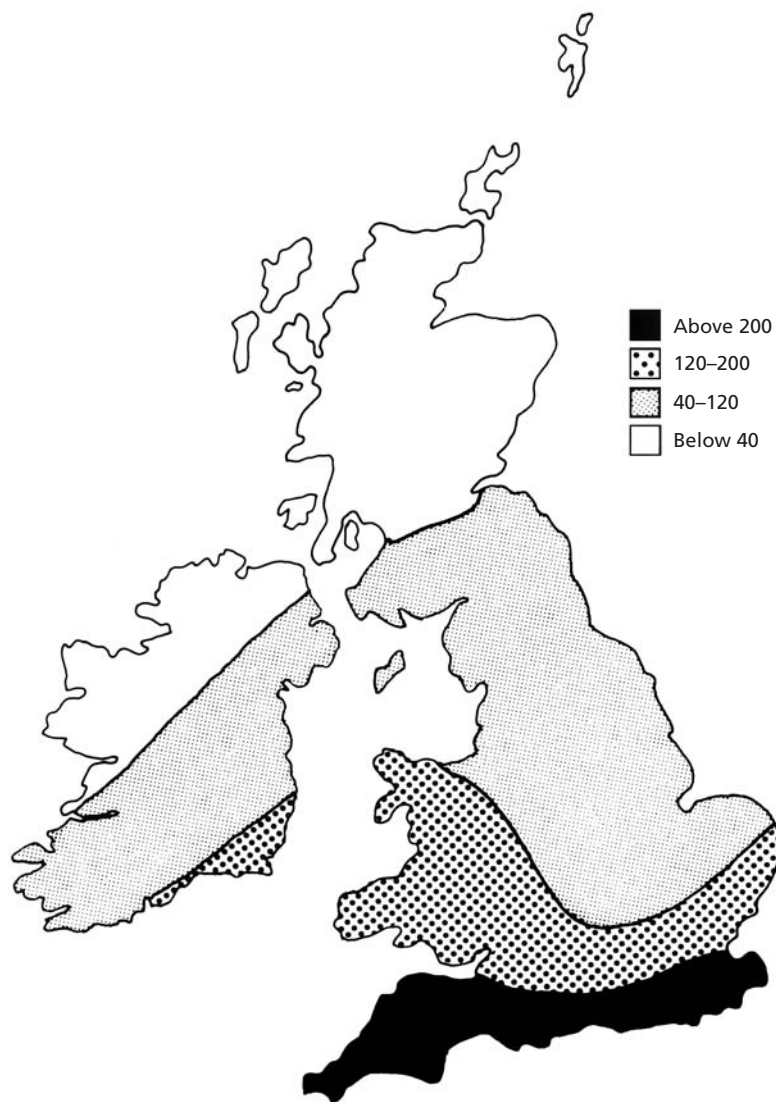


Fig. 11.6 Distribution of ozone over the UK, representing number of hours at which concentration exceeds 60 ppb. Higher concentrations occur more frequently in the sunnier south. (From Department of Health Advisory Group on the Medical Aspects of Air Pollution Episodes [5] with permission.)



of petrol, and are therefore urban pollutants. The amount of benzene produced depends more on the efficiency of the engine than on the concentration of the chemical in the original fuel, although leakage at filling stations makes a contribution to benzene concentrations in the immediate locality. PAHs are produced by coal burning and coke production, as well as by vehicles. Concentrations of these are likely to have been much higher in the days of widespread coal burning than they are today in western cities.

### Other pollutants

Many hundreds of chemicals may be detected in the air by sensitive techniques in relation to industrial and commercial activity, the cultivation and natural growth of plants and the presence of animals. A number of these assume significance when produced or released in locally high concentrations by industrial processes, and some are discussed in Chapter 54. Lead is mainly present in the air in the form of submicrometre-sized particles, derived largely from additives in petrol and locally from smelters and industrial processes. It has known neurotoxic effects, though airborne lead makes a relatively small contribution to the overall exposure of children in the UK, the main contribution being from food and from water in areas where lead pipes are still present. Many countries, including the UK, have taken steps to reduce lead levels in the urban atmosphere by selective taxation of leaded petrol. None of the other pollutants is established as a cause of health problems in the general environment and all occur in concentrations that are currently thought to be too low to constitute a significant threat to health.

### Effects of air pollution

Knowledge of the effects of air pollution comes from three sources: epidemiological studies, experimental exposures of people and animals, and *in vitro* experiments. The most useful, because they are the most realistic, are epidemiological studies, although they have the disadvantages that they often lack good information on exposures and that the exposures are usually due to a combination of pollutants. However, they are normally the only studies that can ethically assess the effects of pollution on the elderly and infirm and they do provide information that can be used in a standard setting. In some cases, epidemiological studies carried out on populations of industrial workers may be used to estimate effects on people exposed to the lower concentrations occurring in the general environment. Experimental studies on people have proved helpful in the search for no-effect thresholds with exposures to irritant gases and in investigating mechanisms of disease. They have the disadvantage that people who are already ill, for example with asthma, and who might be expected to be particularly sensitive are usually unable to

be studied, and they are often quite demanding in terms of both time and the cooperation of the experimental subjects. Animal and *in vitro* studies are best for investigating mechanisms, but are of considerably less value for obtaining information on relationships between exposure and response.

### Particles

In spite of the likely qualitative differences between particles derived from different sources, there is now strong and consistent evidence of relationships between population exposures to PM<sub>10</sub> or black smoke and risks of a number of health outcomes including mortality [7–11]. These relationships have not allowed a threshold to be defined, suggesting that rises in the concentration of particles from whatever level increase the number of people suffering ill-health. Whereas in the London smogs of the 1950s it was easily recognized that excess deaths and hospitalizations occurred, the much lower urban concentrations of particles prevailing in western cities now mean that much more subtle statistical techniques are required to detect any effect. The most important effect is an increase in the numbers of deaths. This occurs mainly in the elderly and is most marked in smokers. The cause of this overall increase is an excess of respiratory and cardiovascular deaths. There is also increasing evidence that the risk of dying from heart and lung disease and from lung cancer is increased in people living in polluted cities [12,13], although it is possible that there are confounding factors related to the social structure of the different places studied that may not have been fully taken into account. At present the evidence suggests strongly that there is an influence of air pollution in bringing forward the time of death, although the consequences in terms of loss of life-years have not yet been estimated.

Rises in concentrations of small particles have also been associated with increases in the numbers of people with asthma seeking help from their doctors or being admitted to hospital, with increased hospital admissions for respiratory disease and with increased incidence of respiratory symptoms and small falls in ventilatory function [14–16]. In some of these studies it has been difficult or impossible to differentiate the effects of particles from those of temperature or other coincident pollutants, usually sulphur dioxide, but meta-analysis has suggested strongly that particles are the most likely cause. Based on the most up-to-date data, the Department of Health in the UK has estimated the approximate consequences of particulate air pollution as an annual 8100 deaths brought forward and some 10500 extra or earlier hospital admissions for respiratory disease [17]. Calculations by the World Health Organization (WHO) of the consequences of particulate air pollution are shown in Table 11.1 [18].

The mechanisms whereby particles exert these effects

**Table 11.1** Health effects of particles.

Health effect	Rise in 24-h particle concentration (PM <sub>10</sub> ) (µg/m <sup>3</sup> )
Daily mortality	
5% increase	50
10% increase	100
20% increase	200
Hospital respiratory admissions	
5% increase	25
10% increase	50
20% increase	100
Asthma symptom exacerbation	
5% increase	10
10% increase	20
20% increase	40
Population fall in peak flow rate	
5%	100
10%	400

are not understood. If, as seems likely, they are true effects and not the consequences of some confounder, the explanation is likely to reside in the common properties of particulate pollution clouds, since the effects seem to be similar wherever they have been investigated. Thus detailed chemistry is unlikely to hold the explanation; rather it seems plausible that the answer lies in the fact that pollution episodes expose people to huge numbers of ultra-fine submicrometre-sized particles with a large surface area and the potential to carry toxic substances deep within the acinus. Experimental studies with such particles have shown that they may behave quite differently to larger particles, even inert substances such as titanium dioxide causing intense alveolar inflammation when inhaled by rats in a very finely divided form [19]. If typical particulate air pollution has similar effects it would be possible to explain its effects on the lungs and airways and, by invoking secondary effects through an acute-phase reaction on blood coagulation mechanisms, on cardiovascular mortality [20]. Some support for this hypothesis comes from the demonstration of free radical release, generated by a transition metal redox mechanism, from the surface of PM<sub>10</sub> and from the demonstration of higher blood viscosities in people during a European air pollution episode [21,22]. With respect to lung cancer, it is at least plausible that the presence of PAHs adsorbed on to particles deposited in the airways might be responsible for increasing risk [23].

### Sulphur dioxide

Sulphur dioxide is an irritant gas that, when inhaled in high concentration in industrial accidents, causes acute tracheobronchitis. At lower concentrations there is consid-

erable variability in responsiveness, although asthmatic individuals are generally more sensitive. In healthy volunteers, falls in ventilatory function have been recorded after inhalation of concentrations around 5000 ppb, while asthmatic individuals may respond at about 200 ppb or even lower, depending on severity [24]. The response is almost immediate, suggesting a neural reflex mechanism, and seems not to become worse with continued exposure. The severity of the response is affected by exercise and thus seems to depend on the amount of gas inhaled during the initial exposure. There is some evidence that people living in areas where there is long-term pollution with sulphur dioxide have an increased risk of exacerbations of chronic lung disease and decrement in lung function. While these studies have often been confounded by concurrent exposures to particles, there is now evidence from parts of Europe where sulphur dioxide has remained elevated as particle concentrations have fallen that long-term exposures to annual average concentrations around 20 ppb may be associated with such adverse health effects.

### Oxides of nitrogen

As stated above, most combustion sources produce nitric oxide, which is rapidly oxidized to nitrogen dioxide. The latter gas is a relatively insoluble pulmonary irritant that, when inhaled in high concentrations (as in exposure in silos or chemical accidents), causes delayed pulmonary oedema and sometimes bronchiolitis obliterans; these effects are described in Chapter 54. Nitrogen dioxide shares with carbon monoxide the characteristic of often reaching higher concentrations indoors than out, since it is a product of gas combustion. Experimental exposure of volunteers in chambers has shown that both normal subjects and asthmatic patients are relatively resistant to nitrogen dioxide, small and inconsistent changes in airway reactivity and resistance occurring at concentrations between 1000 and 4000 ppb [25]. These concentrations far exceed those found in even severe urban pollution episodes, maximum hourly concentrations in the UK usually being below 250 ppb. Epidemiological studies have suggested that there is an increased risk of respiratory illness in children and women living in houses with gas cookers, where the concentrations may rise to 500 ppb or higher [26,27]. The highest background urban concentration recorded in London, 423 ppb in December 1991, was associated with a small rise in overall mortality and hospitalization for respiratory disease among the over 65 years age group but no measurable effect in younger people [28]. These effects were most likely to have been due to a concomitant rise in particles. On balance, it seems unlikely that ambient levels of nitrogen dioxide have a significant direct effect on public health, although they are an important contributor to the formation of ozone.

## Carbon monoxide

Carbon monoxide is a metabolic poison, blocking intracellular respiration by binding to cytochrome oxidase and myoglobin and interfering with red cell transport of oxygen by the formation of carboxyhaemoglobin. It is the most dangerous of all the pollutant gases, regularly causing deaths and long-term brain damage in people exposed accidentally and in self-poisoning episodes. It has been suggested that it may also contribute to acute cardiovascular episodes such as heart attack and angina by reducing the oxygen-carrying capacity of the blood in people with compromised circulations. The main sources are petrol engines, which produce some 6 million t annually in the UK, and domestic use of fuel, which produces some 300 000 t annually.

The effects of carbon monoxide on health probably depend mainly on the blood carboxyhaemoglobin concentration, and no effects have been recorded below a concentration of 2.5% [29]. Whether this level is attained depends on inhaled concentrations, level of activity and duration of exposure. The blood and the surrounding air reach an equilibrium, and moving from a higher to a lower concentration may result in excretion rather than further uptake of the gas. Thus a regular smoker who might have a carboxyhaemoglobin of 3.5% is, in most circumstances, contributing to the ambient carbon monoxide rather than taking it up. During normal activities, it may be calculated that exposures of greater than 10 ppm for 8 h or 25 ppm for 1 h are required to bring the carboxyhaemoglobin concentrations of a non-smoker up to 2.5%. Ambient urban concentrations in the UK only rarely exceed these figures in places where people are likely to be exposed for the appropriate periods. Carboxyhaemoglobin concentrations of around 2–2.5% have been recorded in non-smoking traffic police and people working in underground garages.

In spite of these observations, epidemiological studies have shown associations between ambient carbon monoxide concentrations, hospital admissions and mortality, especially from cardiovascular diseases, in both North America and Europe [16,30,31]. It seems plausible that even quite small rises in ambient carbon monoxide concentrations could influence cardiovascular function in very vulnerable individuals with coronary arterial disease.

## Ozone

Because ozone is produced by atmospheric photochemical reactions, it is a problem in sunnier climates. In the UK concentrations are highest in the south and decline progressively towards the north. Since it is generated by a relatively slow reaction, ozone concentrations increase downwind of the urban areas in which the primary pollutants are produced, making it a mainly rural pollutant in

the UK. Experimental studies have shown it to be a pulmonary irritant, causing increases in bronchial resistance and reactivity in relation to the dose inhaled. This means that exercise, by increasing the ventilatory volumes, increases the effects of a given ambient concentration. The lowest concentration at which effects have been demonstrated is around 80 ppb over several hours in healthy individuals [5]. There is no convincing evidence that people with asthma as a class are more sensitive, but it would be expected that the effects of further airway constriction in someone who already has airflow obstruction would be disproportionately greater, since resistance to flow is inversely proportional to the fourth power of the radius.

Epidemiological studies have in general supported the concept that ozone above concentrations of around 100 ppb may have acute effects on the ventilatory capacity of children. It has been suggested that airway inflammation induced by ozone may increase the likelihood of an individual becoming sensitized to ambient allergen, and there is experimental evidence that ozone inhalation decreases the allergen concentration at which sensitized people react [32]. Spring and summer upper respiratory symptoms are very common in rural areas [33] and it is likely that ozone plays some part in the aetiology of these. In the UK, the ambient concentrations of ozone may reach 150 ppb or more in the south on hot summer days but rarely reach 100 ppb in Scotland.

## Carcinogens

The evidence that the concentrations of carcinogens present in the ambient urban air are responsible for causing bronchial cancer has been mentioned above with respect to particles. Benzene and 1,3-butadiene are probable causes of leukaemia and lymphoma in occupational settings, but at exposure concentrations three or four orders of magnitude higher than those found in cities. It seems unlikely that they will be shown to contribute to the incidence of these conditions as a result of current ambient concentrations in the West.

## Combinations of pollutants

In the normal environment individuals are always exposed to mixtures of pollutants. Typically, in winter pollution episodes, particles and sulphur dioxide or nitrogen dioxide combine; indeed the sulphur dioxide and nitrogen dioxide exist in equilibrium with sulphate and nitrate radicals, which are important contributors to the particulate cloud. It is usually not possible to distinguish the effects of these pollutants in any one study and it is possible that the harmful effects of particles described above are in part due to their acidic nature. Relatively little work has been done on combinations of irritant

pollutants, although it is reasonable to assume that their effects would be additive.

### Indoor air pollution

The main sources of indoor air pollution are cigarette smoke, gas-burning cookers and heaters, paints and treated building materials such as wall panels. Cigarette smoke, as discussed previously, contains a wide variety of carcinogenic and irritant substances. It is the main personal source of benzene exposure. Gas-burning devices and other open-flame burners, if not fitted with an effective flue, may produce carbon monoxide, far and away the most important indoor air pollutant since it is responsible for regular loss of life in houses. Gas cookers are also the major source of nitrogen dioxide; this gas often reaches higher concentrations indoors than out, averaging around  $50\mu\text{g}/\text{m}^3$  over several days when measured in houses with gas cooking and reaching peaks of up to  $1000\mu\text{g}/\text{m}^3$  over 1 h during cooking. In spite of this, the evidence that it causes harm remains equivocal [34] and is consistent with the experimental observations quoted in the section on oxides of nitrogen (see p. 330). Some studies have shown that women and children living in houses with gas cookers suffer more respiratory illnesses than those in houses with other types of cookers [26,27], although there is little consistency in the evidence with respect to adverse effects on lung function. However, there is some evidence that exposure to relatively high concentrations ( $400\text{ ppb}$  for 1 h) increases the subsequent response to challenge to house-dust mite antigen and this may be of some relevance to the health of children [35].

Paints, household cleaning materials and other chemicals are sources of volatile organic compounds, which make a contribution to the overall mass of airborne substances available for the photochemical reactions that lead to the formation of ozone. They probably also contribute to the irritancy of indoor air. Formaldehyde, which is used for treating building materials, may be detected in houses in higher concentrations than outdoors. It is found particularly in newer houses and tends to reach higher concentrations in summer than in winter. In the UK, concentrations have varied between 1 and  $200\mu\text{g}/\text{m}^3$ . The WHO has recommended a standard of  $100\mu\text{g}/\text{m}^3$  over 30 min.

While not strictly pollution, mention should be made of the natural inhabitants of houses that may be responsible for illness. House-dust mites are ubiquitous in beds, carpets and soft furnishings, and their faeces are the source of the major sensitizing antigens in most temperate climates. They reproduce best in warm and damp conditions. Fungi are also found in houses, and in rare circumstances may grow in such profusion as to cause allergic alveolitis. These organisms are discussed further in Chapters 21 and 34.

### Advising patients about air pollution

Many patients with asthma notice changes in their condition with changes in the weather, some commenting that it is the change rather than a particular type of weather that affects them. This does not seem to relate clearly to episodes of pollution, although in epidemiological studies of such episodes it has often been shown that such people make additional demands on health services because of attacks. A number of patients with asthma notice that their breathing gets worse when exposed to traffic fumes or when they visit polluted cities, such as Athens. The most consistent evidence associates these events with a rise in the concentration of small particles in the air, the same type of pollution associated with excess numbers of deaths among older people from cardiorespiratory disease. Such episodes may be predicted with reasonable accuracy the day before from knowledge of the weather forecast and likely traffic volumes, and it would seem reasonable for the authorities to issue a warning. However, it is far from clear what action, if any, might be taken to prevent these adverse effects. With respect to asthma, the sensible advice in the light of present knowledge might be for patients who have been affected by these conditions in the past to avoid places where traffic is heavy and, if they are seriously affected, to keep indoors and keep warm. In the author's view it is not desirable to issue general advice to all asthmatic individuals to restrict their activities, since there is no evidence that this is either necessary or beneficial. In particular, there is no case for restricting the activities of children unless they have quite severe disease. However, it is sensible to advise such people that they may need to increase the doses of their inhalers. Patients with asthma or chronic lung disease contemplating foreign travel should be warned to avoid notorious pollution blackspots, such as Athens, Cairo, Mexico City, Bangkok, Delhi and Calcutta.

There is at present no clear indication as to what measures patients with chronic heart and lung disease might take to prevent a possible increased risk of death; however, if small particles are responsible, as seems likely, avoidance of areas of heavy traffic pollution would seem sensible. There are almost certainly benefits to staying indoors for such people, since indoor particle concentrations tend to be somewhat lower than those outside (except when influenced by cooking or smoking) [36] and the temperature, another factor associated with increased risk, is usually higher.

In the UK the main risks occur during cold still conditions in winter, when traffic-generated fumes are poorly dispersed and lie in a pall over the towns and cities. Summer pollution episodes normally involve ozone, which sometimes reaches concentrations at which some sensitive people might notice symptoms. When such an episode is predicted, it might be reasonable to advise

people with asthma that they may develop bronchial symptoms if they take prolonged exercise, and that they should be prepared to take extra doses of their usual treatment.

## Control of air pollution

Air pollution is perceived by the public and some governments as a serious threat to public health. It also has important economic effects on the environment, on trees, crops and buildings. Health benefits have been shown to occur when pollution is reduced, as has happened in the UK with the control of coal burning in cities. It is not clear how much further improvements in air quality will benefit health in the UK, but evidence shows that there is scope for a reduction in costs associated with the management of acute episodes of respiratory disease and possibly for a reduction in the number of deaths among older people with heart or lung disease. There is little question that substantial benefits to health would accrue with pollution control in those cities in other parts of the world where concentrations approach or exceed those that existed in London in the 1950s.

The control of air pollution is a matter for government policy, taking account of the costs and likely benefits. It requires strategic action to reduce the emissions at source. Thus, halting of the rise in personal ownership of cars and transfer of heavy transport from road to rail, restrictions to the access of cars to city centres, and elimination of vehicles exceeding emission limits are all actions that governments will contemplate. Shorter-term measures include introduction of emission controls, such as catalytic converters on petrol cars and filtration systems on diesels, and tighter enforcement of regulations reducing exhaust emissions. Fiscal measures may be useful; the differential tax on leaded petrol in the UK has reduced lead emissions substantially, and a similar measure might be contemplated to restrict the growth of the private diesel car market, since diesel is now the main source of particles.

Any strategy to control air pollution needs to be audited by appropriate air monitoring. In the UK, the Department of the Environment has a series of monitoring stations to

**Table 11.2** UK air quality standards.

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Sulphur dioxide: 100 ppb (15-min mean)
Nitrogen dioxide: 150 ppb (1-h mean)
Carbon monoxide: 10 ppm (8-h mean)
Ozone: 50 ppb (8-h mean)
Particles (PM <sub>10</sub> ): 50 µg/m <sup>3</sup> (24-h mean)
Benzene: 5 ppb (annual mean)
1,3-Butadiene: 1 ppb (annual mean)
Lead: 0.25 µg/m <sup>3</sup> (annual mean)
Benz[a]pyrene: 0.25 ng/m <sup>3</sup> (annual mean)

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measure a wide range of pollutants. These allow long-term trends to be followed and therefore the achievement of targets to be monitored. The UK Government, along with other organizations such as the European Community and the WHO, is considering a series of air quality standards or guidelines at which health effects are thought to be absent or minimal and against which progress in control of air pollution can be measured. The current UK standards are given in Table 11.2. These figures should not be confused with those levels at which public health warnings may be given, since in general they represent a 'no effects' target, while warnings, if given, usually represent a level at which adverse health effects have been demonstrated.

Ultimately, the control of air pollution depends on sufficient public concern stimulating politicians to propose remedies that are broadly acceptable to the public and that do not entail an unacceptable cost. The complexity of the issue may be recognized by weighing the value one places on one's car for personal transport against the nuisance of pollution and the cost of increased local or national tax to pay for better public transport systems and the likely introduction of increased costs of fuel to reduce energy usage. In some countries, such as western Germany, strategic action and investment has produced great benefits. In others, such as the east of that country, complete inaction has resulted in environmental disaster. In every developed country there is the threat, indeed the likelihood, that the gains of the past 30 years will be lost if a comprehensive transport policy is not part of the government's programme.

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# ACUTE UPPER RESPIRATORY TRACT INFECTION

DOUGLAS SEATON

Upper respiratory tract infections are by far the most common medical complaints worldwide and in the UK account for half the time lost from work through acute illness. They are for the most part self-limiting but nevertheless place a considerable burden of work on general practitioners and other primary care workers and have an important economic impact on communities [1,2]. Such illness may be complicated by lower respiratory tract infection, a fact of global importance to millions of children, particularly in developing countries where lack of antimicrobial therapy results in considerable mortality [3,4]. In adults too there is little doubt that upper respiratory tract infection is complicated by more serious lower respiratory tract disease; thus coryzal symptoms of viral origin frequently precede the onset of pneumococcal pneumonia, which like the common cold shows an increased incidence in the winter months [5,6]. The season of respiratory tract virus infections is also associated with an increased frequency of asthma attacks and exacerbations of other established lower respiratory tract disease, such as chronic bronchitis and cystic fibrosis [7,8]. Upper respiratory tract infections may also be problematical in patients who are immunocompromised as a result of various conditions, including neutropenia, immunosuppression following transplantation and AIDS.

## Common cold (acute coryza, nasopharyngitis)

This term is applied to a self-limiting illness, characteristically of short duration and typified by nasal discharge, sneezing and a sore throat. These 'catarrhal' symptoms result from infection of the upper respiratory tract by one or more of a large number of different viruses. Although the illness produced by this nasopharyngitis is generally mild, its importance stems from the fact that:

1 it is the commonest human disease and is one of the most common reasons for patients seeking medical advice;

2 it is a major cause of absenteeism from school in children and from the workplace in adults;

3 it may be complicated in susceptible individuals by bacterial infection and by exacerbations of pre-existing respiratory disease.

## Causative organisms

'Catching a cold' has for many years been thought to result from the spread of infection. Early observations of the contagious nature of the 'coryzal syndrome' led to the demonstration over 80 years ago that bacteria-free filtrates of the nasal secretions of cold sufferers produced a similar illness when inoculated intranasally into healthy volunteers [9]. Further animal and human work led to the conclusion that the filterable agents were viral [10] and the isolation of specific cold-causing viruses followed in the 1950s, first with the rhinoviruses [11,12].

The *Rhinovirus* genus, which belongs to the family Picornaviridae (*pico-* denotes small size and *-rna-* their type of genome), contains over 100 antigenically distinct rhinovirus species and is the largest genus known to cause common cold symptoms, accounting for about 30% of cases.

The next most common group of viruses, causing up to 15% of 'colds', is the *Coronavirus* genus. This contains many species that are pathogenic to humans and is the only member of the family Coronaviridae, so called because of the crown-like appearance of these viruses under electron microscopy.

Other viruses that have been identified as causing 'colds' include the parainfluenza viruses and the respiratory syncytial virus (RSV), both of which are species of virus belonging to different genera but the same Paramyxoviridae family. As well as causing lower respiratory tract infections in infants and small children, RSV and parainfluenza viruses may be responsible for up to 15% of 'colds' in adults.

There are a number of species of human adenovirus that may cause coryzal symptoms. These organisms belong



to the Adenoviridae family. They are the only DNA-containing viruses to cause the common cold and account for about 5% of these infections. Some human adenovirus serotypes cause diverse disease, including conjunctivitis, meningitis and gastroenteritis as well as pneumonia.

The influenza viruses may produce common cold-like symptoms but are often associated with a more prostrating infection, as described in a later section. Like parainfluenza and RSV, influenza viruses are loosely termed 'myxoviruses', belonging as they do to the Orthomyxoviridae family.

The *Enterovirus* genus, which also belongs to the Picornaviridae, includes some Coxsackie [13] and echovirus species that may produce upper respiratory symptoms, as indeed may polio virus infection. Some exanthematous viruses such as chickenpox (varicella), rubella and measles may also produce coryzal symptoms.

Since the isolation of the coronaviruses in the 1960s [14,15], no new common cold viruses have been discovered. Despite this, a causative organism cannot be found in over 30% of cases and undiscovered common cold viruses are therefore presumed to exist. Most of the common cold viruses undergo frequent mutations so that it has not been possible to develop an effective vaccine.

### Pathology

Pathological changes in the common cold result from the invasion of the nasopharyngeal mucosa by 'cold viruses'. These are not usually present in asymptomatic individuals [16], although subclinical infection may occur and viral carriage is sometimes prolonged in children [17]. The infecting virus attaches to and penetrates the respiratory columnar epithelial cell by a variety of mechanisms, before replicating and being shed so that neighbouring cells become infected. There are no specific histological changes but characteristic findings include mucosal oedema with shedding of columnar epithelial cells, which are found within the proteinaceous nasal discharge. These shed cells show degenerative changes and contain both viral antigenic material and nuclear inclusion bodies [18,19]. The shedding of epithelial cells and virus is usually completed within a few days [18,20,21] and although mucosal damage is only slight in the majority of cases [22], cellular recovery by regeneration of epithelial cells from the deeper layers takes about 2 weeks [23]. Neither neutrophils nor mast cells feature prominently in the mucosa or submucosa in this process, although the inflammatory picture may be changed in cases where the normal nasopharyngeal flora is altered as a result of secondary bacterial infection. One ultrastructural study showed damage to epithelium with loss of cilia peaking 1 week after the onset of infection, complete repair having been achieved by 3 weeks [24].

### Epidemiology

Upper respiratory tract viruses are distributed worldwide [25], antibodies to them being commonly detectable in the serum of subjects living in both temperate and tropical zones [25,26]. These antibodies are found with increasing frequency and variety throughout childhood and adolescence [27,28]. Infants are protected by maternal antibodies for 2–3 months [22], after which a child contracts six to eight colds per year [29,30]. Children tend to act as a reservoir of infection in the community [31,32], both in the classroom [33] and at home [29,34], where the presence of a child of school age doubles the chance of common cold infections in parents and preschool siblings [35]. The attack rate diminishes to two to four per year in adulthood as a result of a gradual build-up of immunity [29,30], subjects aged 40 years and over being less susceptible than those aged less than 30 years. Despite the acquisition of immunity, the existence of very large numbers of strains of common cold virus results in sporadic infection throughout life except in small very isolated communities where protection from exposure may occur.

The incidence of colds in temperate climates is seasonal, increasing in the autumn and remaining at a high level throughout the winter months before declining to a low level in the summer [29,30,36]. The winter peak may be a consequence of increased environmental crowding at this time of the year rather than the cold temperature *per se*, and the deliberate chilling of volunteers has not been shown to increase attack rates.

Although it seems logical that colds should be spread from person to person by droplet infection, direct contact with infected secretions may also be important for some viruses. Rhinoviruses are shed heavily in nasal secretions and, in experimental infection, the peak viral titres in such secretions occur from the second to the fourth day, coinciding with the time of maximum communicability. Although in human infection rhinovirus-containing nasal secretions may be passed from hand to hand more easily than by air, thence transmitting infection to the nasal mucosa or conjunctivae of the contact [37], it seems more likely that infection is more easily spread, as was traditionally thought, by 'coughs and sneezes' [38]. It is possible that some other cold viruses may also be more easily spread by droplet transmission [39]. There is some evidence to suggest that psychological stress or 'feeling run down' may increase an individual's susceptibility to colds [40].

### Clinical features

The incubation period from exposure to the onset of illness is a day or two. The symptoms of the common cold are only too familiar to all of us as a result of personal experience. There is a feeling of malaise and tiredness, coupled

with mild to moderate nasal obstruction, rhinorrhoea and sneezing, with dryness or soreness of the throat, slight aching in the musculature and often a feeling of irritation about the eyes that usually stops short of clinically obvious conjunctivitis. There may be headache. A cough may occur either as a result of postnasal discharge or because of more distal respiratory tract involvement by the virus [41,42]. These symptoms may combine to act as a moderate disincentive to get out of bed in the morning but, depending on both the severity of the infection and the individual's motivation, need not necessarily prevent a day's work. Such is the usual pattern with rhinovirus and coronavirus infection. The occurrence of painful red eyes with a sore throat and coryzal symptoms is suggestive of adenovirus infection ('pharyngoconjunctival fever'), whereas a more prostrating illness with a fever raises the possibility of a myxovirus infection such as influenza.

There are no specific physical signs. Nasal obstruction, a dripping nose, a cough and sneezing may be obvious, as is conjunctivitis in some patients with enterovirus or adenovirus infection. A fever is a more frequent feature in children than in adults, in whom it is only low grade, if present at all. Examination of the chest in otherwise healthy individuals reveals no physical signs.

The full clinical features of the common cold syndrome usually develop within 24 h and are somewhat variable in their progression. Thus improvement often begins after the second or third day, although recovery may take from a few more days to 2 weeks, provided that no complicating features arise. The upper respiratory tract symptoms of colds usually bear no hallmark of the particular virus responsible and fortunately ignorance in this respect is of no practical importance.

About 0.5% of common colds have been found to be complicated by bacterial sinusitis and 2% by otitis media [29].

## Diagnosis

Subjects with mild and self-limiting colds frequently make their own diagnosis without 'bothering the doctor'. More protracted symptoms may be due to allergic rhinitis, in which case a painstaking history may identify either a seasonal pattern or a relationship to exposure to a consistent antigenic source. The recurrent or chronic nature of such symptoms distinguishes allergic rhinitis and perennial non-allergic (vasomotor) rhinitis from the common cold and inspection of the nasal mucosa may reveal polyps [43]. Visible inflammation of the pharynx, with a particularly red throat, raises the possibility of adenovirus infection or of causative agents other than those responsible for the common cold. These other causes of sore throat (discussed in the section on pharyngitis; see pp. 338–340) include streptococcal sore throat and infectious mononucleosis.

Childhood exanthematous infection will become obvious with the later development of a characteristic rash.

## Serological tests

In epidemiological work, serological evidence of adenovirus infection or myxovirus infection by RSV, influenza and parainfluenza virus infection may be obtained by the submission of serum obtained at the onset of the illness and 2–3 weeks later. A fourfold or greater rise in the titre of antibodies to the virus concerned implies recent infection. Such is the mild and self-limiting nature of common colds that information of this sort is unnecessary and is seldom sought in ordinary clinical practice. Indeed, where rhinoviruses are concerned it is unavailable because of the great multiplicity of antigenic strains that exist.

Various methods for detecting viral antibodies are available and these include neutralization, complement fixation and haemagglutination inhibition tests. Neutralizing antibodies may persist for prolonged periods and need not indicate recent infection, merely previous exposure. Complement fixation tests, although less sensitive, are more widely available because the antigens are easily prepared and the results more rapidly obtained. Haemagglutination inhibition tests are used to identify cultures infected with influenza and parainfluenza viruses and probably detect similar antibodies to those identified by neutralization tests. Rapid direct fluorescent antibody techniques or enzyme-linked immunosorbent assay (ELISA) are available for the detection of influenza A and B viruses, parainfluenza viruses, adenoviruses and RSV in nasopharyngeal material; washes or aspirates have a higher yield than swabs, which contain fewer columnar epithelial cells than liquid specimens.

## Viral culture

Although many respiratory viruses may be isolated in cell culture, such methods are both unnecessary and unavailable in routine clinical practice. Where investigative work demands the proper identification of respiratory viruses, close cooperation between the researcher and the virologist is essential. As the shedding of viruses may occur for only a short time, specimens should be collected early. These specimens usually take the form of nasal and pharyngeal washings or swabs, although faeces should be obtained where evidence of enterovirus infection (such as Coxsackie or echovirus) is sought. The tips of swabs are placed in an appropriate transport medium and are conveyed to the laboratory with as little delay as possible, some viruses such as RSV and parainfluenza being particularly labile. Many different tissue culture systems have been described and are in use. Rhinoviruses can be grown in human embryonic lung cells and myxoviruses and

paramyxoviruses in rhesus monkey kidney cells. Hep2 cells, originally derived from malignant tissues, support the growth of RSV. Cell culture of coronaviruses is seldom possible. The presence of a virus in tissue culture may be indicated by a cytopathic effect, by a modification of cell growth, by haemadsorption tests or by so-called 'interference', i.e. the prevention of the cell line from supporting the growth of a second virus.

### Treatment

Despite a plethora of over-the-counter remedies, no medication has been convincingly shown to cure the common cold and treatment can be only symptomatic. It has been noted that 'if common colds are left alone they clear over the course of a week, whereas if treated vigorously they disappear within seven days'. This epigram has been borne out by a relatively recent randomized, double-blind, placebo-controlled trial to assess the efficacy of the capsid-binding antipicornaviral agent pirodavis delivered by intranasal spray six times daily. This agent had been previously shown to be effective in preventing experimental colds caused by rhinoviruses [44]; when used to treat subjects with naturally occurring rhinovirus colds, the median duration of symptoms in both the active treatment and placebo group was indeed 7 days, although viral shedding was significantly reduced in the pirodavis-treated group [45].

Among the symptomatic remedies, topical nasal decongestants have their effects by causing vasoconstriction [46]. The most common of these are drops or sprays containing weak solutions of ephedrine, phenylephrine or imidazoles. Although these produce immediate relief, this may be followed by rebound nasal congestion requiring further dosage and the nasal mucous membrane may be damaged if such cyclical usage continues for more than 4 or 5 days [47], with the potential for delayed mucosal healing. Other agents that may afford symptomatic relief include an atropine-like ipratropium nasal spray, which has the effect of reducing nasal secretions [48], and inhalations of menthol. Systemic nasal decongestants are of doubtful value. Viral sore throat does not benefit from local antiseptic treatments but may be relieved by warm saline or soluble aspirin gargles. Cough suppressants containing substances such as codeine are commonly prescribed but are of doubtful benefit and, as an alternative, simple linctus BP (British Pharmacopoeia) is a harmless preparation that may have some useful soothing effect. Aspirin may be used as an antipyretic and for myalgia but should not be prescribed in children because of the remote chance of causing Reye's syndrome [49], paracetamol being a suitable alternative. Bland ointments or creams are useful in preventing cutaneous excoriation about the nostrils and lips. The breathing of warmed humidified air has been shown to produce symptomatic relief [50]. A gener-

ous tot of Scotch whisky adulterated with honey and hot water, to be taken before bedtime, is probably as effective as any of the foregoing!

Antibiotics are of no value in treating the *uncomplicated* cold but are sometimes prescribed prophylactically to patients with chronic lower respiratory tract disease at the onset of upper respiratory tract symptoms in order to prevent an exacerbation due to secondary bacterial infection. Large doses of vitamin C, although sometimes taken in ritual manner to prevent colds, have unfortunately not been demonstrated to be effective in preventing experimental rhinovirus infection [51]. There is at present no prospect of an effective vaccine in view of the enormous multiplicity of serologically distinct causative viruses. Apart from pirodavis, other antiviral agents such as interferons, applied intranasally, have been investigated [52] and have shown some promise as a short-term prophylactic for rhinovirus colds [53], but have not come into general use because of expense and tiresome side-effects such as local mucosal dryness and bleeding.

Patients who are susceptible to lower respiratory tract infections do not usually have to be reminded to avoid contact with cold sufferers whenever this is possible, and simple measures such as hand-washing may help to prevent viral spread.

### Complications

A small proportion of common colds are complicated by bacterial infection and may require antibiotic treatment. The mechanisms may involve direct viral invasion, disruption of mucosal surfaces and damage to the mucociliary escalator. This mucosal injury produces local oedema, which in turn has the effect of blocking those channels or passages that normally open into the nasopharynx. These include the ostia of the frontal, maxillary and sphenoidal sinuses, the ethmoidal cells, the eustachian tubes and the nasolacrimal ducts. Such obstruction creates conditions favourable to the development of acute sinusitis and otitis media [29], as well as the symptom of watery eyes. Extension of infection caudally may predispose to tracheobronchitis and in patients with asthma may well provoke wheezing. There are occasionally reports of non-bacterial pneumonia occurring in otherwise healthy adults in association with infection by coronaviruses, parainfluenza viruses and Coxsackie viruses.

### Acute pharyngitis and tonsillitis

Of cases of acute pharyngotonsillitis 80–90% are caused by viruses, particularly adenoviruses, although rhinoviruses, coronaviruses and the other viral causes of common cold symptoms mentioned above may also be responsible. RSV infection usually causes only a mild pharyngitis in adults, although it may cause severe bronchiolitis in infants, often

in epidemic form from late autumn to early spring. Group A  $\beta$ -haemolytic streptococcal (*Streptococcus pyogenes*) infection may produce a more severe bacterial illness, this organism having a predilection for the tonsils. Such infections are commonest in children but may also occur in adolescence and adult life. *Strep. pneumoniae* and *Haemophilus influenzae* may be secondary invaders. Less commonly, group C  $\beta$ -haemolytic streptococci may be implicated, as may the 'atypical' organisms *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Febrile pharyngitis is a feature of primary human immunodeficiency virus (HIV) infection. Sexually transmitted pharyngitis may be caused by *Neisseria gonorrhoeae* and *Treponema pallidum*.

### Clinical features

Symptoms and signs are very variable. Most patients experience a slight sore throat, often of brief duration. Acute pharyngitis caused by some adenovirus serotypes may be associated with fever, cervical lymphadenitis and conjunctivitis, a syndrome that may occur in epidemic form in children in the summer months, so-called pharyngoconjunctival fever. When Coxsackie A virus causes a sore throat it is accompanied by small vesicles that appear on the palate and ulcerate. The illness, sometimes known as the herpangina syndrome, is short-lived and may be accompanied by malaise and fever. Primary infection by herpes simplex virus may cause a somewhat similar appearance. A 'mononucleosis syndrome' similar to that caused by Epstein-Barr virus (see below) may be caused by cytomegalovirus infection or HIV infection and should be suspected when there is a persistent and more severe sore throat, often accompanied by malaise, sometimes with lymphadenopathy, splenomegaly and an atypical lymphocytosis on the blood film. Primary HIV infection may also cause a 'mononucleosis syndrome', accompanied by malaise, fever and sore throat, sometimes with lymphadenopathy and a maculopapular rash.

A few patients with acute pharyngitis or tonsillitis experience a more severe febrile illness with general symptoms of systemic toxicity and dysphagia in which there is pharyngotonsillar oedema, hyperaemia and cervical lymphadenopathy. A white pharyngeal or tonsillar exudate may form in severe cases, such as those caused by group A  $\beta$ -haemolytic streptococci.

Other less usual causes of membranous pharyngitis are considered below.

### Diphtheria

Diphtheria caused by infection with *Corynebacterium diphtheriae* and occurring in unvaccinated populations exhibits prominent systemic symptoms: there is a greyish pharyn-

geal membrane with little surrounding hyperaemia; cervical lymph nodes may be much enlarged, producing a 'bull neck', not to be confused with mumps; the pulse rate is increased disproportionately to the fever, which is low grade. The diagnosis depends upon a high index of clinical suspicion, and prompt hospital treatment with diphtheria antitoxin may be life-saving. Subsequent laboratory confirmation of the diagnosis follows a throat swab culture.

### Vincent's angina

Vincent's angina (anaerobic pharyngitis or 'trench mouth') is a membranous pharyngotonsillitis that may arise in a patient with poor oral hygiene as a result of anaerobic infection by the Gram-negative spirochaete *Borrelia vincenti* and other anaerobic fusobacteria. The diagnosis is supported by microscopic examination of throat swab smears of the exudate, stained to show fusobacteria and spirochetes. Treatment is with penicillin.

### Infectious mononucleosis

Infectious mononucleosis is associated with pharyngitis in 80% of cases, sometimes with membrane formation. Coryzal symptoms are absent and the presence of posterior cervical lymph node enlargement and splenomegaly may be of diagnostic assistance. Tonsillar enlargement is common; very rarely, fatal upper airway obstruction may occur [54]. The diagnosis of infectious mononucleosis is confirmed by the presence of atypical mononuclear cells in the blood film and positive tests for heterophile antibodies (Paul-Bunnell test). When the Paul-Bunnell test is negative, Epstein-Barr virus-specific antibodies may be detected in the serum.

### Oral thrush (candidiasis)

Oral thrush, which may produce a sore mouth and throat, is caused by *Candida albicans* infection and usually occurs in patients after they have received broad-spectrum antibiotics or immunosuppressives, including corticosteroids whether systemic or inhaled. It is characterized by the presence of typical white plaques on the gums, tongue, palate and fauces. Diagnosis is based on the clinical findings and treatment is with nystatin or amphotericin locally. More persistent or severe infection may be treated with an oral azole such as fluconazole. Underlying blood dyscrasias such as leukaemia or other causes of a compromised immune system should be considered in any persistent or severe pharyngitis. *C. albicans* is a frequent pathogen in leukaemic patients and may also cause infection in transplant recipients and patients with AIDS. Serious invasive infection in this group may require treatment with amphotericin.

## Treatment

Treatment is symptomatic in a case of mild uncomplicated pharyngotonsillitis and the vast majority of such infections resolve spontaneously. Antimicrobial therapy is usually reserved for more severe infections, in which case haemolytic streptococci are usually responsible. These can be cultured from a throat swab and the result should be available within 24 h. Commercially produced kits now exist for detecting group A streptococcal antigen from throat swabs within 1 h. Their specificity is high (>98%), so that a positive result dispenses with the need for culture. Sensitivity is less satisfactory (80–90%), so that if antigen is not detected culture should still be performed [55]. Oral penicillin is the antibiotic of choice, a macrolide being used if the patient has a history of allergy to the former drug. Ampicillin/amoxicillin (amoxycillin) should be avoided for fear of causing a rash in infectious mononucleosis. Penicillin is also used to treat Vincent's angina. It is usual practice to treat diphtheria with intravenous antitoxin, a measure that has been shown to reduce mortality, further toxin formation being reduced by eradication of the organisms with penicillin or a macrolide.

## Complications

Complications of pharyngotonsillitis are rare and are generally associated with bacterial rather than viral infections. They include peritonsillar abscess (quinsy), which is treated with benzylpenicillin and sometimes requires surgical drainage; cervical abscess, similarly treated with penicillin and drainage; and retropharyngeal abscess, which may produce respiratory difficulties and which is demonstrable on a lateral radiograph of the neck and on CT, as is the laterally extending parapharyngeal abscess. In addition to antibiotic treatment, these complications also require surgical drainage, both to relieve symptoms and to prevent extension of infection down the fascial planes to the mediastinum. Rheumatic fever and acute glomerulonephritis are nowadays unusual complications of streptococcal pharyngotonsillitis in Western practice.

## Acute supraglottitis (epiglottitis)

This is a febrile illness in which acute infection is mainly localized to the epiglottis and surrounding supraglottic tissues, which become cellulosic, assuming a swollen 'cherry-red' appearance. It is primarily caused by *H. influenzae* type b, although streptococci and staphylococci have occasionally been implicated. Although rare, prompt diagnosis is essential as it may cause a fulminant and potentially fatal illness in a previously healthy patient, the upper airway becoming critically obstructed by gross soft tissue swelling within a few hours. The infection produces a sore throat, hoarseness and dysphagia followed by

inspiratory stridor with the onset of supraglottic obstruction. A high index of suspicion is needed as deaths may occur when patients presenting with a rapidly developing severe sore throat are sent home from emergency departments before the onset of obstructive symptoms [56]. Although the peak incidence of acute epiglottitis is between 2 and 4 years of age, it is emphasized that this condition is also an important illness in adults, in whom a mortality rate of 7% has been recorded [57]. Attempts to examine the throat by depressing the tongue may result in fatal upper airway obstruction in children but in adults indirect or flexible laryngoscopy is safe [57,58]. In childhood the patient is typically feverish and unwell, developing breathing difficulties within a few hours, tending to sit upright, drooling from the open mouth because of an inability to swallow and breathing in a tentative and cautious manner with muffled inspiratory stridor and absence of cough.

The immediate treatment in all cases is to secure the airway by endotracheal intubation in preference to tracheostomy, and the 'at-risk' patient should not be left unattended by responsible medical personnel until this has been achieved. Intubation should ideally be carried out by an experienced anaesthetist using general anaesthesia. This allows the epiglottis and supraglottic area of a child to be inspected under controlled conditions without the risk of precipitating total upper airway obstruction, as might happen if inspection is carried out in the conscious child with a tongue depressor. Blood cultures should be taken after intubation as these are positive in over 20% of patients, and a swab of the epiglottis should be taken while passing the tube. There may be radiographic evidence of pneumonia in about one-quarter of patients. Characteristic soft tissue changes have been described if a lateral radiographic view of the neck is obtained [59], but valuable time may be lost in obtaining the films.

Antimicrobial therapy should cover the possibility of amoxicillin-resistant  $\beta$ -lactamase-producing *H. influenzae*. The use of a third-generation cephalosporin (e.g. cefotaxime) is recommended until sensitivities are known. Amoxicillin may be substituted if the organism is not a  $\beta$ -lactamase producer, and should be continued for 2 weeks [60]. Prophylactic rifampicin for 4 days is recommended for unimmunized household contacts up to the age of 4 years. There is evidence of a decline in the incidence of paediatric supraglottitis since the introduction of *H. influenzae* type b vaccination programmes [61].

## Acute laryngitis

Laryngitis in adults may occur as part of a generalized acute upper respiratory tract infection. It may produce only a subtle alteration in the quality of the voice, obvious hoarseness or in extreme cases virtual aphonia. It is a common accompaniment of colds and sore throats. Per-

sisting hoarseness may occur because of excessive use of the voice or cigarette smoking and requires laryngoscopy to exclude a laryngeal carcinoma [62]. The use of inhaled corticosteroids is a common cause of dysphonia in respiratory practice and is dealt with in Chapter 9. Dysphonia as a result of posterior laryngitis may occur as a consequence of gastro-oesophageal reflux and these patients may respond to empirical treatment with a proton pump inhibitor such as lansoprazole [63]. It has also been described as a consequence of occupational exposure to inhaled chemicals [64]. Management of acute laryngitis is usually expectant, as the condition in adults is self-limiting. Subjective symptoms usually improve spontaneously after about 1 week in most cases so that antibiotic treatment is not warranted as a general rule. Patients are advised to rest their voice until symptoms have subsided. When attempts have been made to culture bacteria in adult cases of acute laryngitis, high isolation rates of about 50% have been reported for *Moraxella catarrhalis*, with much lower rates for *H. influenzae* and *Strep. pneumoniae* [65]. An antibiotic may be justified in patients who are professionally dependent on the quality of their voice, in which case one should be chosen that is likely to be effective against *M. catarrhalis*. Tuberculous laryngitis is now rare in Europe and North America but is seen in populations in which the prevalence of tuberculosis is high [66,67]. Other unusual causes include herpes simplex virus, varicella-zoster virus, cytomegalovirus, diphtheria, syphilis, fungal infection and actinomycosis. The clinician needs to be alert for these and other unexpected organisms in patients who are immunocompromised [68].

### Sinusitis (rhinosinusitis)

Some knowledge of sinusitis is important to the respiratory physician because it is a common cause of persistent cough and therefore referral and because of its association with lower respiratory tract infection. It is estimated to affect about 15% of the population [69]. It is defined as an inflammation of the mucous membrane lining one or more of the paranasal sinuses and is somewhat arbitrarily described as acute or chronic (see below). The nasal passages themselves may also be inflamed, hence the term 'rhinosinusitis'. The causative organisms may be viral, bacterial or fungal. Bacterial infection may be predisposed by any condition that interferes with free drainage of mucus from the sinuses, and ostial narrowing from whatever cause is of prime importance in the development of sinusitis. A common cold or allergic rhinitis results in not only hypersecretion of mucus but also mucosal oedema, which may narrow or close off the ostia through which the sinuses normally drain. Ciliary function may be impaired by inflammation and infection, with further compromise of mucous drainage, and cilia may be lost when mucosal cells undergo metaplastic change as a consequence of per-

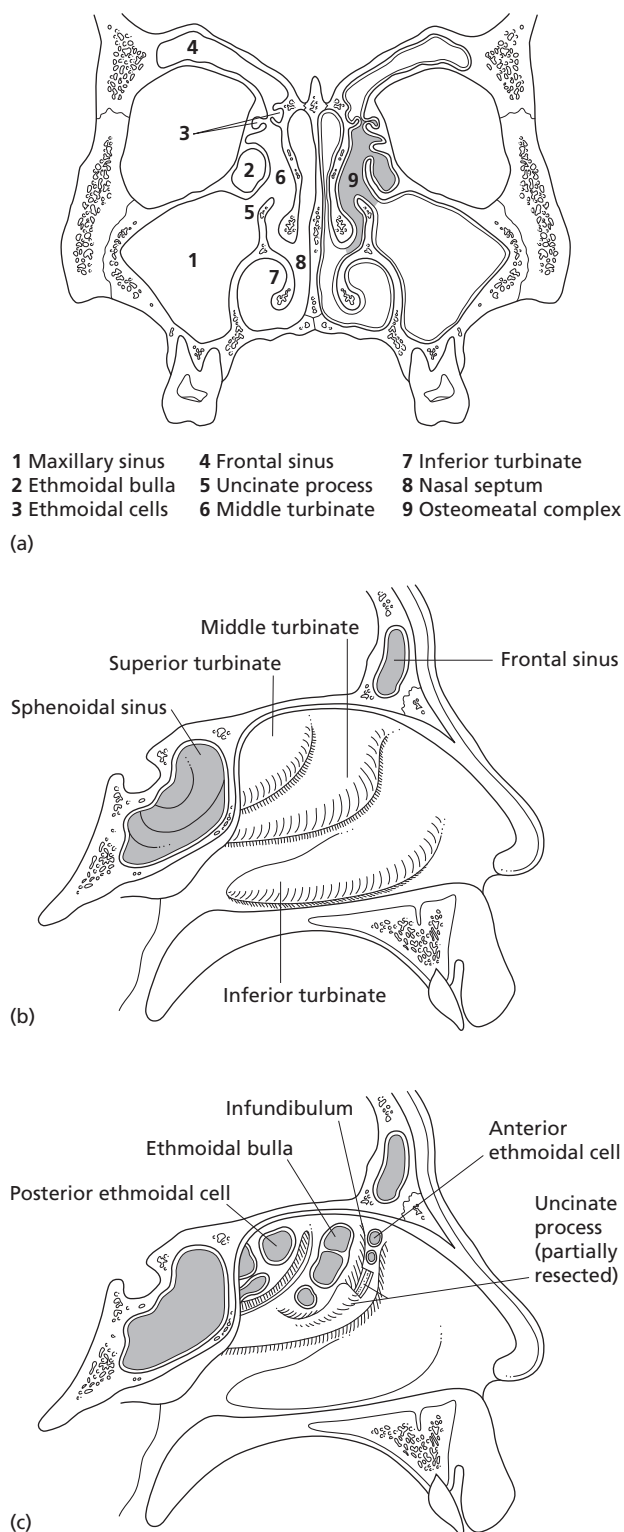
sistent infection. Hereditary ciliary dyskinetic disorders (see Chapter 28) may also impair drainage and predispose to sinusitis as does cystic fibrosis. Infection may extend directly into the maxillary sinus as a result of dental sepsis and it has been estimated that 10% of sinus infections may arise in this way [70]. A sudden involuntary cough triggered by the act of choking on a piece of food may result in the anterograde passage of this foreign body through the nose with subsequent infection, as the author found to his cost while wolfing down the contents of a jar of pickled mussels! Immunodeficiency disorders also predispose to infection, this sometimes being caused by unusual organisms including fungi [68].

The paranasal sinuses become fully developed in adolescence, the maxillary and ethmoidal sinuses being present from birth and the frontal and sphenoidal sinuses developing in infancy. They are lined by mucus-secreting ciliated pseudostratified columnar epithelium and are normally sterile, the surface mucus being continually cleared by the concerted action of the cilia. The four pairs of paranasal sinuses (frontal, maxillary, sphenoidal and ethmoidal) communicate with the nasal cavity (Fig. 12.1) and are susceptible to the spread of infection from the nasopharynx. The maxillary, frontal and anterior ethmoidal sinuses all drain mucus by means of their 'mucociliary escalators' in much the same way as does the tracheobronchial tree. This drainage of all these three sinuses is directed through small ostia into a single narrow area known as the osteomeatal complex (Fig. 12.1a), which is situated in the middle meatus, lateral to the middle turbinate. Swelling of the mucosal lining of the middle meatus may therefore block the osteomeatal complex and interfere with the drainage of all these sinuses and it is of note that most sinus infection occurs in the spaces subtended by this complex. The posterior ethmoidal sinus drains similarly but into the superior meatus and the sphenoidal sinus more posteriorly into the sphenothmoidal recess.

### Acute sinusitis

Acute sinusitis is an infection that occurs very commonly in the population, complicating about 1 in 200 upper respiratory tract infections [29]. The initiating infection is thought to be most frequently viral, 'common cold' and other respiratory viruses having been recovered from aspirates of the maxillary sinus [72]. It is supposed that viral replication in the mucosal lining of the sinus disrupts its normal defensive mechanisms, resulting in the production of a mucous exudate that then becomes secondarily infected by bacterial pathogens with the accumulation of neutrophil-laden mucopurulent secretions within the sinuses themselves. The mucosal swelling associated with allergic rhinitis and nasal polyp formation may also produce conditions favourable to bacterial infection, as





**Fig. 12.1** (a) Coronal section through the nose and paranasal sinuses (cf. Fig. 12.2), the stippled area representing the osteomeatal complex. (b, c) Sagittal sections with (c) showing a view through the middle and superior turbinates, displaying the ethmoidal cells. (After Wald [71].)

may dental sepsis affecting the upper molars and premolars, the roots of which penetrate the maxillary sinuses.

Methods of microbiological sampling other than sinus aspiration are likely to pick up nasal commensals. The most common bacteria responsible for sinusitis in adults are *Strep. pneumoniae* and *H. influenzae* [73];  $\beta$ -lactamase production has been reported in over 15% of *H. influenzae* in some series and is increasing [74]. Although *M. catarrhalis* is a common sinus isolate in children, it is less common in adults [73]. Mixed infections are not uncommon and anaerobes may be cultured if attempts are made to do so, accounting in these circumstances for about 10% of isolates. Anaerobic infection may occur as the result of dental sepsis and is therefore more commonly found in adults. Other organisms include *Staphylococcus aureus*, *Strep. pyogenes* and Gram-negative bacteria, including *Pseudomonas aeruginosa*, which has been most commonly isolated in patients with cystic fibrosis [75]. The isolation of *Staph. aureus* may not always be significant as it is carried as a commensal in a high proportion of asymptomatic subjects but it may be a pathogen particularly in sphenoidal and frontal sinusitis [76,77].

### Chronic sinusitis

Sinusitis may be arbitrarily described as 'chronic' if it has been present for 3 months. In chronic sinusitis the ciliated columnar epithelium becomes replaced by a thickened stratified squamous lining denuded of cilia and which in advanced cases may grossly diminish the volume of the affected sinus. These changes are irreversible and result from prolonged infection, the sinus cavity continuing to harbour bacterial flora and being susceptible to repeated acute exacerbations of infection by pathogenic organisms, commonly *Strep. pneumoniae* and *H. influenzae*. Anaerobes occur more commonly in chronic than acute sinusitis.

Intractable sinusitis raises the possibility of fungal infection, which may occur in both immunocompetent and immunosuppressed patients [78]. Allergic fungal sinusitis may be suspected in atopic individuals with chronic sinus symptoms and nasal polyposis. *Aspergillus* species may be implicated as may other genera and the process may take the form of an IgE-mediated hypersensitivity reaction akin to bronchopulmonary aspergillosis [78]. Occasionally a sinus mycetoma may form within a maxillary sinus [78]. Invasive fungal sinusitis may occur acutely in immunocompromised, neutropenic, malnourished and diabetic patients, although more chronic forms that sometimes occur in immunocompetent patients are also recognized [78].

### Clinical features

The symptoms of acute sinusitis frequently follow a common cold or other viral upper respiratory tract infec-



tion but may also follow an episode of allergic rhinitis, so that any initial nasal discharge may be watery and accompanied by sneezing. All the sinuses may be affected to some extent. Maxillary sinusitis causes an uncomfortable feeling of fullness or pain over the cheek that may radiate anteriorly. There may be maxillary toothache [79–81]. Frontal sinusitis may cause supraorbital headache. Anterior ethmoidal sinusitis may give pain over the bridge of the nose and medial angle (or canthus) of the eye. Sphenoidal sinusitis may cause retro-orbital headache, which may be referred over a wide area of the scalp to the temples and occipital region. All these pains may be worsened by leaning forward or straining. Headache may be severe. There may be nasal blockage that is reflected in the quality of the voice. The sense of smell may be lost as a result of inflammation of the olfactory mucosa. With the onset of bacterial infection, there may be mucopurulent rhinorrhoea and any postnasal discharge may produce coughing. Such discharge clearly depends on the patency of the ostia. The patient may complain of an unpleasant taste and bad breath. Fever and malaise are frequent but inconstant features. The symptoms in chronic sinusitis are similar but are commonly less severe. There may be a persistent 'catarrhal' discharge.

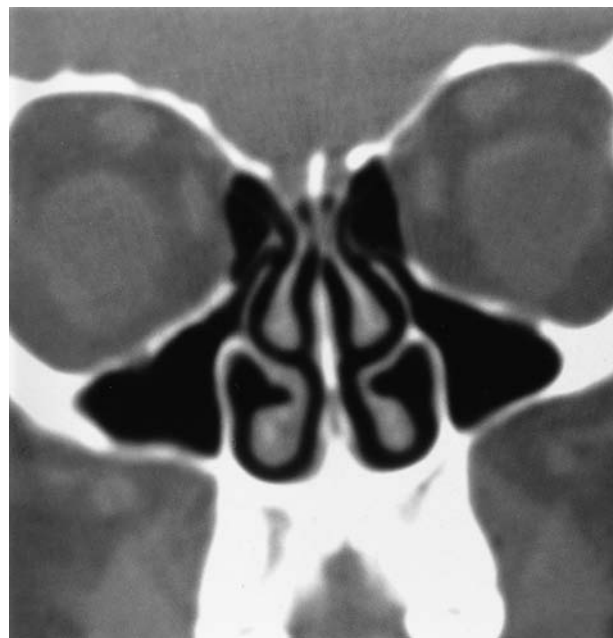
Physical examination may show a predisposing anatomical abnormality such as a deviated septum. It may reveal reddened or oedematous nasal mucosa. Any persistent inflammation may cause the mucosa to 'balloon' with the formation of polyps, as may also happen in allergic rhinitis [82]. Purulent secretions may sometimes be present in the middle meatus of the nose and may also be seen against the posterior pharyngeal wall. The breath may smell foul, raising the possibility of anaerobic infection. There may be tenderness over an affected frontal or maxillary sinus; occasionally tenderness and swelling over the maxilla may indicate a dental abscess. Further evidence of active infection may be provided by the failure of the frontal or maxillary sinuses to transilluminate when a torch is held against them in a darkened room [83].

### Investigations

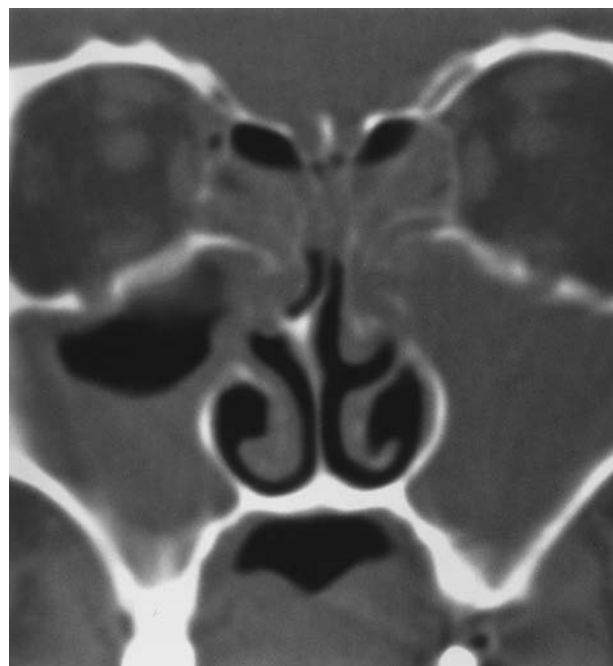
'Routine' laboratory tests such as white cell count, erythrocyte sedimentation rate and C-reactive protein are frequently normal [84]. Although paranasal sinus radiographs are a simple means of obtaining diagnostic information, they are unfortunately notoriously unreliable, even with the use of multiple projections, and cannot adequately show the anterior ethmoidal sinuses. These films may be reported as showing a variety of changes depending upon the extent of the infection, ranging from thickening of the mucosal lining, which need not indicate active disease, to an air–fluid level or complete opacification of the sinus, both of which are significant. In chronic

sinusitis the abnormalities may persist, making discrimination from an acute exacerbation difficult.

CT (Fig. 12.2) gives a much more accurate representation of pathology, the ethmoidal sinuses showing well on two axial cuts and the remaining sinuses being imaged with about seven cuts in the coronal plane, this delivering



(a)



(b)

**Fig. 12.2** Coronal CT of the paranasal sinuses for comparison with Fig. 12.1: (a) clear maxillary sinuses and ethmoidal cells with patent osteomeatal complexes; (b) a patient with chronic sinusitis showing opacification with evidence of mucosal disease in these three areas. (Films courtesy of Dr K.R. Karia.)

a comparable radiation dose to three standard radiographic views of the sinuses. One problem with CT, apart from its cost, is that although it demonstrates abnormalities with alacrity, these may not represent bacterial infection. Thus over 80% of subjects with viral 'colds' have maxillary sinus abnormalities on CT [85] and 24–39% of the asymptomatic population may demonstrate mucosal abnormalities [86]. It is probable that CT examination of the paranasal sinuses should be reserved for delineating the anatomy and pattern of inflammatory paranasal disease prior to possible surgical intervention in patients in whom medical treatment has failed or in whom an inflammatory complication or malignant disease is suspected [87]. Calcification within the sinus on CT is suggestive of fungal infection [78]. Antral puncture to enable diagnostic aspiration is seldom necessary but may sometimes be used in difficult cases or when an unusual organism is suspected, such as may be the case in an immunosuppressed patient. Endoscopically directed middle meatus aspiration culture may be an acceptable alternative [88]. Fungal sinusitis can only be reliably diagnosed by adequate aspiration with silver staining and fungal culture [78]. In the case of allergic fungal sinusitis the aspirated mucinous material, which resembles peanut butter or cottage cheese, may be the sinus equivalent of the bronchial plugging or 'mucoid impaction' associated with allergic bronchopulmonary aspergillosis. It contains hyphae but these do not invade the submucosa and adjacent tissues. The use of ultrasound, in experienced hands, is about as reliable as radiography in diagnosing fluid retention in the maxillary sinuses [89].

### Treatment

Time-honoured measures to obtain symptomatic relief in acute sinusitis include the inhalation of moist warm air, compliance being encouraged by the addition of a volatile aromatic substance such as benzoin tincture compound BP (Friar's balsam). The use of topical decongestant drops, such as ephedrine 0.5%, may also produce relief. This and other sympathomimetic agents may give rise to rebound vasodilatation and congestion as their effect wears off and their prolonged use is not encouraged. They may be more effective if applied in the head-down position and this attitude held for 2 or 3 min. Simple analgesia may be necessary. Predisposing allergic rhinitis should be treated with antihistamines and topical steroids or sodium cromoglycate (cromoglycate).

There is a dearth of well-constructed, placebo-controlled, double-blind, randomized trials of antibiotic treatment in adult patients presenting with symptoms suggestive of acute sinusitis in primary care; the few that have been carried out do not show consistent superiority of response in the antibiotic-treated groups [90–92]. Whereas patients who have only mild symptoms may be

managed expectantly, it is nevertheless usual to treat those with more severe or persistent symptoms with an antibiotic. Effective management of such cases of acute or acute-on-chronic sinusitis usually depends on the selection of an antibiotic appropriate to the infecting organisms. As reliable identification of the pathogen in an individual patient is impossible without direct needle puncture of the involved sinus, treatment is empirical and designed to deal with the likely pathogens. A reasonable initial choice for the community-acquired case in most of the UK is amoxicillin 500 mg 8-hourly or, in penicillin-allergic patients, trimethoprim 200 mg 12-hourly. Both of these inexpensive preparations have a spectrum of activity that can still deal with *Strep. pneumoniae* and *H. influenzae* more often than not. In cases where infection is more severe or if it remains unresponsive after 7–10 days of treatment, the spectrum may be broadened to cover  $\beta$ -lactamase-producing *H. influenzae* and *M. catarrhalis* by substituting amoxicillin-clavulanate (co-amoxiclav) or, in the penicillin-allergic patient, one of the newer macrolides such as clarithromycin is an option. There are many alternatives and a knowledge of local patterns of antimicrobial resistance is helpful in making a rational choice; thus in geographical locations where there is a high prevalence of  $\beta$ -lactamase-producing aminopenicillin-resistant *H. influenzae*, these can be covered from the outset. There is little information about the optimal duration of antimicrobial treatment but it is logical in acute sinusitis to extend the course to 14 days because of the walled-off nature of the infected spaces. Antimicrobial treatment in chronic sinusitis may be prolonged for 1 month or more, the optimal length of treatment remaining *sub judice* [93]. Where the sinus infection is thought to be associated with dental sepsis, co-amoxiclav in combination with metronidazole are reasonable options, although the sinus infection will recur until the predisposing dental cause has been satisfactorily dealt with.

In the unusual and difficult case, the sinus contents may be aspirated by direct puncture and submitted for culture, the appropriate antibiotic being selected on the basis of sensitivities. This may be necessary where it is thought that the infection has been acquired in hospital or where unusual organisms are suspected in immunocompromised patients. In these situations it is advisable to institute urgent treatment with broad-spectrum parenteral antibiotics to cover not only the usual bacterial pathogens but also *Ps. aeruginosa*, Gram-negative enteric bacilli and anaerobes while awaiting the outcome of investigations [68]. Invasive fungal sinusitis may occur acutely in neutropenic, malnourished and diabetic patients [78]. It is confirmed by isolation of the organism from sinus contents and by demonstrating mucosal and bony invasion on surgical biopsy material, treatment being by adequate surgical clearance of infected material and administration of amphotericin. More chronic invasive forms are also

described, usually but not invariably in patients with impaired immunity, and these too require surgical and antifungal treatment [78]. Allergic fungal sinusitis is treated surgically with removal of polyps and inflammatory material. The condition tends to recur and surgical follow-up is necessary [78]. It is not yet clear whether systemic steroids prevent recurrence but they may be used in the short term after surgical clearance, and are followed by long-term intranasal steroids [94].

### Surgery

Surgical treatment may become necessary when:

- 1 sinusitis becomes chronic, with poor control of symptoms despite seemingly appropriate medical treatment;
- 2 a predisposing anatomical abnormality needs correction in order to achieve adequate drainage;
- 3 complications either occur or are considered likely to happen [95].

Whereas earlier surgical attempts concentrated on the maxillary sinuses, with inferior meatal antrostomy and the more radical Caldwell–Luc procedure of sublabial antrostomy, more recent technological advances have provided ear, nose and throat surgeons with an accurate CT ‘road map’ of their territory and the endoscopic means to modify it, particularly in the crucial region known as the osteomeatal complex (see Fig. 12.1a), the small space into which the maxillary, frontal and anterior ethmoidal sinuses all drain. This has led to the development of functional endoscopic sinus surgery, the aim of which is to eradicate ethmoidal disease with the resolution of severe mucosal changes and the re-establishment of proper sinus ventilation and drainage [96,97]. This usually involves dissection of the ethmoidal sinuses and removal of the uncinate process and diseased mucosa. It is followed by a prolonged period of regular nasal douching and antibiotic treatment until infection is eradicated and mucosal changes have reversed. The complication rate in experienced hands is low but problems include blindness as a result of damage to the optic nerve, intraorbital haemorrhage and infection, damage to the internal carotid artery and leakage of cerebrospinal fluid through a damaged cribriform plate.

### Complications

The complications of sinusitis are due to the spread of infection to the contiguous cranial cavity and orbit [98–101]. These problems are unusual in economically developed societies given the ready availability of antibiotics. Intraorbital cellulitis or abscess formation may cause proptosis and threaten vision, so that urgent axial CT, antibiotics and surgical drainage of significant accumulations of pus are called for. Spread of infection from the eth-

moidal and sphenoidal sinuses may result in cavernous sinus thrombosis, while spread from the frontal sinuses may cause intracranial sepsis. Osteomyelitis with destruction of the bony margins of a sinus may also occur; ‘Pott’s puffy tumour’, described in the pre-antibiotic era, is caused by osteomyelitis of the frontal bone.

## Acute bronchitis, tracheitis and tracheobronchitis

All three terms refer to common inflammatory conditions affecting a part or the whole of the tracheobronchial tree. These conditions, which overlap and are ill-defined clinically, frequently follow infection with any of the common cold viruses. Acute bronchitis is common during epidemics of influenza and measles may also be causally related. *Mycoplasma pneumoniae* or *Bordetella pertussis* may also occasionally initiate infection. Secondary bacterial infection may follow an initial viral insult, *H. influenzae* and *Strep. pneumoniae* being common isolates; *Staph. aureus* is less common but may complicate influenza. Seasonal variations occur, acute bronchitis being reported more commonly in the winter months [102]. Varying degrees of inflammatory change are found in the respiratory mucosa, depending on the responsible organisms, and tend to be more severe in influenza than in rhinovirus infections [103,104].

### Clinical features

Tracheobronchitis may affect any age group but has been reported more commonly in children and the elderly [102]. An affected adult commonly complains that ‘the cold has gone on to my chest’, which usually means that acute coryza or symptoms of pharyngitis have been followed by a cough which persists once the original symptoms have abated. The cough is often dry at first but later frequently becomes productive of mucoid or mucopurulent sputum. This sometimes contains streaks of blood for short periods, a symptom that may alarm otherwise stoical patients sufficiently to cause them to seek medical advice. A fever with symptoms of rhinovirus infection is less common in adults than in children but is common when the infecting organism is an influenza virus, *Mycoplasma pneumoniae* or an adenovirus.

Patients affected by acute bronchitis are often previously healthy; however, in a tobacco smoker who already has a chronic productive cough, albeit mild, the infective episode may be termed ‘acute-on-chronic bronchitis’ or ‘acute exacerbation of chronic bronchitis’ or ‘acute exacerbation of chronic obstructive pulmonary disease’. Otherwise healthy smokers who develop acute bronchitis tend to cough for longer than similarly afflicted non-smokers [42]. Breathlessness and cyanosis do not occur unless the patient has coexisting cardiopulmonary disease or unless

the acute bronchitis is complicated by pneumonia. Wheezing is not usually a feature in adults, unless the patient has chronic bronchitis or asthma, but is more common in children, many of whom do have asthma. When tracheitis is present the patient may complain of, or admit to, retrosternal discomfort or tightness, sometimes described as burning, that may be heightened by inspiration or coughing.

Physical examination of the chest commonly reveals no sign of disease. Low-pitched wheeze and coarse crackles may be heard, and if this is the case they may frequently be shifted if the patient coughs, thereby clearing the larger airways of loose secretions. Higher-pitched wheeze is unusual and is suggestive of asthma or chronic obstructive pulmonary disease.

### Diagnosis

The diagnosis is based on the history and the self-limiting nature of the illness. Attention should be paid to detail, and if the cough lasts longer than 2 weeks a chest radiograph should be obtained, this being normal in uncomplicated acute bronchitis. Persistent symptoms in a tobacco smoker may be an indication that more serious respiratory disease has perhaps become superimposed on underlying simple chronic bronchitis, the patient or spouse frequently noticing a change in the character of the cough or some other new feature that should alert the physician to investigate further for neoplastic disease. Haemoptysis in a cigarette smoker over the age of 40 years usually merits a bronchoscopy despite a normal chest film [105]. Attempts to identify a viral cause in acute tracheobronchitis do not result in information of any practical use and, although of possible epidemiological interest, are omitted in ordinary clinical practice. However, mucopurulent sputum may be cultured for bacterial pathogens.

### Treatment

Treatment of acute tracheitis or tracheobronchitis in previously healthy subjects is usually confined to the provision of symptomatic remedies. If cough proves tiresome it may be relieved by codeine linctus. Expectorant preparations have no value [106]. When the patient is febrile, rest and attention to hydration should be encouraged. If the sputum is mucopurulent, an antibiotic such as amoxicillin 250 mg 8-hourly or clarithromycin 250 mg 12-hourly may be prescribed, 7 days of treatment usually being sufficient provided that the organism is sensitive. Antibiotic treatment is more important in patients with coexisting cardiopulmonary disease but may sometimes be omitted in otherwise healthy people with mild infections [107].

## Other forms of tracheobronchitis

### *Fungal tracheobronchitis*

Fungal tracheobronchitis may occur in immunocompromised patients. *Aspergillus* species may be responsible and cause a rapidly evolving, often fatal, febrile respiratory distress syndrome with necrosis, ulceration and the formation of pseudomembranes that may obstruct the tracheobronchial tree [108–110]. Treatment of serious fungal tracheobronchitis in immunocompromised patients is with amphotericin.

### *Diphtheria*

Diphtheria may spread from the pharynx to involve the larynx and tracheobronchial tree, sometimes leading to asphyxia as a result of membrane formation in the respiratory tract [111]. There may be a greyish-white tonsillar membrane. Morbidity and mortality relate not only to the effects of airway obstruction but also to the production of endotoxin, which may result in myocarditis and peripheral neuropathy, so that diphtheria is treated with both diphtheria antitoxin and penicillin or erythromycin. The condition occurs in unimmunized populations and there have been recent epidemics in Russia [111].

### *Acute laryngotracheobronchitis*

Acute laryngotracheobronchitis in children produces the syndrome known as 'croup', which is of interest to adult respiratory physicians chiefly when it affects their own issue. The peak age of onset of croup is 1–2 years, when the diameter of the trachea is relatively small. Croup is characterized by a barking cough, a hoarse voice and inspiratory stridor with distressed breathing. It is commonly preceded by a cold and is usually the result of parainfluenza virus infection, although other viruses may also be causal, including RSV, rhinoviruses and adenoviruses [112]. Treatment is supportive and the steam kettle traditional. The development of sternal and intercostal recession with a rising pulse and respiratory rate are indications for hospital admission, which occurs in about 10% of cases, in order to provide a higher level of supportive care. Nebulized budesonide may help to diminish local inflammation and oedema.

Croup needs to be distinguished from bacterial tracheitis, sometimes called bacterial or pseudomembranous croup, a toxic condition with a high pyrexia that may occur throughout childhood. *Staph. aureus* is most frequently implicated but other pathogens, including *H. influenzae*, *M. catarrhalis*, group A haemolytic streptococci and *Strep. pneumoniae*, have been isolated. It is suspected that this condition represents bacterial superinfection fol-

lowing an initial viral insult. The trachea may become obstructed by purulent secretions so that ventilatory support may become necessary [112].

## Influenza

Influenza is an acute, usually self-limiting, febrile illness of viral origin that differs from other respiratory viral infections with respect to both the mortality it may cause and the epidemic outbreaks for which it has become infamous.

### The virus

The influenza virus is assigned to the Orthomyxoviridae family. There are two generic types, A and B, type C belonging to another genus. Within these types, both subtypes and strains are described, depending upon the antigenic structure of the individual virus particles. Type specificity is based upon the antigenicity of their ribonucleoprotein (nucleocapsid) composition. Subtypes and strains are characterized by antigenic changes in the haemagglutinin (H) and neuraminidase (N) glycoprotein 'spikes' that constitute a major part of the virus envelope [113]. For any influenza virus the letter A, B or C therefore refers to the *type*; the *subtype* is denoted by the haemagglutinin (H<sub>1</sub>, H<sub>2</sub> or H<sub>3</sub>) and neuraminidase (N<sub>1</sub> or N<sub>2</sub>) present; and the *strain* is denoted by the place and the year in which the virus was first isolated. Thus A/Scotland/74/H<sub>3</sub>N<sub>2</sub> refers to a type A influenza virus of subtype H<sub>3</sub>N<sub>2</sub> isolated in Scotland in 1974.

Outbreaks of influenza occur within communities every 1–3 years, often first declaring themselves by an increased number of febrile respiratory illnesses in young school-children, who are the most susceptible group, and thereafter in the adult population. Reporting systems vary according to national practice. In England and Wales an epidemic is declared by the Communicable Disease Surveillance Centre based at Colindale when the weekly incidence of reported influenza cases exceeds 100 per 100 000 people in the population in question. This monitoring is dependent on numbers of 'influenza-like illnesses' reported by spotter practices as well as serological reports from public health virology laboratories.

Outbreaks tend to be abrupt, the peak of an epidemic occurring within 1 month in an affected community and the numbers of new cases tailing off over the following few weeks [114]. Average attack rates are about 20% of the population but may be as high as 50% in certain sections of the community [115]. Epidemics in the Northern Hemisphere occur in the colder months from October to May. Sporadic cases may occur in the summer months but are rare. At variable and unpredictable intervals, usually 10 years or more, waves of infection have spread across

the world, reaching pandemic proportions. The largest recorded pandemic occurred between 1918 and 1919 when so-called 'Spanish flu' resulted in 20 million deaths worldwide in one winter, over 0.5 million of them in the USA and an estimated 200 000 in England and Wales [116,117]. This was therefore the worst infectious pandemic in history, accounting for many more deaths than the hostilities of the first World War. Subsequent pandemics occurred in 1957, 1968 and the most recent in 1977. In the USA, influenza is estimated to kill 10 000 people annually in non-epidemic years and at least 30 000 people during epidemics [118] so that it is rightly regarded as a major public health problem.

### Antigenic drift and shift

Spontaneous changes in the antigenicity of influenza A virus particles are particularly characteristic of this disease and are considered to be responsible for its epidemic behaviour. These antigenic variations result from spontaneous mutations affecting the RNA coding of the surface N and, more frequently, H glycoproteins. When these antigenic changes are minor mutations in response to host immunological pressure, they are referred to as *drift* and may result in epidemics. When a major antigenic variation in N or H glycoprotein occurs, the change is referred to as *shift* and pre-existing immunity to 'old strains' confers little or no protection against the new mutant virus, which is likely to sweep through the population in pandemic fashion. Subsequent epidemics involving the same subtype with minor antigenic variations (drift) occur every few years, during which time the population's level of immunity increases until such time as a further major shift occurs, with pandemic consequences. Such shifts occurred in the severe pandemics of 'Asian flu' in 1957 (A/H<sub>2</sub>N<sub>2</sub>), the moderate pandemic of 'Hong Kong flu' in 1968 (A/H<sub>3</sub>N<sub>2</sub>) and the mild pandemic of 'Russian flu' in 1977 (A/H<sub>1</sub>N<sub>1</sub>), all of which are thought to have originated in China. The severe 1918 outbreak is thought to have been A/H<sub>1</sub>N<sub>1</sub> [119], bearing some antigenic resemblance to the 1977 virus. The fact that the A/H<sub>1</sub>N<sub>1</sub> era continued until 1957 may account for the mild nature of the 1977 pandemic, much of the world population still having some immunity to the earlier virus.

Such major antigenic shifts may reflect recombinational events, i.e. genetic intermingling between animal and human virus genes that allows spread and pathogenicity amongst humans. It has been speculated that the introduction of such new strains may come from aquatic bird reservoirs emerging in southern China, with pigs as intermediates or 'mixing vessels' as they possess receptors for both avian and human influenza viruses [120]. South-East Asian rural domestic practices, where humans live under the same roof as fowl and pigs, may facilitate these

processes. In such circumstances, the prevailing human H or N gene may be replaced by the allelic gene of an animal influenza virus via reassortment. There was recent international anxiety because of a small outbreak of 'Chinese avian influenza' in Hong Kong, in which a previously recognized avian strain (A/H<sub>5</sub>N<sub>1</sub>) believed to cause disease only in birds caused a number of human cases, with some deaths. This fuelled speculation about the possible beginning of a new pandemic caused by a major antigenic shift, although fortunately there has been no evidence so far of person-to-person spread. The entire chicken population of Hong Kong was nevertheless slaughtered as a precaution [121].

There is no clear explanation why epidemics occur only in winter months [122]. Influenza B produces lesser epidemics and lower mortality than influenza A, and influenza C is not thought to cause epidemics at all, occurring only sporadically. The influenza virus is transmitted from person to person in respiratory secretions, most probably in the form of a small-particle aerosol produced when an infected person coughs, sneezes and talks [123]. The incubation period is 18–72 h, the virus entering and replicating in respiratory epithelial cells unless the exposed subject is protected by specific IgA antibody. Once replication has occurred, the host cell dies and nasal and tracheobronchial epithelial cells desquamate; these are shed with the release of more virus particles, which in turn infect adjacent cells. The virus continues to be shed in respiratory secretions for about 1 week, rising to a peak at about 48 h, high numbers of viral particles being shed by symptomatic patients [124].

### Clinical features

The subject with partial immunity to an infecting strain of influenza may shed and transmit the virus without developing more than the mildest of symptoms [125]. However, those with little or no immunity develop an abrupt and often prostrating febrile illness, non-specific symptoms including malaise, feelings of hot and cold, anorexia, myalgia, a sore throat, an initially dry cough and headache. The degree of prostration is usually commensurate with the level of the fever which, in the absence of antipyretic therapy, runs in continuous fashion between 38 and 40°C over the course of 3 or 4 days. Once the fever has settled recovery is usually rapid and accompanying symptoms generally clear within a week or two, although the cough may persist for longer. Physical signs are non-specific, the patient appearing flushed and unwell. A few small cervical lymph nodes may be palpable as with any pharyngitis. The chest is usually clear to auscultation in uncomplicated cases. It should be appreciated that the symptoms and signs are often indistinguishable from those produced by other respiratory viruses that may be active in the community at the same time.

### Complications

The effects of the influenza virus may occasionally extend beyond the nasopharynx, with resultant laryngotracheobronchitis and/or pneumonia. Influenza, in common with other respiratory virus infections, may result in exacerbations of chronic obstructive pulmonary disease [126,127]. Laryngotracheobronchitis may also occur, and in the first 5 years of life mucosal oedema may give rise to sufficient upper airway narrowing to cause the barking cough and inspiratory stridor that typify croup. Sinusitis and middle ear infections may also occur. The hospital mortality from the respiratory complications of proven influenza may be high, 39% of 36 cases of influenza admitted to Nottingham hospitals dying as a consequence of their illness [128].

### Pneumonia

A prospective British Thoracic Society survey that included 453 patients with community-acquired pneumonia found evidence of influenza A virus infection in about 7% of cases [129]. Pneumonia usually develops as a result of secondary bacterial infection, although primary influenzal pneumonia can occur [130,131]. If respiratory symptoms are severe in a suspected case of influenza or if they do not show the expected improvement within 1 week, a chest radiograph should be obtained and any sputum cultured in order that bacterial infection should not be overlooked.

#### *Primary influenza virus pneumonia*

Primary influenza virus pneumonia (see Chapter 13) is a diagnosis of exclusion made when the usual clinical features of influenza are accompanied by breathlessness and hypoxia, with bilateral non-homogeneous shadowing on the chest radiograph, the absence of a bacterial pathogen in the sputum and subsequent confirmatory serological testing. This complication can occur in a previously healthy subject and carries a high mortality. Although unusual it may be encountered during epidemics. Those cases coming to postmortem examination show inflammation and necrosis of the laryngotracheobronchial mucosa and a haemorrhagic pneumonia with relatively few intra-alveolar inflammatory cells.

#### *Secondary bacterial pneumonia*

Secondary bacterial pneumonia (see Chapter 13) may complicate influenza, particularly in the elderly or those with chronic cardiopulmonary disease. This complication may occur at an early stage of infection or after the patient has shown initial signs of improvement. The most frequent pathogen is *Strep. pneumoniae* followed by *Staph.*

*aureus*, which is more feared, and *H. influenzae* [132]. These infections are characterized by signs of consolidation, are often unilateral with lobar or segmental distribution and are usually responsive to appropriate antibiotic treatment. It is strongly recommended that antimicrobial therapy in patients who develop pneumonia during influenza epidemics should include cover for *Staph. aureus*. The fungus *Aspergillus fumigatus* may occasionally cause severe pneumonia after influenza.

### Non-respiratory complications

Central nervous system complications include encephalitis, transverse myelitis and Guillain-Barré syndrome, although definite aetiological links between these conditions and influenza virus infection remain somewhat tenuous [133–136]. All these complications are rare and have been described either at the height of the illness or during the recovery phase. Encephalitis is attended by drowsiness and confusion, sometimes leading to seizures and coma, in which case the prognosis is poor. Transverse myelitis may produce girdle pain at the level of spinal cord involvement, this being followed by a sensory and motor deficit with a clear sensory level detectable on physical examination. Loss of bladder control and paraparesis are usual accompaniments. Although recovery is frequent the outcome is somewhat unpredictable. Guillain-Barré syndrome (infective polyneuropathy) may cause peripheral sensory loss and limb weakness, sometimes starting in the legs and progressing upwards to cause a flaccid paralysis with absent tendon reflexes. Respiratory muscle paralysis and bulbar palsy may occur. The cerebrospinal fluid characteristically shows a high protein content with a normal or minimally raised white cell count. In encephalitis and transverse myelitis, the protein and cell counts are variable depending upon the degree of inflammatory response present. Reye's syndrome may occur as a complication of a wide range of viral infections, not all of them respiratory, but is particularly associated with epidemic influenza B and, to a lesser extent, influenza A infection [137]. It is almost entirely confined to children aged between 2 and 16 years and results in both cerebral and hepatic dysfunction, the former leading to coma and the latter to measurable disturbances of liver function. The pathophysiology is incompletely understood, although the observed increase in frequency of Reye's syndrome in children who have received aspirin for influenza [138] has led to the recommendation that salicylates are contraindicated in children with febrile illnesses. The mortality of Reye's syndrome approaches 40%. Other rare complications include myositis [139], with muscle pain and weakness associated with a high creatine kinase level sometimes with myoglobinaemia and renal failure, and myocarditis/pericarditis [133] that may be accompanied by cardiac dysrhythmias. A causal association between

influenza A infection and fetal loss has been suspected but not substantiated [140].

### Diagnosis

The diagnosis is often accurately made on clinical grounds when data from the Public Health Laboratory Service or the Centers for Disease Control indicate that an epidemic is occurring in a particular region. Serological evidence (usually by complement fixation or haemagglutination inhibition tests), although of epidemiological interest, is of limited clinical value because of the requirement for a convalescent sample, a fourfold change in titre being confirmatory [141]. The influenza virus can be directly identified in nasal or throat secretions or from sputum within a few hours by immunofluorescent antibody techniques, ELISA or gene amplification where facilities are available. Immunofluorescence has the advantage of being relatively cheap but sensitivity is poor compared with cell culture methods [117], which may be used if it is necessary to accurately type the virus.

### Treatment and prevention

In the majority of cases the treatment of influenza need be supportive only, the patient being advised to rest and to take liberal oral fluids. Paracetamol or aspirin may be used as antipyretic agents, although the latter should be avoided in children because of the risk of Reye's syndrome. A broad-spectrum antibiotic is indicated in patients who develop evidence of secondary bacterial infection; when severe community-acquired pneumonia is present, antimicrobial cover should include drugs active against *Staph. aureus*. There are a number of agents that have been shown either to have significant antiviral effects when used as treatment once infection has developed or to be prophylactic during outbreaks. These agents are described in Chapter 9 but are mentioned below.

### Antiviral drugs

Amantadine and rimantadine (see Chapter 9) are adamantanes that are broadly similar both structurally and in their mechanisms of action. They are about as effective as available vaccines in preventing influenza A virus infections, and when used as treatment shorten the duration of the illness [125,142]. They may be used prophylactically in susceptible individuals such as the elderly and in those with coexisting cardiopulmonary disease, being potentially useful in situations where vaccination has not been given and where infection seems likely, as might be the case for those living in crowded conditions during an epidemic [143]. Amantadine need only be taken for 2 weeks in these circumstances, provided that vaccination is given simultaneously. It may also



be taken throughout an epidemic in the following circumstances:

- 1 by patients in whom vaccination is contraindicated because of hypersensitivity to hens' egg products;
- 2 if the vaccine becomes unavailable;
- 3 by healthcare workers in major epidemics in order to reduce disruption in the delivery of their service.

Amantadine is prescribed at a dose of 100mg daily in patients aged over 65 years (see Chapter 9). Central nervous system side-effects such as headache, dizziness and sleep disturbance may occur but are usually mild.

Adamantanes may also be used as treatment in patients in whom a clinical diagnosis of influenza has been made, particularly in those in whom complications might be expected to occur, such as the elderly or those with chronic cardiac or respiratory disease. It is reasonable to treat as soon as possible after the onset of symptoms and to continue for up to 1 week in such circumstances. It is unwise to use these drugs for both postexposure prophylaxis and treatment in the same home because the selection and transmission of resistant influenza A virus may occur.

Rimantadine (see Chapter 9) is an alternative and structurally related adamantane that is available in the USA but not in the UK. It reportedly has fewer central nervous system side-effects [144]. Zanamivir (see Chapter 9) is a sialic acid analogue that selectively inhibits both influenza A and B neuraminidases (sialidases). Clinical trials suggest that in otherwise healthy patients with influenza A or B infection it may reduce the median duration of symptoms by 1–2 days if a 5-day course of inhaled treatment is initiated within 48 h of the onset [145]. There are, as yet, no comparative studies of adamantanes and zanamivir.

### Vaccination

Influenza vaccination is the most satisfactory prophylactic measure and is justified by a mortality rate of 1–2 per 10 000 cases of influenza per year [146]. In the USA the total excess deaths has been estimated to be 10 000–40 000 per year, being particularly high in the elderly and those with serious coexisting disease [118]. In the UK the annual number of deaths attributed to influenza is 3000–4000 in most years, although these figures rise substantially in epidemic years such as the winter of 1989–90 when it is estimated that 30 000 deaths may have been caused [147].

The available vaccines contain formalin-inactivated influenza virus that has been cultured in embryonated hens' eggs and which *cannot* cause influenza. The viral components contained in the vaccine are reviewed annually and modified according to World Health Organization recommendations based on the A and B virus subtypes most prevalent in the preceding winter. Current activity still relates to strains of influenza A subtypes H<sub>1</sub>N<sub>1</sub> and H<sub>3</sub>N<sub>2</sub> with sporadic cases of influenza B strains, so that these constituents are incorporated in trivalent vaccines. Modern vaccines may be effective in preventing

illness in 60–70% of recipients, and in those subjects who contract influenza despite vaccination its severity and complication rate is reduced [148]. In patients over the age of 60 years the risk of influenza infection has been shown to be halved [149]. The vaccine takes 1–2 weeks to achieve protective antibody levels and must be repeated annually, protection lasting for only one season [150].

Vaccination is recommended for elderly people, especially those who live in institutions such as nursing and residential homes, and for patients with chronic cardiac or pulmonary disease (including asthma), chronic renal failure, diabetes mellitus and those whose immunity is otherwise compromised as a result of disease or its treatment [151–153]. The rationale for these recommendations is based on observations that influenza-associated mortality increases substantially in the seventh and eighth decades [154,155] and in the presence of serious coexisting medical complaints [155,156]. The aim of the annual vaccination programme in the UK is to encourage the vaccination of 'high-risk' patients by early November each year. The target population in England and Wales is estimated to be about 6 million people or 11.8% of the population as a whole [157]. Uptake in this group has been found to be less than 50%. The spread of influenza in hospitals and nursing homes may also be reduced if medical and nursing staff are vaccinated. This is not currently recommended as a routine measure in non-pandemic years in the UK, although it is in the USA [151].

Employers sometimes consider offering influenza vaccination to their employees with a view to reducing sickness absence rather than from more altruistic motives. Such action may not be justifiable on economic grounds since the number of cases prevented are likely to be small because (i) uptake of offered vaccination is often low, (ii) large epidemics are relatively infrequent and impossible to predict accurately, and (iii) the attack rate even in epidemics is only about 20% [158]. There is also a high prevalence of other non-influenzal respiratory illness at the same time of year that is also likely to result in absences from work.

Influenza vaccination may cause local reactions in up to 50% of recipients and 2% may experience low-grade febrile reactions in the first 24 h, although these are more common in young subjects than the elderly, in whom they occur with similar frequency in groups treated with placebo [159]. The mass influenza vaccination programme carried out in the USA in 1976 against swine influenza was associated with one case of Guillian–Barré syndrome per 100 000 cases inoculated and with one consequential death per 2 million recipients [160]. Such a fatality has not knowingly been associated with vaccines in later years. The vaccine is given by deep subcutaneous or intramuscular injection and should not be administered to subjects with a history of hypersensitivity to hens' eggs.

A live attenuated trivalent vaccine administered by nasal spray has recently been the subject of a clinical trial

in children in the USA [161], this type of vaccine having been previously used in the former Soviet Union. It contained the same influenza A and B virus strains used in that year's standard inactivated influenza vaccine and was found to be effective. Such a vaccine may prove useful for certain groups of children, such as those at high risk of developing otitis media, and also high-risk adults [162].

### **Pertussis (whooping cough)**

Pertussis or whooping cough is a clinical syndrome caused by the genus *Bordetella*, of which *B. pertussis* is the most common species. Infection with this minute coccobacillus results in the elaboration of local toxins that cause ciliostasis with inflammation and oedema of the tracheal and bronchial mucosa, which may lead to necrosis with sloughing of cells. Despite a worldwide vaccination programme, pertussis remains a serious global problem, particularly in developing countries. It has been estimated that 40 million cases of pertussis occurred worldwide in 1994 [163]. The illness is endemic in the UK and the USA, being highly infectious and occurring either in epidemic form in susceptible groups or sporadically in unimmunized populations [164]. It is spread by droplet infection and has a peak incidence in the later winter months and early spring. Public anxiety regarding possible neurological sequelae of vaccination led to epidemics in the UK in the late 1970s and 1980s [165], although uptake of vaccination is once again high in the UK. Whooping cough is highly communicable, affecting 70% of unvaccinated family contacts and 20% of those who have been vaccinated [166,167]. It produces only mild illness in infected adults and adolescents but these groups may be the source of potentially life-threatening illness in infants.

### **Clinical features**

The incubation period is 7–10 days, after which the patient, usually a young child, develops prodromal symptoms with a low-grade fever, malaise, profuse rhinorrhoea, sneezing and sometimes conjunctivitis. This so-called catarrhal stage lasts about 1 week and is indistinguishable from a variety of viral upper respiratory tract infections. A dry cough develops during the first few days of the illness. This progresses to distressing short bursts of paroxysmal coughing without an inspiratory pause between coughs, so that the patient may become almost apnoeic, cyanosed and often vomits. Each paroxysm may culminate in a long inspiratory effort through the partly closed glottis, a manoeuvre that produces the inspiratory stridulous 'whoop' from which this illness derives its name. The patient is most infective in the catarrhal stage, communicability falling off in the paroxysmal stage. Although the cough frequently starts to improve within 4 weeks of the onset of the illness, the paroxysmal stage may last 6–8 weeks and the cough may take several months to

clear completely. Whooping is unusual during this convalescent stage but it can recur as a result of other coincidental upper respiratory tract infection. The presence of a whoop is not a prerequisite for the diagnosis and may indeed be absent in many cases.

Whooping cough is most dangerous when it affects an infant in the first year of life, about three-quarters of all pertussis-associated deaths occurring in this age group [168]. In older children it causes an unpleasant illness but is rarely fatal in those aged over 5 years. Adolescents and adults may be infected, in which case the cough need not be paroxysmal or associated with a whoop and may be of shorter duration. Nevertheless these individuals serve to transmit infection in the community [169] and may experience an unpleasant cough for a prolonged period. The diagnosis of pertussis should therefore be a consideration in adults and teenagers with persistent cough. Persistent sore throat may be another feature [170].

### **Diagnosis**

The diagnosis is often based on the clinical history of a paroxysmal cough lasting for 2 weeks during a community outbreak [171,172]. There are various laboratory methods for detecting *B. pertussis*, its products or the patient's immunological response [173]. Microbiological confirmation is usually obtained using per-nasal calcium alginate (rather than cotton) swabs, which are positioned in the nasopharynx to induce a cough and then immediately plated on to Bordet–Gengou medium. Positive cultures may be obtained in only about 30% of cases [166], although these rates may be increased by repeated swabbing. Respiratory secretions may also be examined directly using a fluorescent antibody technique, thereby avoiding the 4-day wait inherent in the culture method, the organism being relatively slow-growing. However, false-negative results are still common. Unfortunately this and other newer techniques are not widely available and traditional culture methods do not lend themselves to use in general practice [174], although positive results from per-nasal nasopharyngeal swabs may be obtained up to 3 months from the onset of the illness when coughing persists [175]. It should be noted that positive cultures may sometimes be obtained from asymptomatic individuals. A raised white cell count (predominant lymphocytosis) is a common finding. The chest radiograph may show evidence of peribronchial thickening that overlies the cardiac contours and this need not indicate pneumonic change [176].

### **Treatment**

Children in their first year are at the highest risk and the disease at its most severe in the first 3 months of life, so that it is usual for infants below the age of 6 months to be admitted to a paediatric unit where appropriate

supportive care can be provided. Other categories of patient may be satisfactorily managed at home. Erythromycin has been shown to be active *in vitro* against *B. pertussis* [177]; although also active *in vivo* in the eradication of nasopharyngeal infection, it was initially not thought to alter the course of the illness once it had become well established [178]. More recent data have indicated that erythromycin does appear to reduce both the severity and duration of the disease even if started in the paroxysmal stage, so that it has become accepted practice to prescribe this drug for 14 days to infected cases [179]. Although the 2-week course was thought to be optimal in terms of eradicating infection with *B. pertussis*, this recommendation has not been based on prospective controlled studies and a recent trial showed no significant difference in failure rate (bacteriological persistence or relapse) between two groups treated with 7 and 14 days of erythromycin estolate respectively [180]. It is probable that a 7-day course of clarithromycin or a 5-day course of azithromycin is as effective [181].

There was similar doubt about whether erythromycin would be effective prophylaxis for family contacts, thereby helping to contain household transmission and wider outbreaks [182,183]. However, a more recent retrospective cohort study of 246 families has shown that the secondary attack rate was reduced from 25% in families without erythromycin prophylaxis to 17% in families in whom prophylaxis was used. When prophylaxis was used before the onset of a secondary case, it was found that the secondary attack rate was 4% compared with 35% when it was given after a secondary case [184]. It is current practice for antibiotic prophylaxis to be recommended for contacts of active cases and it is now generally accepted that this is an important factor in controlling outbreaks [185].

## Complications

The most common early complications are otitis media and pneumonia, both of which are caused by secondary bacterial infection that is treated with appropriate antibiotics. Occasionally the retention of sticky secretions may cause segmental or lobar collapse. Infants may convulse, though whether this is due to hypoxaemia or to some other cause is unknown. Paroxysmal coughing may cause epistaxes and conjunctival or petechial haemorrhages on

the face. Pneumomediastinum or rarely pneumothorax may occur. Before the availability of antibiotics, whooping cough was a major cause of mortality in children and still is in poor countries, death usually resulting from pneumonia due to secondary infection with other bacteria. Bronchiectasis was a serious long-term complication [186]; although this is now seldom the case in Europe and North America, nevertheless subjects with a past history of pertussis infection do have more respiratory symptoms than controls and may show minor impairments of measured lung function [187].

## Prophylaxis

The most effective form of prophylaxis is active immunization with pertussis vaccine. This is usually administered as a primary course of 'triple vaccine' (diphtheria, pertussis and tetanus), the first inoculation being given at 2 months and the second and third at 3 and 4 months [153]. Detailed guidance on immunization has been published by the Joint Committee on Vaccination and Immunization and the British National Formulary [153,188]. Convulsions and encephalopathy were considered to be rare complications but such reports may have been coincidental, no epidemiological link having been conclusively shown. Such problems, although of obvious concern, pose a much smaller risk to the population than the known mortality and complications arising from the development of pertussis infection in unvaccinated infants; indeed neurological complications after whooping cough itself are much more common than following the vaccine. However, immunization should not proceed when an earlier dose has caused a severe general reaction [153]. Where there has been a severe local reaction or pyrexia, acellular pertussis vaccine, which has a lower reactogenicity, may be substituted for later doses [153]. It is believed that neither pertussis immunization nor pertussis infection in childhood provide lifelong immunity from reinfection [189]. Since recent epidemiological studies have indicated that *B. pertussis* infections in adults are common and endemic, it has been suggested that an adult booster vaccination programme, using the newer acellular vaccines, might decrease the circulation of the organism in adults and that this might even lead to the elimination of the organism from populations [190].

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# PNEUMONIA

DOUGLAS SEATON

The first part of this chapter discusses general aspects of pneumonia and its management. The second part discusses specific microbiological types of pneumonia as well as radiation pneumonitis and lipoid pneumonia. Pneumonia in the immunocompromised patient is covered in Chapter 52. Fungal, actinomycotic and nocardial causes of pneumonia are dealt with in Chapter 21, parasitic causes in Chapter 22, tuberculosis and other mycobacterial causes in Chapters 16–20. Drug-related inflammation of the lung is described in Chapter 37. The reader is referred to Chapter 9 for further information on antimicrobial agents.

## Definition

When the word 'pneumonia' is used in medical practice, it almost always refers to a syndrome caused by acute infection, usually bacterial, characterized by clinical and/or radiographic signs of consolidation of a part or parts of one or both lungs. However, the use of the term has been greatly extended to include non-bacterial infection of the lungs caused by a wide variety of microorganisms (Tables 13.1 & 13.2). Pneumonitis is occasionally used as a synonym for pneumonia, particularly when inflammation of the lung has resulted from a non-infectious cause, such as chemical or radiation injury.

## Epidemiological factors

Pneumonia accounted for approximately 198 deaths per 100 000 per year in England and Wales in 1997, and was the commonest infectious cause of death both in this country and the USA, being the sixth leading cause of all deaths in the UK and the USA [1–3]. Records from the early part of the twentieth century show a steady decline in the reported mortality from pneumonia that antedated the arrival of antibiotics. At around 1950, and coinciding with the beginning of the antibiotic era, the mortality rate levelled off and remained fairly constant. This mortality rate is heavily weighted against the elderly, so that death

rates were 35 and 21 per 100 000 for men and women respectively aged 55–64 years compared with 775 and 572 per 100 000 for those aged 75–84 years [1]. This predilection of pneumonia for the elderly is not new and led William Osler in 1898 to describe the condition as 'the friend of the aged', allowing them a merciful release from 'those cold gradations of decay that make the last state of all so distressing' [4]. Whereas pneumonia in the elderly is frequently a terminal event in a patient disabled or dying as a result of some other incurable disease, this is clearly not usually the case in younger previously healthy patient groups, such as military recruits or students, in whom mortality is low. Because pneumonia is caused by a variety of microorganisms of widely differing behavioural characteristics and antibiotic sensitivities, it presents a considerable challenge to the clinician, whatever the age group and whether or not there are important comorbid conditions.

The true incidence of pneumonia acquired in the community is unknown and undoubtedly many pneumonic episodes are treated by primary-care physicians as 'lower respiratory tract infection' or 'bronchitis' without recourse to chest radiographs. Overall estimates of the annual incidence of community-acquired pneumonia vary between 2 and 12 cases per 1000, being highest in infants and in the elderly [5,6]. Estimates for the USA run to 4 million cases annually with an attack rate of 12 per 1000 adults, causing 600 000 hospital admissions per year at a cost of \$23 billion [3]. The annual incidence of community-acquired pneumonia in those aged over 65 years has been estimated to be between 25 and 44 cases per 1000, with a rate varying from two to eight times greater than this in subjects of similar age but living in institutions such as residential or nursing homes [7,8]. Elderly patients are also much more likely to acquire pneumonia in hospital than are those belonging to younger age groups [9]. The subject of pneumonia in the elderly has been well reviewed [10]. Pneumonia is the most common hospital-acquired infection accounting for death, occurring with an estimated frequency of 0.5–5% of admissions [11].

In the relatively few countries of the world fortunate



**Table 13.1** Bacterial and related pneumonias both common and rare.

More common	Less common/rare
Pneumococcal pneumonia <i>Streptococcus pneumoniae</i>	<i>Pasteurella multocida</i> <i>Streptococcus pyogenes</i> <i>Neisseria meningitidis</i>
Atypical pneumonia <i>Legionella</i> spp. (legionnaires') <i>Mycoplasma pneumoniae</i> * <i>Chlamydia</i> spp.* <i>Coxiella burnetii</i> (Q fever)†	<i>Brucella</i> spp. <i>Francisella tularensis</i> (tularemia) Rickettsial pneumonias <i>Salmonella</i> spp. Leptospiral pneumonia Listerial pneumonia <i>Pseudomonas pseudomallei</i> (melioidosis) <i>Pseudomonas mallei</i> (glanders) <i>Yersinia pestis</i> (pneumonic plague) <i>Bacillus anthracis</i> (inhalational anthrax) Actinomycotic and nocardial pneumonia (Chapter 21)
Staphylococcal pneumonia <i>Staphylococcus aureus</i>	
Gram-negative enteric pneumonia <i>Klebsiella</i> spp. <i>Pseudomonas aeruginosa</i> <i>Escherichia coli</i> <i>Enterobacter</i> spp. <i>Serratia</i> spp.	
<i>Haemophilus influenzae</i> pneumonia	
<i>Moraxella catarrhalis</i> pneumonia	
Anaerobic pneumonia (mixed flora) <i>Bacteroides</i> spp. <i>Fusobacterium</i> spp. <i>Peptococcus</i> spp. <i>Peptostreptococcus</i> spp.	
Mycobacterial pneumonia (Chapters 16–20) <i>Mycobacterium tuberculosis</i> , etc.	

\* Bacteria-like organisms } included for convenience  
† Rickettsia-like organism }

enough to be able to afford a high standard of medical care, pneumonia in children is a problem that is dwarfed when comparisons are drawn with poorer countries. About 15 million children worldwide die each year as a consequence of acute respiratory infections, one-third of them from pneumonia, and 96% of these deaths occur in developing countries [12,13]. The infant mortality rate from pneumonia and influenza in Paraguay was found to be 30 times that in the USA [14]. Although there may be large differences in the incidence of childhood pneumonia between communities in rich and poor countries [15,16], the huge differences in mortality rates alluded to are more

**Table 13.2** Non-bacterial pneumonia.

Viral pneumonia
Influenza
Measles
Adenoviruses
Varicella
Cytomegalovirus
Respiratory syncytial virus
Parainfluenza virus
Coronaviruses
Coxsackie virus
Rhinoviruses
Epstein-Barr virus
Herpes simplex virus
Hantavirus, etc.
Bacteria-like and rickettsia-like pneumonia (Table 13.1)
Fungal and actinomycotic pneumonia (Chapter 21)
Parasitic pneumonia (Chapter 22)
Chemical pneumonia, e.g. lipid
Physical pneumonia, e.g. ionizing radiation

likely to be explained by the lack of effective antimicrobial therapy and other supportive treatment [17,18].

Certain sections of the community, such as drug abusers, are susceptible to pneumonia. This may arise due to 'seeding' of the lung by staphylococci or other organisms from right-sided infective endocarditis [19], or as a result of the aspiration of oropharyngeal contents while in a stuporose state, which may result in a predominantly anaerobic or Gram-negative pneumonia (see Chapter 15 and Fig. 15.1).

The death rates from pneumonia may be influenced by seasonal factors, being greater in the cold winter months than in the summer. This difference is more evident in lower socioeconomic groups and is unaccounted for by influenza epidemics alone [20]. It is possible that greater overcrowding and poorer ventilation in cold weather may be factors enabling the spread of infection. In contrast, pneumonia due to *Legionella pneumophila* tends to occur more commonly in the warmer months.

As influenza epidemics (see Chapter 12) are associated with increased attack rates of pneumonia in adults, so respiratory syncytial virus (RSV) infection is complicated by pneumonia in infants and children, RSV infection tending to occur between November and February and influenza being mainly recorded between the end of December and March in the UK [21–26].

Population studies have shown that susceptibility to epidemics of pneumonia exists in communities where large numbers of individuals live in close contact with one another, for example gold miners in South Africa and long-house dwellers in Papua New Guinea. A study of an American Navajo Indian reserve showed an attack rate of 20 per 1000 inhabitants per year, of whom half required

hospital admission, these rates being highest in the very young and the elderly [27].

The largest decrease in incidence of pneumonia over the last 30 years has been in the infant population. The increased incidence in the elderly over the same period may be partly a consequence of the fact that two-thirds of all deaths now occur in hospitals compared with one-half 30 years ago and partly because hospital practitioners now certify the cause of death as ‘pneumonia’ more frequently than ‘heart failure’, as was their previous habit.

That knowledge of the method of coding disease has a crucial influence on the interpretation of available data is borne out by an apparent 55% reduction in the number of deaths from ‘bronchopneumonia’ and a 45% reduction in deaths classified as ‘pneumonia, unspecified’ in 1 year in the over-65 age group in England and Wales. This occurred when the Office of Population Censuses and Surveys issued new guidance to coders in 1984. Prior to that date the cause of death was always recorded from part 1 of the death certificate, whereas the new instruction, based on a World Health Organization rule, stated that where one of a range of conditions (including pneumonia) was the only cause of death mentioned in part 1 of the certificate, and a major disease was recorded in part 2, then the underlying *cause* of death should be taken from part 2 of the certificate [28].

Classification and terms in common usage

No categorization of pneumonia is entirely satisfactory (Table 13.3) but for descriptive purposes the classification should be both anatomical (the terms used communicate the extent and distribution of the process in the lung or lungs) and causal (the responsible microorganism is named). When, as is often the case, the infecting organism is not known it is useful in a predictive sense to consider

whether the pneumonia is community-acquired or hospital-acquired (nosocomial). It is also useful to consider whether the pneumonia may have resulted from overt pharyngeal aspiration and whether it is occurring in an immunocompetent or immunocompromised host. Finally, the workaday respiratory physician will recognize two sorts of pneumonia: that which is easy and responds to initial treatment and that which is difficult and fails to respond so that further investigation is required.

The anatomical terms used indicate whether the pneumonia involves one or more entire lobes or whether the process is confined to a segment or segments. In its most confined form, pneumonia may be subsegmental. Such anatomical descriptions are in life entirely dependent upon the chest radiographic appearances, which show the extent of pneumonia more accurately than can be gauged by physical examination. Early clinicians distinguished between bronchopneumonia and lobar pneumonia in pathological terms. Bronchopneumonia was regarded as a complication of bronchitis in which the patchy inflammatory process was confined to the territory of small or terminal bronchi and the lung lobules subtended by them, hence the alternative term ‘lobular pneumonia’. Lobar pneumonia, on the other hand, frequently occurred *de novo* in a previously healthy lung and was characterized by an inflammatory outpouring or exudation of fluid extending throughout most of a lobe or lobes [29].

It is commonplace for the term ‘lobar pneumonia’ to be used when there is clinical and radiographic evidence of confluent consolidation occupying the greater part of one or more lobes of one or both lungs. The term ‘segmental pneumonia’ is used when such consolidation is not extensive enough to occupy most of a lobe but corresponds more closely to the anatomy of a bronchopulmonary segment in one or more lobes. Where the area of radiographic shadowing is even more confined, then ‘subsegmental pneumonia’ is an appropriate descriptive term, although this still implies a confluent and localized process. Where subsegmental shadowing is patchy (non-confluent) and poorly localized, being scattered throughout part or the whole of one or both lungs, the term ‘bronchopneumonia’ remains entirely acceptable. Bronchopneumonia therefore tends to be multifocal and the pathologist commonly finds it to be bilateral and often basal [30].

This anatomical classification is complementary but subservient to a causal classification and is of only limited value in establishing the likely infective agent, for although lobar pneumonia is usually caused by *Streptococcus pneumoniae*, it can be caused by many other microorganisms besides, as indeed can all other anatomical types. Reasonable efforts should therefore be made to establish the identity of the pathogenic organism responsible for pneumonia in each patient in order that specific antimicrobial therapy can be directed against it, for without this

Table 13.3 Classifications of pneumonia.

Morbid anatomist’s classification
Lobar pneumonia
Segmental pneumonia
Subsegmental pneumonia
Bronchopneumonia
Microbiologist’s classification
See Tables 13.1 and 13.2
Empiricist’s classification
Community-acquired pneumonia
Hospital-acquired (nosocomial) pneumonia
Aspiration pneumonia
Immunocompromised host pneumonia
Behaviourist’s classification
Easy pneumonia (responds to initial treatment)
Difficult pneumonia (fails to do so)

information some patients do not recover who otherwise would have done so.

The causal organism can only be guessed at when the patient is first seen and it is useful in this respect to classify the case as one of either community-acquired or hospital-acquired (nosocomial) pneumonia. These two groups are *not* mutually exclusive for particular pathogens but the spectrum of infecting organisms in the two groups does vary, partly because the hospital population has selected disproportionate numbers of elderly patients and those whose bacterial flora has been modified as a result of their stay as well as those whose immune defences are compromised by severe underlying disease or suppressed by drugs. Nosocomial pneumonia is a particular problem in postoperative patients and in those treated in intensive care units, the latter group being highly susceptible to lower respiratory tract infection [31–33]. The different lung pathogens found in hospitals result from the alteration in bacterial flora caused by the use of antibiotics and also often from the instrumentation or intubation of the upper airways of patients, which provides the organisms with easy access to the lungs. Such hospital-acquired infections are more frequently due to aerobic Gram-negative bacilli and *Staphylococcus aureus* (increasingly methicillin resistant) compared with those acquired in the community [34–36]. It is not uncommon for multiple organisms to be simultaneously involved in a single patient in intensive care units.

## Pathogenesis

Pneumonia is predisposed by any condition that (i) reduces or suppresses the cough, (ii) impairs mucociliary activity, (iii) reduces the effective phagocytic activity of alveolar macrophages and neutrophils, and (iv) impairs immunoglobulin production. Potential pathogens reach the lung to cause pneumonia chiefly by microaspiration of secretions containing oropharyngeal flora [37], but also by overt aspiration, by inhalation from the environment, from a nebulizer or anaesthetic circuit and by blood spread. Colonial organisms in an already diseased lower respiratory tract may also spread directly to cause pneumonia in previously unaffected lung; sometimes pathogens may spread directly from an adjacent extrapulmonary site of infection, such as the mediastinum, spine, chest wall or abdominal cavity.

## Aspiration and microaspiration

Aspiration of small amounts of oropharyngeal contents is known to occur in healthy people during sleep [38]. This tendency is increased by states in which the ability to cough is depressed or otherwise impaired (see Chapter 15), such as following surgery, general anaesthesia, tracheostomy, or the passage of an endotracheal or nasogas-

tric tube [39–42]. The intrinsic defences of the lungs may be unable to cope with the inoculum if it contains particularly pathogenic organisms or if there are sufficiently large numbers of less pathogenic organisms. Favourable conditions for infection may also be provided by chemical injury to the lungs resulting from overt gastric acid aspiration or by pulmonary oedema, and alcoholism is an important predisposing factor [43].

Many of the organisms that cause lower respiratory tract infections may exist commensally in the oropharynx. These include *Strep. pneumoniae*, *Haemophilus influenzae*, *Staph. aureus* and anaerobic bacteria, to name but a few. The oropharyngeal flora in hospital patients is often altered, with the presence of Gram-negative bacilli; hence the increased incidence of pneumonia caused by these organisms in such patients. Elderly patients in the community also tend to harbour a higher proportion of Gram-negative organisms in the oropharynx, so that this type of pneumonia tends to be more common in old patients both in and out of hospital [44,45]. It is also possible that mucosal ageing increases the ability of Gram-negative bacteria to attack the epithelial surface [46].

## Inhalation

The inhalation of microbes contained in small particle aerosols is thought to be important in the transmission of viral infections and also in *Legionella* pneumonia. The inhalation of infected particles from animals may be responsible for psittacosis and *Coxiella* pneumonia (Q fever). Oropharyngeal colonization followed by microaspiration is probably more important in other bacterial pneumonias, whereas patient-to-patient spread may occur by both direct contact (via fomites) and droplet spread. Pathogens may also be introduced to the lower respiratory tract by contaminated nebulizer circuits or other respiratory equipment, this route being avoidable by proper preventive measures [47,48].

## Colonization

The lower respiratory tracts of patients with pre-existing lung diseases, such as chronic bronchitis, emphysema, bronchiectasis and cystic fibrosis, may become colonized by potentially pathogenic organisms, which may cause acute exacerbations of infection, including pneumonic consolidation, from time to time [49].

## Blood spread

Occasionally, pneumonia may result from the haematogenous spread of bacteria from a focus of infection elsewhere. This may occur with Gram-negative and staphylococcal bacteraemia [50–52]. Patients with intravenous cannulae, temporary pacing wires and those

receiving chronic haemodialysis are particularly susceptible [53].

Investigation

Laboratory identification of infecting organisms

Laboratory investigation of a case of pneumonia should not delay treatment with antibiotics, the choice of which is based on a knowledge of the likely pathogens and an estimation of the severity of the infection (see p. 365). The lengths to which the clinician is prepared to investigate the microbiological cause of a case of pneumonia is likely to be determined by the severity of the illness at presentation (Table 13.4), its response to initial treatment and the laboratory facilities available. There are many investigational possibilities but a practical approach for community-acquired pneumonia is illustrated in Fig. 13.1.

Sputum microscopy

Laboratory examination of expectorated sputum remains the most commonly requested microbiological investigation in suspected lower respiratory tract infections. It remains useful, provided that samples are properly collected and promptly examined. Specimens that are clearly salivary should be discarded at the bedside to save labora-

tory time. Mucopurulent sputum is characteristic of bacterial pneumonias and bronchitis, but may also be found in viral pneumonia [55]. The adequacy of an expectorated sample may be judged microscopically in terms of the

Table 13.4 Markers of severity in pneumonia at initial assessment.

Altered mental state/confusion*
Tachypnoea $\geq 30$ breaths/min*
Hypotension, systolic $\leq 90$ mmHg, diastolic $\leq 60$ mmHg or need for vasopressors*
Arterial hypoxaemia $P_{aO_2} \leq 8$ kPa (60 mmHg) or $P_{aO_2} : F_{IO_2}$ ratio $\leq 33$ kPa (250 mmHg) on oxygen or need for $> 35\%$ $F_{IO_2}$ to keep $S_{aO_2} > 90\%$
Arterial hypercarbia $P_{aCO_2} > 6.5$ kPa (50 mmHg) or consideration of the need for mechanical ventilation
Chest radiograph shows more than one lobe involved or rapid progression
Evidence of renal insufficiency serum urea $\geq 7$ mmol/L* low urine output $< 20$ mL/h
Need for admission to intensive care unit

The risk of death has been found to increase over 20-fold when two or more of the features marked with an asterisk are present in the same patient (see text).

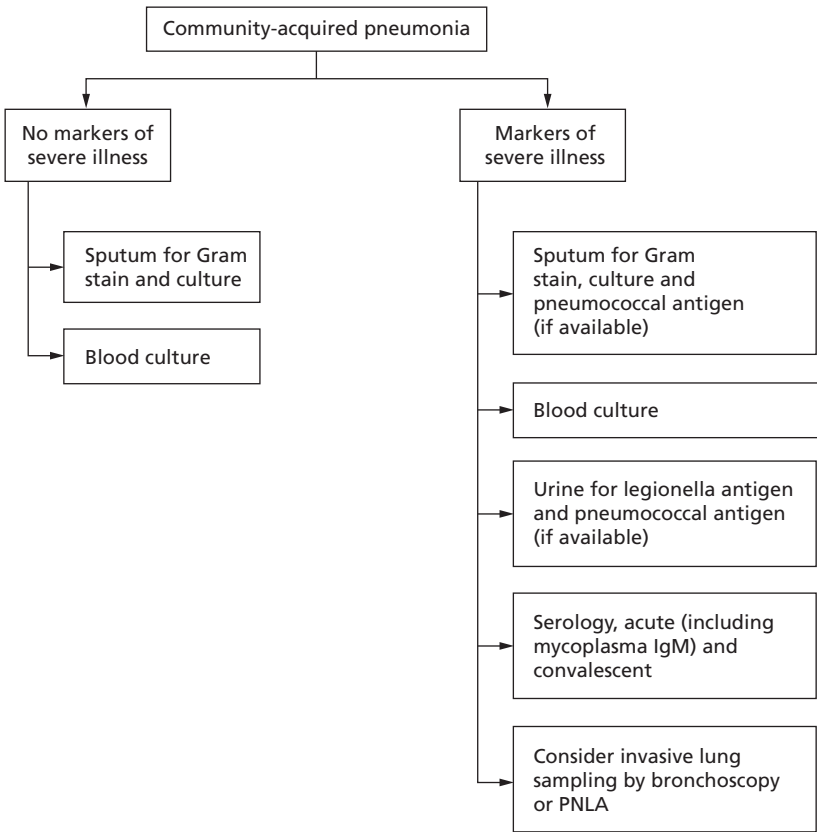


Fig. 13.1 Microbiological investigation of the patient admitted to hospital with community-acquired pneumonia (see text). PNLA, percutaneous ultra-thin needle lung aspiration (for those experienced with this technique). (After Finch & Woodhead [54].)

number of buccal epithelial cells present. Thus if 10 or more buccal squamous epithelial cells are noted per low-power ( $\times 100$ ) field, the specimen is likely to be salivary and unsuitable for culture [56]. Conversely, more than 25 neutrophils per low-power field indicate the presence of inflammation, although this may not apply to immunosuppressed patients. Similarly, a leucocyte to squamous epithelial cell ratio of greater than 5 may also be taken to indicate an adequate sputum sample rather than a salivary one.

Gram's stain may be helpful in identifying the cause when large numbers of one predominant type of organism are found in association with evidence of inflammation [57]. Less clear evidence of infection than the foregoing has to be interpreted cautiously since commensal organisms are likely to be picked up by sputum as it passes through the oropharynx [58]. Thus Gram-positive lancet-shaped diplococci suggest *Strep. pneumoniae*, Gram-positive cocci in clusters may be seen in *Staph. aureus* pneumonia, tiny Gram-negative coccobacilli suggest *H. influenzae*, numerous intracellular Gram-negative diplococci imply *Moraxella (Branhamella) catarrhalis* infection and larger Gram-negative bacilli suggest *Klebsiella pneumoniae* or other enteric pathogens. However, it should be noted that large numbers of Gram-negative bacilli have been found in sputum samples of patients on intensive care units without evidence of infection [59]. The absence of large numbers of organisms in an adequate sputum sample raises the possibility of *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Coxiella burnetii* or a viral pneumonia. The application of routine Gram staining to sputum is an area of controversy, some experienced clinicians using it, others not [3,60].

The possibility of tuberculosis should never be forgotten and an acid-fast smear using either carbolfuchsin (Ziehl-Nielsen) or fluorochrome (auramine) should be requested when the chest radiographic appearances are compatible. False positives are rare and the smear provides early evidence of tuberculosis in about 50% of cases that are subsequently confirmed with positive cultures; positive smears are much more common when the radiographic changes are extensive and typical of active tuberculous infection [61]. Sputum may be induced with hypertonic saline in patients with suspected tuberculosis who are unable to raise secretions spontaneously; 20 mL of 2.7–5% saline is nebulized at a high flow rate and delivered by mask to the nose-breathing patient by a physiotherapist or other trained person, who then obtains the specimen and shepherds it to the laboratory in order to avoid more invasive procedures such as bronchoscopy.

Pathogenic fungi that may affect immunocompetent subjects (*Coccidioides immitis*, *Cryptococcus neoformans* and *Blastomyces dermatitidis*) can be detected under the microscope unstained on so-called potassium hydroxide 'wet-mount' preparations, as can *Aspergillus* spp. *Candida*

spp. are easily identifiable on a Gram stain, other fungi requiring specialized stains such as the Grocott-Gomori methenamine silver method. This last stain is also used to find the cysts of *Pneumocystis carinii*, being the most valuable *Pneumocystis* 'search stain', whereas the trophozoites require Giemsa or the quicker modified Wright-Giemsa (or 'Diff Quik') stains that may show them as minute dots in the alveolar spaces.

### Sputum immunodetection

Other tests sometimes applied to sputum include pneumococcal antigen detection (see below) by one of a number of possible methods, including latex agglutination, counterimmunoelectrophoresis (CIE), coagglutination or the Quellung reaction (p. 380) [62,63]. *Legionella pneumophila* is one of a number of organisms that may be detected rapidly in respiratory secretions by the direct immunofluorescent antibody test (DFAT). The specificity of this test for this organism is about 94% but the sensitivity is low at 50% [64]. Specific fluorescein-labelled monoclonal antibodies using the DFAT technique may also be used to detect *Chlamydia pneumoniae* in sputum and also *Pneumocystis carinii* in bronchoalveolar lavage fluid or induced sputum. An advantage of these tests is that their sensitivity is not reduced by the prior use of antibiotics.

### Sputum culture

The usefulness of standard sputum culture is limited by the delay, usually at least 24 h, between submission the specimen and receipt of a result. Culture also suffers from the same potential problem of contamination by oropharyngeal flora as does microscopy [65]. Furthermore, pathogens that were identified on the Gram stain may not grow in culture because of the prior use of antibiotics, which clearly reduces the sensitivity of culture techniques [66]. Where sputum samples have been found to be microscopically adequate (i.e.  $<10$  epithelial cells and  $>25$  neutrophils per low-power field), comparability with the positive yield obtained from transtracheal aspiration (see below and Chapter 8) has been claimed [56]. The sensitivity of sputum culture for pneumococci is about 50% [66].

The finding of *Escherichia coli* or *Proteus* spp., often reported as 'coliforms', usually implies an altered oropharyngeal flora as a result of antibiotic usage. *Klebsiella aerogenes* may be cultured for the same reason and is not a cause for concern; however, when the report is less specific, stating only '*Klebsiella* spp.' and if the patient is unwell, the laboratory should be asked to carry out further speciation so that pathogenic *Klebsiella pneumoniae* (the cause of Friedländer's pneumonia) or *Klebsiella ozaenae* (which may colonize areas of bronchiectasis) are not overlooked. *Pseudomonas aeruginosa* and *H. influenzae* may similarly colonize such lungs.

*Legionella* spp. may be cultured on a selective charcoal yeast extract medium if the patient is sufficiently ill to cause anxiety or if there are other grounds to suspect this organism. A result is relatively slow, taking about 3 days, and in the mean time further information may be forthcoming from DFAT on sputum, as mentioned above. Although culture of *Legionella* spp. is slower, it is more sensitive than DFAT and species other than *L. pneumophila* may be grown.

Fungal culture is not technically difficult and may be appropriate in certain clinical settings. The request for this is best made to the microbiologist in order to ensure that suitable media and incubation temperatures are used. The isolation of yeasts is common and usually results from oropharyngeal colonization, candidal pneumonia being an unusual accompaniment of severe immune compromise.

The microscopic and culture findings in sputum obtained by suction devices from patients who have an endotracheal or tracheostomy tube *in situ* are less reliable because the trachea rapidly becomes colonized by Gram-negative organisms once the tube has been placed and these organisms need not be representative of infection in the lung itself. Precautions have been described to reduce the contamination of such samples and, more recently, quantitative culture techniques have been developed as outlined in the next section [67].

#### Invasive methods for obtaining respiratory secretions

Other methods for obtaining respiratory secretions are more invasive and may be associated with morbidity. Their use is therefore confined to patients who are severely ill and in whom it is considered important to identify the organisms rather than relying on an initial empirical antimicrobial approach or in whom such an approach has already been tried and failed. Any specimens so obtained should be submitted for microscopy (e.g. Gram and Giemsa stains to detect intracellular and extracellular organisms in the lower respiratory tract) and culture, as well as for the immunological and other tests mentioned in these sections, depending upon local availability. It has been shown that these severe infections may be polymicrobial and that the mortality is almost doubled in such cases [68].

Transtacheal aspiration may be carried out in patients who are unable to raise sputum or in whom the response to the chosen antibiotics is poor. This technique has been discussed in detail in Chapter 8 but is now rarely used. The success of the procedure relies on the assumption that the tracheobronchial tree below the larynx is sterile, but false-positive results occur in patients with chronic lung disease because of tracheobronchial colonization [69]. The technique has also been applied when anaerobic lung infection is suspected.

Fibreoptic bronchoscopy (see Chapter 8) picks up oropharyngeal contaminants unless special precautions are taken using a protected specimen brush (PSB). The preservative in the local anaesthetic may also have a significant antibacterial effect [70,71]. The PSB may be combined with, or used separately from, bronchoalveolar lavage (BAL) to obtain quantitative cultures in order to discriminate between the presence and absence of pneumonia, usually on ventilated patients in an intensive care setting [72,73]. The diagnostic threshold for pneumonia, rather than airway colonization, has been reported as  $10^3$  cfu/mL (colony forming units per millilitre) in respiratory secretions obtained by PSB, which yields only 0.01–0.001 mL of material. On the other hand, BAL subtends a wide area of tissue and lung secretions are diluted between 10 and 100-fold, so that when interpreting results a threshold of  $10^4$  or  $10^5$  cfu/mL may be taken [74,75]. By combining PSB and BAL and by counting intracellular organisms, Chastre and colleagues [74] claimed a sensitivity of 100% (compared with 86% for either technique alone) and a specificity of 96%. Bronchoscopy can therefore provide clues in the difficult case when other methods have failed, even when the picture has been clouded by the almost inevitable prior use of antimicrobials. Infection with less usual organisms, such as *Legionella* spp., *Mycobacterium tuberculosis*, *Pneumocystis carinii*, other fungi or anaerobes, may also be detected in such cases as well as the occasional unsuspected predisposing cause like the mechanical narrowing of a bronchus [76,77]. On the other hand, negative results have to be treated with caution in patients already receiving antimicrobial therapy, since they may indicate either that the antibiotics were appropriate and that the organisms have been suppressed or that there was no infection there in the first place and that the infiltrate was due to a non-infective cause, as may be so in over 40% of cases [78].

Percutaneous ultra-thin needle lung aspiration without fluoroscopic guidance has obtained a positive culture rate of about 60% in non-ventilated patients with hospital-acquired pneumonia in one recent study [79]. A previous positive microbiological diagnosis had been made non-invasively in less than 10% of these patients and the investigation resulted in a change in antimicrobial therapy in 30% of cases, being complicated by shallow pneumothoraces in 3% of patients [79]. Higher complication rates and lower yields have been reported in earlier studies [80,81]. The success rate of ultra-thin needle aspiration is dependent upon the experience of the operator, the size of the infiltrate and its proximity to the pleura. It is reduced by prior antimicrobial therapy but enhanced if a pneumococcal antigen-detecting technique is applied to the aspirate [82,83]. The technique uses a 25-gauge needle and is discussed in Chapter 8.

These invasive techniques have mainly been used in research settings and their wider clinical role remains

undecided and somewhat controversial. The bronchoscopic option in immunocompetent patients may be appropriate once they have reached the stage of intubation and mechanical ventilation. A simpler option in the intubated and ventilated patient is the quantitative culture of endotracheal aspirates. When a threshold of  $10^6$  cfu/mL is used, this technique has been found to have a sensitivity of 68% and a specificity of 84% [84]. This will miss one-third of cases with pneumonia and compares less favourably with PSB and BAL either separately or together but is nevertheless an option if bronchoscopy is not readily available. A further quantitative culture technique that has been developed uses a protected telescoping catheter and has produced results approaching those obtained with the bronchoscopic methods [85,86].

Transbronchial, thoracoscopic or open lung biopsies tend to be reserved for diffuse pulmonary infiltrates of undetermined cause and, in the context of suspected infection, are occasionally carried out in sick immunocompromised hosts including transplant recipients, those receiving chemotherapy for lymphoma and in patients with AIDS, in whom the presence of an unusual opportunist pathogen is likely and in whom less invasive diagnostic approaches like BAL have failed to identify the cause (see Chapter 52) [87–92].

### Blood culture

It is normal practice to carry out blood culture on all patients admitted to hospital with suspected pneumonia since a positive culture may occur in 10–30% of cases, the higher percentage applying to pneumococcal pneumonia. This provides definitive proof (i.e. high specificity) of a pathogenic organism, often lacking where sputum culture and other tests are concerned, and is also of prognostic importance because bacteraemia is a marker of a more severe infection. However, a recent retrospective study of 517 immunocompetent patients with community-acquired pneumonia found positive blood cultures in only 6.6%, with an antibiotic change based on the culture occurring in only 1.4% [93]. The implication of this is that appropriate antimicrobial therapy will be initiated on empirical grounds in nearly all cases before the results of blood cultures are available.

### Pneumococcal antigen detection

Pneumococcal antigen detection using latex agglutination (sputum, blood) or, less commonly, CIE (sputum, urine, blood) is carried out routinely in some centres but is impractical for all patients, being usually reserved for those who are severely ill. CIE depends upon the migration of pneumococcal antigen and of antibody from two wells cut in an agarose-coated slide when an electric field is placed across it. Where the two meet they react and form

a precipitin line. Pneumococcal antigen detection may produce a result within 1 h. It has been found to be less sensitive when applied to blood (<25%) than urine (about 40%), being most sensitive when used on mucopurulent sputum (about 80%) [94,95]. This compares with a sensitivity of about 50% when the Gram stain is applied to sputum for the same purpose. The investigation can also be applied to pleural fluid and to lung secretions obtained invasively (ultra-thin needle aspiration and BAL), so that the sensitivity of these tests may be increased [96–98]. The specificity of sputum pneumococcal antigen for detecting cases of pneumococcal pneumonia is reduced to about 70% because *Strep. pneumoniae* is often isolated from the sputum of patients with chronic bronchitis who do not have pneumonia. A positive sputum pneumococcal antigen test may also not differentiate between oropharyngeal colonization and pulmonary infection; furthermore some capsular antigens are difficult to detect by these methods. Pneumococcal antigen testing has been useful in research to establish the relative frequencies with which different organisms are found in population studies of pneumonia, since its sensitivity is not reduced by the prior use of antibiotics, but it has not established itself as a routine test in most general hospital laboratories. It has the advantage of providing rapid information and might be usefully applied in the sicker patient in whom routine cultures are likely to have been suppressed by previous treatment with a broad-spectrum antibiotic. Pneumococcal antigen may be detected in the serum or urine of 50% of patients with pneumococcal pneumonia who are non-bacteraemic in terms of negative blood cultures. The antigen remains detectable for 7–14 days after bacteraemic pneumococcal pneumonia.

### Standard acute and convalescent serological testing

The usual serological tests involve the measurement of complement-fixing antibody levels in the blood, although more sensitive enzyme-linked immunosorbent assay (ELISA) and immunofluorescent tests are tending to replace them. Serological tests may be used for infections caused by *Mycoplasma pneumoniae*, *Chlamydia* spp., *Coxiella burnetii* and *Legionella* spp. By its nature, the complement fixation test (CFT) is seldom of immediate value and when positive usually provides diagnostic information retrospectively, as two paired samples are required in order to demonstrate a fourfold rise or fall in the titre of specific antibodies. It is usual to wait about 14 days between the two samples, although in some infections, such as *Mycoplasma*, a rise may be detected earlier; in others, notably *Legionella*, the rise may take several weeks. A single titre greater than 256 is suggestive of infection and if information on an unpaired sample is needed, the laboratory should be informed to discourage them from storing it until the second sample materializes. The problem with



paired sampling is that the results are likely to come too late to be of clinical relevance. For *Mycoplasma pneumoniae*, both IgG and specific IgM titres may be measured by ELISA. High IgG titres may persist for over a year but a raised titre of *Mycoplasma*-specific IgM is consistent with acute infection and is said to be positive in about 70% of patients admitted to hospital with this infection [99]. When *Mycoplasma* is suspected, cold agglutinins should be looked for and are present in over 50% of cases; this may be easily done on the ward by cooling a tube of the patient's citrated blood to about 4°C in a refrigerator (see p. 394). For *Legionella* both the rapid microagglutination test (RMAT) and indirect immunofluorescent antibody test (IFAT) are widely available (see section on *Legionella* pneumonia).

### Newer microbiological technologies

The tantalizing promise of new methods for the rapid detection and identification of specific organisms using molecular genetic techniques seems close to being fulfilled but for most laboratories and clinicians has yet to be delivered, largely because of financial constraints. DNA probes have been developed for characterizing target organisms and minute amounts of target DNA can be amplified by the polymerase chain reaction (PCR) to improve the chance of their detection by the DNA probe so that the sensitivity of the test is increased. A PCR assay has recently been tested on the serum of patients with bacteraemic pneumococcal pneumonia and was found to have a sensitivity of 100% and a specificity of 94% [100]. Similar probes have been, or are being, developed for a wide range of organisms including *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Neisseria meningitidis*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Mycobacterium tuberculosis*, *Mycobacterium avium* complex and *Mycobacterium kansasii* [101]. Thus the identification of a mycobacterial infection may take hours rather than weeks, although the organism still requires culture in order to allow antimicrobial sensitivities to be confirmed.

### Pleural fluid

If a pleural effusion is present in a patient suspected of having pneumonia, it should always be examined to exclude an empyema (see Chapter 14). Gram and acid-fast stains may be useful. The culture of pathogenic organisms, assuming a clean technique, is always significant and valuable. When the diagnosis of pneumonia is in doubt, a pleural biopsy should be carried out as described in Chapter 8. Pleural biopsy is also routine if a tuberculous effusion is suspected, one specimen being submitted unfixed for culture and the remainder being sent for histology in the usual way. Tuberculous pleural effusions are predominantly lymphocytic, whereas the finding of a predominance of neutrophil leucocytes is suggestive of non-

tuberculous bacterial infection, the protein content being that of an exudate in both cases (see Chapter 43). Some biochemical findings (low pH, high lactate dehydrogenase, low glucose) have been used to predict which parapneumonic effusions may be likely to develop into empyemas (see Chapter 14) [102].

### Chest radiography

An abnormal chest radiograph is a *sine qua non* in pneumonia, providing an immediate visual impression of the extent of involvement. The clinician can, at best, make an informed guess about the likely microbiological cause of pneumonia on the basis of the radiographic findings but as so much overlap occurs between one organism and another, this approach is often inaccurate. It is emphasized that almost every causative agent can produce a wide variety of different radiographic appearances, so that it is unwise to assume that a confluent lobar pneumonia is bound to be caused by *Strep. pneumoniae* despite the probability that this is the case. Similarly, cavitation need not be due to *Staph. aureus* pneumonia but may occur in necrotizing Gram-negative pneumonias, such as those caused by *Klebsiella pneumoniae*, or pneumonia arising from the aspiration of anaerobic bacteria or even from infection with *Strep. pneumoniae* when serotype 3 is involved.

Radiographic response to treatment usually lags well behind clinical improvement and pneumococcal pneumonia may take 6 weeks to clear on the chest film [103]. Persistent, recurrent or worsening shadowing may indicate either inappropriate treatment or bronchial obstruction by a foreign body or, more commonly, tumour particularly in patients over the age of 60 years [104].

### Arterial oxygen saturation and blood gas analysis

Oxygen saturation as a screen followed by arterial blood gas analysis when desaturation is evident should be carried out in order that hypoxaemia may be corrected and to help gauge the severity of the infection. The need for an inspired oxygen of 35% or more to maintain the oxygen saturation above 90% implies severe pneumonia; so does a  $P_{aO_2}$  of 8 kPa (60 mmHg) or less or a  $P_{aCO_2}$  of 6.5 kPa (50 mmHg) or more. These findings warn that assisted ventilation may become necessary.

### Other laboratory findings

The white cell count is frequently raised in bacterial pneumonia, with a neutrophilia. Elderly patients are not always able to mount such a response. Sometimes when sepsis is overwhelming there may be a leucopenia. A lymphocytosis may occur in viral infections or in those due to 'atypical' organisms, such as *Chlamydia*, *Coxiella* or

*Mycoplasma*. The white count may be normal in viral pneumonia. The detection of cold agglutinins is discussed under standard serological testing (above) and under the later section on *Mycoplasma pneumoniae* (p. 394).

Numerous non-specific biochemical abnormalities have been noted, such as a raised blood urea, bilirubin, transaminases and alkaline phosphatase. Hypophosphataemia may also occur [105]. Hyponatraemia due to inappropriate antidiuretic hormone (ADH) secretion may occur in any pneumonia and is notably more common in *Legionella* infection.

Urinalysis may detect small amounts of protein and both red and white blood cells may be seen on microscopy in pneumonia. These findings are of no discriminatory value and may occur in any systemic infection. As mentioned above, pneumococcal antigen may be detected in urine more frequently than in blood but less frequently than in sputum. *Legionella* antigen may also be detected in urine by ELISA, indicating *L. pneumophila* type 1 infection (thought to account for about 80% of human legionellosis), and this test is well worth doing for a rapid answer in severely unwell patients with pneumonia.

## Antimicrobial treatment

A provisional diagnosis of pneumonia is generally based on the history of an acute febrile illness associated with a cough usually productive of mucopurulent sputum, physical findings suggestive of consolidation and consistent chest radiographic appearances. More often than not in general hospital practice some or most of the classical features of pneumonic consolidation are not elicited by the resident medical staff, who initiate treatment on the basis of probable 'lower respiratory tract infection'. Frequently a patient has received an antibiotic prior to hospital admission and this may make microbiological identification of the infecting agents more difficult, as alluded to above; nevertheless blood cultures should be taken routinely and sputum obtained expeditiously if it is readily available (Fig. 13.1) before commencing or continuing antibiotic treatment on what is perforce empirical grounds, at least initially. However, antibiotics should *not* be delayed if a sputum specimen cannot be immediately obtained. Such empirical treatment is acceptable and entirely necessary and has been enshrined by the production of so-called 'guidelines', which are simply statements of what the authors were prepared to sign up to as good clinical practice for the population they were considering at the time of writing [106–111]. Empirical therapy of this sort is not without problems, being based on epidemiological data or large case series, so that recommended regimens may apply to one population but not another. Furthermore, a mechanism for regular review should ideally be in place to take account of changing patterns of disease, such as the reduced susceptibility of common

organisms to standard antibiotics (e.g.  $\beta$ -lactamase producers), the increasing incidence of certain organisms in susceptible sections of the population (e.g. *Pneumocystis carinii* pneumonia in human immunodeficiency virus, HIV, infection) and the emergence of 'new' or previously unrecognized organisms (e.g. *Legionella* in the 1970s and more recently *Chlamydia pneumoniae*). Guidelines should not be taken as entirely prescriptive and it is up to the responsible clinician to be prepared to deviate should the circumstances of the individual case require this.

## Outpatient treatment

Milder cases of pneumonia may be managed out of hospital; in the UK, many patients are treated by their family practitioner for 'lower respiratory tract infection' and respond without even coming to chest radiography. Most cases (85–90% in the UK), particularly in younger ( $\leq 60$  years) and previously healthy patients, are due to pneumococcal infection [112] and respond well in most geographical locations to an aminopenicillin such as amoxicillin (amoxycillin) 250–500mg three times daily, which is cheap, well tolerated and a reasonable first choice for oral therapy in subjects not known to be allergic to penicillin. Those who do not respond and who are still not ill enough to require admission require a change in tactics. They may have *Mycoplasma pneumoniae* infection (see p. 392), particularly in epidemic years, in which case they respond if their treatment is switched to a macrolide such as erythromycin, this class of drug also containing the antibiotics of first choice in penicillin-allergic patients. The knowledge that erythromycin is also usually effective against the pneumococcus led the authors of the American and Canadian guidelines to recommend its use as the first-line antimicrobial in this category of patient [60,113]. However, some pneumococci (approximately 9% in the UK) are resistant to erythromycin [114,115]; also since these initial guidelines were written, newer (and more costly) macrolides have become available, clarithromycin 250mg twice daily being as effective as erythromycin 500mg four times daily as well as causing less nausea, with the likelihood of better outpatient compliance [116]. Azithromycin has a half-life of over 40h, allowing once-daily dosage, and has been recommended as a 3-day course for infective bronchitis and is apparently also effective in pneumonia [117]. It is concentrated very well intracellularly, with low blood levels, so that there are some theoretical reservations about its effectiveness in potentially bacteraemic pneumococcal infection [118,119]. When considering whether to cover for atypical pathogens such as *Mycoplasma*, *Chlamydia*, *Coxiella* and *Legionella* in non-severe pneumonia, it should be borne in mind that a large meta-analysis covering over 33000 patients found such atypicals to account for only 2.9% of infections [120].

Those patients who fail to respond to amoxicillin or a macrolide are frequently older and often have coexisting lung disease, such as chronic bronchitis and emphysema. The resistant pathogens in such patients are not infrequently  $\beta$ -lactamase-producing *H. influenzae* or *Moraxella catarrhalis*. Resistance rates for *H. influenzae* against ampicillin/amoxicillin in the UK are around 5% of isolates, although levels of over 15% have been recorded in certain districts, with higher rates in the USA [121], so that it is essential to be informed about the sensitivity patterns in one's own locality. *H. influenzae* is also commonly resistant to erythromycin, although less so to the newer macrolides such as clarithromycin. These resistant cases can often be treated successfully with an orally administered  $\beta$ -lactam-stable antibiotic, such as an aminopenicillin, combined with a  $\beta$ -lactamase inhibitor, e.g. amoxicillin/clavulanate (co-amoxiclav) or ampicillin/sulbactam (in the USA). Alternative oral  $\beta$ -lactam-stable antibiotics that may be used in this situation include second-generation (e.g. cefaclor) or third-generation (e.g. cefixime) cephalosporins. Fluoroquinolones such as ciprofloxacin or ofloxacin are also very effective against *H. influenzae* and *Moraxella catarrhalis*, the latter being given once daily. However, this group should *not* be used as first-line therapy because of their relatively poor *in vivo* activity against the pneumo-

coccus [122], although newer members such as spar-floxacin may be more successful in this regard. A scheme of treatment is illustrated in Figs 13.2–13.4. Duration of empirical treatment is ordinarily 1 week.

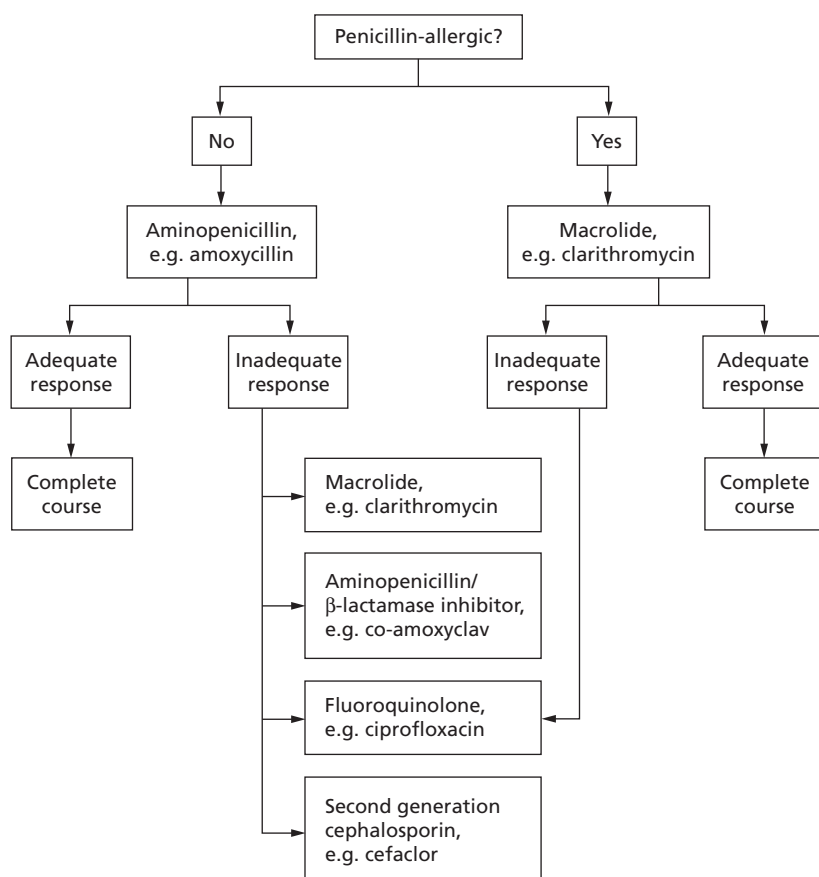
### Inpatient treatment of community-acquired pneumonia

#### Factors influencing initial antimicrobial treatment

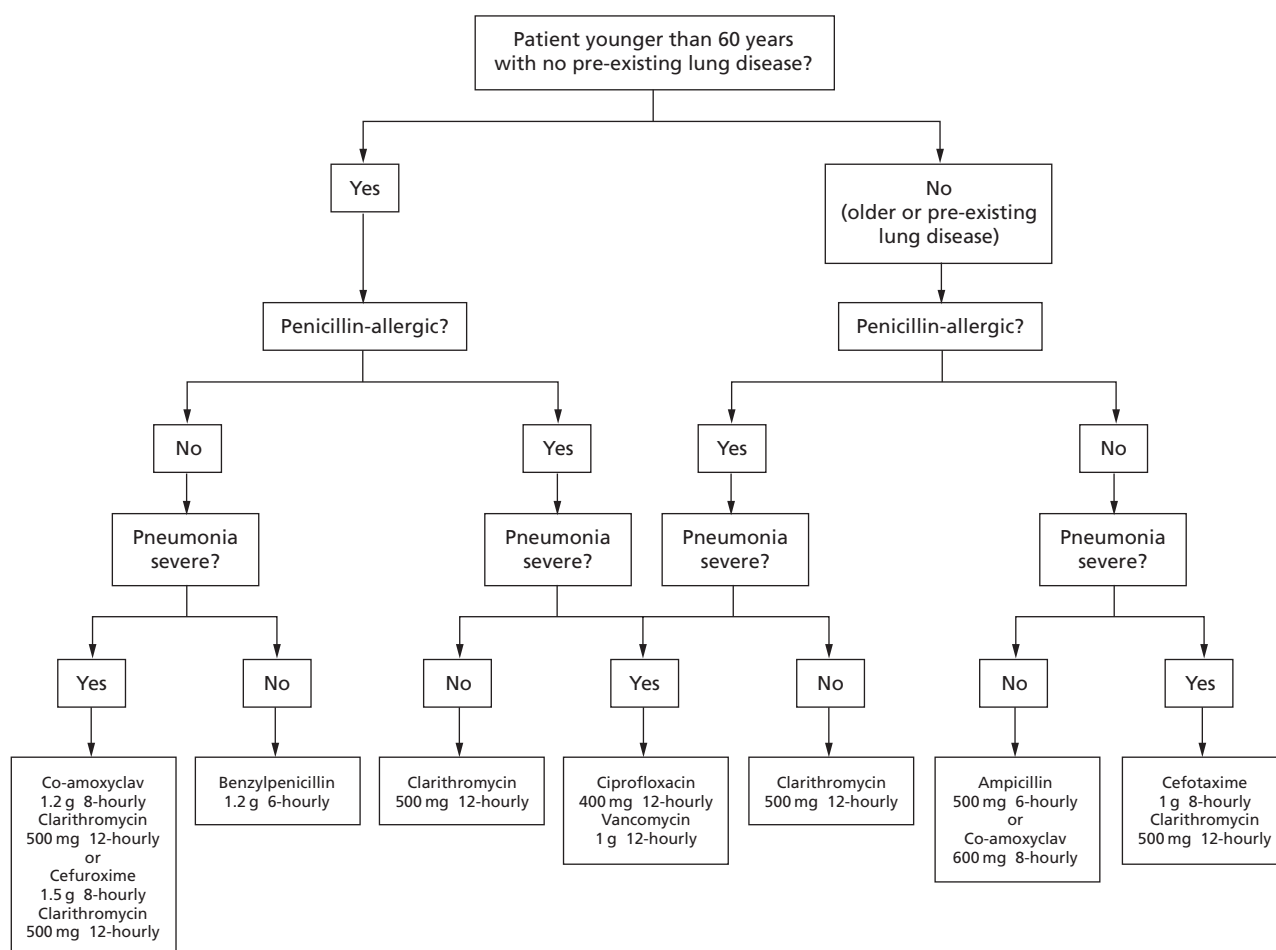
Patients admitted to hospital from the community with pneumonia are likely to be iller and often receive intravenous antimicrobial treatment at first. The initial choice of antibiotic regimen should be influenced by:

- 1 whether the infection is judged to be severe or not;
- 2 the presence of comorbid disease;
- 3 the patient's age;
- 4 antimicrobials already received in the community.

An early estimation of the severity of the infection is an important consideration in determining initial antibiotic cover (see below and Table 13.4, p. 360) [60,109]. The possible consequences of missing the responsible pathogen in a very ill patient is obvious and cover must therefore be broad, whereas in a patient who is less sick failure to respond to a first-line antibiotic can lead to a change in



**Fig. 13.2** An empirical orally administered antimicrobial approach for mild pneumonia treated in the community (see text).



**Fig. 13.3** An empirical intravenously administered antimicrobial approach for the initial treatment of hospital-acquired pneumonia in hospital (see text).

therapy. It is a good principle to keep the antimicrobial spectrum as narrow as clinical circumstances allow and, where effective choices exist, to consider the cost.

The presence of certain comorbidities will focus the physician's attention on the increased probability of particular organisms or groups of organisms. Examples are those associated with overt oropharyngeal aspiration (see section on aspiration pneumonia, p. 412), with immunosuppression (see Chapter 52) and with spread from elsewhere, e.g. following recent bowel surgery. When the patient has chronic lung disease, such as emphysema, chronic bronchitis or bronchiectasis, the initial choice of antibiotic may also be influenced by a knowledge of likely colonists such as *H. influenzae* or of previous microbial isolates, such as *Moraxella catarrhalis* or *Ps. aeruginosa*, in earlier infective exacerbations. The treatment of infection in cystic fibrosis is another such case and is discussed in Chapter 30.

Finally, with the increasing prevalence of  $\beta$ -lactamase-producing pathogens and the development of other forms

of resistance, some knowledge of local patterns of microbial susceptibility to those antibiotics in common use is helpful.

#### Assessment of severity in community-acquired pneumonia (Table 13.4, p. 360)

It will come as no surprise that universal agreement on the definition of severe community-acquired pneumonia has not been reached. This is largely because comparisons between different studies are not always easy, bearing in mind the many different clinical settings and methodological approaches that have been reported. However, a number of seemingly valid observations can be made. First, the patient who shows outward signs of respiratory distress is at increased risk of dying [35,123–125]. These signs include tachypnoea with a respiratory rate upwards of 30 breaths/min, especially if the patient has altered cerebration with drowsiness or confusion [124,126]. Clearly such a patient is likely to be hypoxic and cyanosed; indeed the finding of a  $P_{aO_2}$  of less than 8 kPa (60 mmHg) when the patient is breathing room air is accepted as a marker of severity, as is hypercarbia [60,109]. By the time

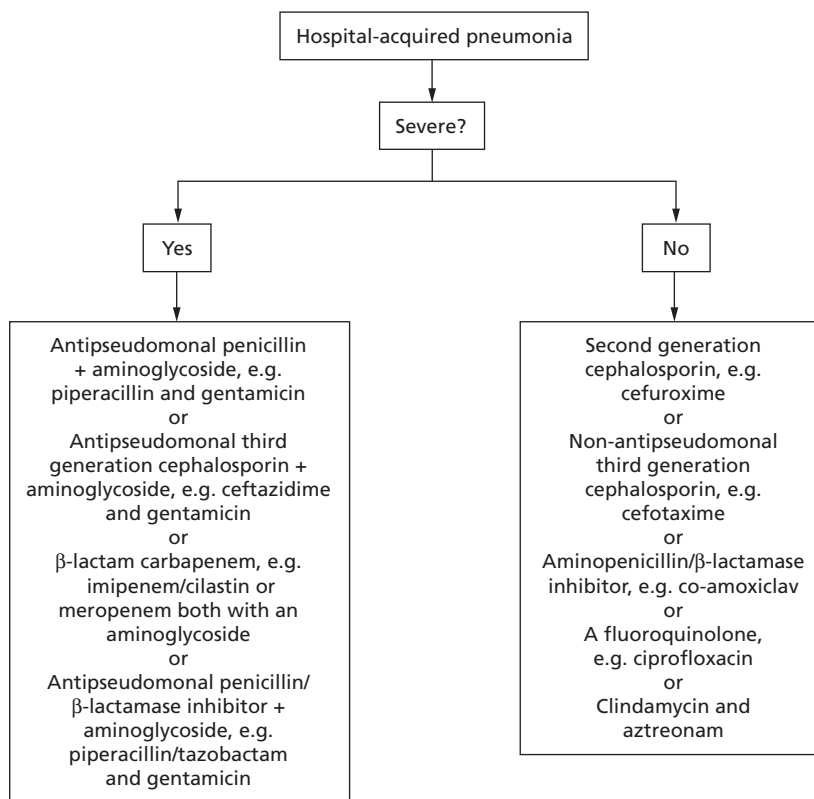


Fig. 13.4 An empirical approach for the treatment of hospital-acquired pneumonia (see text).

these measurements have been made many patients are receiving supplemental oxygen already, in which case the ratio of arterial oxygen tension to fractional inspired oxygen concentration has been used, a  $P_{aO_2}/F_{IO_2}$  ratio equal to or less than 33 kPa (250 mmHg) having the same significance [60]. Cardiovascular compromise as evidenced by hypotension is also prognostically serious, with systolic and diastolic blood pressures equal to or less than 90 and 60 mmHg (12 and 8 kPa) respectively being prognostically serious [35,109,123]. Evidence of renal impairment, with even a modest increase in the serum urea to 7 mmol/L or greater, has also been found to increase the chance of mortality, particularly when combined with tachypnoea and hypotension; indeed the risk of death was found to increase over 20-fold when two or more of the features marked with an asterisk in Table 13.4 were present in the same patient [35,123,127]. Radiographic evidence of involvement of both lungs or more than one lobe of lung or a worsening radiographic picture within the space of 48 h is also of prognostic significance and alerts the physician to a serious situation [60,128]. A marked leucocytosis ( $>30 \times 10^9/L$ ) or leucopenia ( $<4 \times 10^9/L$ ) has also been found to be associated with a poorer prognosis [4]. Patients with severe pneumonia may deteriorate rapidly so that they require close monitoring and active management, which can often be most easily provided in an intensive care or high-dependency unit. The following

recommendations, based on age, the presence or absence of underlying lung disease and a determination of severity, offers a practical approach likely to be effective and are condensed in Fig. 13.3.

### Community-acquired pneumonia in younger, previously healthy patients

#### Non-severe infection

It is recommended that a younger (<60 years) and previously healthy patient who is ill enough to be admitted to hospital with community-acquired pneumonia, who has no suggestion of immunosuppression or other risk factors but who is not severely ill according to the criteria outlined above should be treated initially with intravenous benzylpenicillin 1.2 g 6-hourly. In common practice an intravenous aminopenicillin (ampicillin/amoxicillin) 0.5–1 g 6-hourly is often used instead, but this should not be necessary as *H. influenzae* and *Moraxella catarrhalis* are unlikely to be implicated. It is also common practice to add a macrolide, although this too is not necessary unless the patient is judged to be sufficiently ill, unless the admission occurs during a *Mycoplasma pneumoniae* epidemic or unless there are features to make the clinician suspicious of *Legionella* infection (see p. 385) [129]. Those available include erythromycin 0.5–1 g 6-hourly, clarithromycin

500mg 12-hourly or azithromycin 500mg once daily, the newer macrolides being better tolerated (less nausea) and requiring less frequent administration but being more expensive than erythromycin.

The first choice is based on the probability of the infection being caused by *Strep. pneumoniae* [35], for which benzylpenicillin is still the most effective antibiotic in most geographical locations (minimum inhibitory concentration, MIC, usually <0.06 mg/L); the choice of a macrolide is based on the possibility that the pneumonia might be caused by *Mycoplasma pneumoniae* or *Legionella pneumophila* [35]. The more infrequent causes of pneumonia such as *Chlamydia pneumoniae*, *Chlamydia psittaci* and *Coxiella burnetii* are also covered by macrolides, which tend to accumulate within tissues and hence their effectiveness against these intracellular 'atypical' pathogens. A macrolide alone, particularly a newer one, would probably be effective against *Strep. pneumoniae* as well but blood levels are not as high and the potentially bacteraemic pneumococcus is likely to be eradicated more effectively by benzylpenicillin if this can be used. Other organisms, such as *H. influenzae*, *Moraxella catarrhalis*, Gram-negative enteric bacilli and anaerobes, are unlikely to be implicated in this category of patient and antimicrobial cover for them should not ordinarily be required.

A history of penicillin allergy in a non-severe case requires the omission of benzylpenicillin and inclusion of a 'stand-alone' macrolide, although increasing resistance rates to erythromycin are being reported for the pneumococcus so that occasional treatment failures might occur with this class of drug [114,115,130,131]. Alternatively and if the history of 'allergy' is not severe, consisting at worst of an uncomplicated rash rather than angio-oedema or anaphylaxis, then it is entirely reasonable to use a second-generation cephalosporin, such as cefuroxime, initially.

As soon as it is clear that the patient is responding, antimicrobial treatment may be switched from the parenteral to the oral route, usually by means of an aminopenicillin (with or without a  $\beta$ -lactamase inhibitor) or macrolide; indeed some might use oral treatment from the start. Uncomplicated pneumonia is usually treated for 1 week. Longer courses of treatment are conventional for *Legionella* and *Chlamydia* pneumonias.

### Severe infection

Should the patient appear severely ill from the start or fail to respond to initial treatment, then the antimicrobial spectrum must cover *Legionella* with a macrolide as above and should be broadened by the inclusion of antistaphylococcal cover. Approaches include (i) the use of co-amoxiclav 1.2g i.v. 8-hourly and a macrolide, which as well as covering the pneumococcus and *Legionella* also provides some cover for methicillin-sensitive *Staph. aureus* through amoxicillin/clavulanate

and (ii) the use of cefuroxime 1.5g i.v. 8-hourly and a macrolide, which as well as covering the pneumococcus and *Legionella* also provides some cover for methicillin-sensitive *Staph. aureus* through cefuroxime. The alternative use of benzylpenicillin to cover the pneumococcus effectively, a macrolide to cover *Legionella* and other 'atypicals' and flucloxacillin to provide cover for methicillin-sensitive *Staph. aureus* is also likely to be effective but fails to cover the unusual case of *H. influenzae* or other Gram-negative pneumonia.

Where it has been decided that methicillin-sensitive *Staph. aureus* is the probable major pathogen, it is usual practice to direct two antibiotics against it; thus the antistaphylococcal effect of flucloxacillin 1–2g 6-hourly i.v. can be supported by rifampicin 600mg 12-hourly i.v. or orally, this also being a potent antistaphylococcal antibiotic. Options for the penicillin-allergic patient include clindamycin, vancomycin and (provided the allergy is not severe) cefuroxime, all of which may be combined with rifampicin. Suspicions of staphylococcal infection may be heightened by the occurrence of severe pneumonia in seasons of the year when influenza infection is common (winter and early spring) or by the appearance of cavitation on the chest radiograph. Similarly for *Legionella* pneumonia, rifampicin is often added to a macrolide for increased effect when this infection is confirmed in the laboratory. An alternative approach is required when methicillin-resistant *Staph. aureus* (MRSA) is suspected or confirmed (see p. 405).

The American Thoracic Society guidelines recommend cover for Gram-negative enteric bacilli including *Ps. aeruginosa* in patients with severe pneumonia from the start [60]. Infection with this latter organism has been associated with a high mortality [132]. However, there is some evidence to suggest that the majority of such isolates occur in association with underlying structural lung disease such as bronchiectasis [81]. The author does not regard this approach as necessary in the initial treatment on medical wards of the younger previously healthy patients under discussion in this section, with the caveat that admission and mechanical ventilation on an intensive care unit for more than a few days can be expected to result in recolonization of the upper respiratory tract with Gram-negative enteric bacilli with the potential for nosocomial pneumonia.

A past history of *serious* penicillin allergy in a case of severe pneumonia is unusual but requires the omission of these agents and other  $\beta$ -lactam antibiotics. The use of vancomycin (Gram-positive cocci) and ciprofloxacin (*Legionella* and other 'atypicals') is one option; clindamycin (Gram-positive cocci) with a macrolide such as clarithromycin (*Legionella* and other 'atypicals') is another. If as is much more common, the history of 'allergy' is not severe, consisting at worst of an uncomplicated rash rather than angio-oedema or anaphylaxis, then it

is entirely reasonable to add a cephalosporin such as cefuroxime to the macrolide in order to provide some cover for methicillin-sensitive *Staph. aureus*.

Again, the switch from parenteral to oral treatment is made as soon as possible and uncomplicated pneumonia is usually treated for 1 week. Longer courses of treatment are conventional for *Legionella*, *Chlamydia* and often staphylococcal pneumonias.

### Community-acquired pneumonia in older patients and those with chronic lung disease

Irrespective of the severity of infection, the spectrum of antimicrobial cover should be broadened beyond benzylpenicillin in patients with chronic lung disease, including those with chronic bronchitis due to previous tobacco smoking, and also in older (>60 years) previously healthy subjects admitted to hospital with community-acquired pneumonia. Those organisms that might be encountered in younger previously healthy patients (see above) should still be anticipated but increased consideration needs to be given to *H. influenzae*, *Moraxella catarrhalis* (usually occurring in purulent bronchitis rather than pneumonia) and to a lesser extent aerobic Gram-negative enteric bacilli, e.g. *Enterobacter* spp., *E. coli*, *Serratia marcescens*, *Klebsiella* and *Proteus* spp., *Ps. aeruginosa* and *Acetivobacter* spp. Gram-negative enteric bacilli are uncommon causes of community-acquired pneumonia except in elderly and debilitated patients often with comorbid conditions, whose flora has been modified by previous antibiotics, and in alcoholics [133]. Diagnostic uncertainty following the isolation of Gram-negative enteric bacilli in sputum is compounded by the frequency of oropharyngeal colonization by such organisms in these categories of patients.

### Non-severe infection

Most patients with community-acquired pneumonia in this group still respond to an aminopenicillin such as intravenous ampicillin 500mg four times daily or amoxicillin, which is appropriate in patients who are not severely ill. Failure to respond to this approach suggests the presence of  $\beta$ -lactamase producers or other resistant organisms, so that a  $\beta$ -lactamase-stable penicillin such as co-amoxiclav may be substituted. Alternatively,  $\beta$ -lactams such as cefuroxime (second-generation cephalosporin), cefotaxime or ceftriaxone (third-generation cephalosporins) may be given intravenously in this situation, since they are also resistant to the  $\beta$ -lactamases produced by *H. influenzae* and *Moraxella catarrhalis* while maintaining useful activity against the pneumococcus. The third-generation cephalosporins have less activity against the pneumococcus but excellent activity against Gram-negative enteric bacilli.

Where the patient is allergic to penicillin, amoxicillin is

omitted and a macrolide such as clarithromycin may be used alone initially in less ill patients. If the history of 'allergy' is not severe, then it is entirely reasonable to substitute a cephalosporin such as cefuroxime for the macrolide.

### Severe infection

Should the patient appear severely ill, the antibacterial spectrum may be broadened from the start by using the combination of an intravenous macrolide and an intravenous  $\beta$ -lactamase-stable antimicrobial such as cefotaxime or ceftriaxone. This retains adequate cover for the commonest organism (*Strep. pneumoniae*), which in the UK is almost invariably responsive to these  $\beta$ -lactams, as well as covering *H. influenzae*, *Moraxella catarrhalis* and *Staph. aureus* and the Gram-negative enteric bacilli, in addition to *Legionella pneumophila*, *Mycoplasma pneumoniae* or other macrolide-sensitive 'atypicals' such as *Chlamydia* spp. and *Coxiella burnetii*.

If staphylococcal infection is confirmed, then two antimicrobials active against this organism may be used as described above. Patients in this category who are known to be carriers of MRSA or who are admitted from a nursing home or other institution in which MRSA is known to be endemic may be treated with vancomycin 1g 12-hourly with the possible addition of rifampicin 600mg 12-hourly.

If the patient with severe infection has not improved within 24h, further diagnostic information may have become available that allows rational antibiotic adjustments. For example, urine testing by ELISA may indicate *Legionella* antigen, implying *L. pneumophila* type 1 infection, in which case intravenous rifampicin may be added to the macrolide.

As above, a past history of *serious* penicillin allergy in a case of severe pneumonia requires the omission of  $\beta$ -lactam antibiotic in general. Options include the use of clindamycin (Gram-positive cocci) with a macrolide such as clarithromycin (*Legionella* and other 'atypicals') or vancomycin (Gram-positive cocci) with ciprofloxacin (*Legionella* and other 'atypicals'). If as is usually the case, the history implies that allergy is not severe, consisting at worst of an uncomplicated rash rather than angio-oedema or anaphylaxis, then it is entirely reasonable to add a cephalosporin such as cefotaxime to the macrolide in order to provide some cover for methicillin-sensitive *Staph. aureus*.

The American Thoracic Society recommendation to cover Gram-negative enteric bacilli including *Ps. aeruginosa* from the start in patients with severe pneumonia is more relevant in elderly and debilitated patients with severe infection than it is in younger previously healthy patients, as the upper respiratory tracts of elderly patients are more likely to be colonized by these organisms, which



are also associated with underlying structural lung disease such as bronchiectasis or cystic fibrosis [60]. Gram-negative enteric bacilli are considered a rare cause of community-acquired pneumonia in the UK, so that although infection with *Ps. aeruginosa* has been associated with a high mortality [132], clinicians must use their own judgement in deciding whether to cover this organism. The options for covering Gram-negative enteric bacilli, including *Ps. aeruginosa*, while retaining activity against *Strep. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *Legionella* and the other 'atypicals' in this group of patients include a macrolide *plus* one of the following:

an antipseudomonal third-generation cephalosporin, e.g. ceftazidime;  
an antipseudomonal penicillin, e.g. azlocillin;  
ciprofloxacin;  
imipenem/cilastin or meropenem;  
aztreonam.

An aminoglycoside such as gentamicin may be added in order to augment antipseudomonal activity, at least initially. Aztreonam is unlikely to cause problems in a penicillin-allergic patient and ciprofloxacin is safe in the same situation.

As previously mentioned it should be noted that admission to an intensive care unit for more than a few days can be expected to result in overgrowth of the upper respiratory tract with Gram-negative enteric bacilli, especially if mechanical ventilation is used, with the potential for superadded Gram-negative enteric bacillary nosocomial pneumonia.

### Hospital-acquired (nosocomial) pneumonia

Hospitals can be regarded as areas of microbiological conflict in which the usual populations of oropharyngeal colonizers found in the community have a tendency to be driven out and to be replaced by other groups of organisms better suited to survival in these peculiarly hostile environments. This is important because it is known that small quantities of oropharyngeal secretions commonly find their way into the lower respiratory tract by microaspiration in entirely healthy individuals during sleep [38,134], so that in hospitalized patients these new colonials follow the same route and given the right circumstances may cause pneumonia.

Pneumonia occurring within 48 h of admission to hospital in an immunocompetent patient can usually be treated with the same antimicrobial approach as has been outlined above for community-acquired pneumonia, these patients being likely to have retained their community flora. Thereafter, assuming that infection was not being incubated at the time of admission, the pneumonia is regarded as being hospital-acquired with a potentially altered flora including Gram-negative enteric bacilli and *Staph. aureus*, so that a different approach is likely to be necessary [135].

### Concept of 'core organisms'

An individual physician's perception of the problem of hospital-acquired pneumonia may be easily skewed, as most of the published data refer to seriously ill patients in intensive care units rather than the mild to moderately ill ward-based cases often encountered in general hospital practice. Those patients who develop pneumonia earlier in their stay might still be expected to respond more in the manner of community-acquired pneumonia, the 'earlier' colonizers in these 'healthier' patients still tending to include *Strep. pneumoniae* and *H. influenzae*, followed in frequency by *Staph. aureus* [136], whereas those who develop pneumonia later are increasingly likely to be colonized by Gram-negative enteric bacilli, particularly if they have already received antibiotics [137–139]. The list of likely pathogens therefore becomes wider in nosocomial pneumonia [140]. The aerobic Gram-negative enteric bacilli include organisms such as *Enterobacter* spp., *E. coli*, *Serratia marcescens*, *Klebsiella* and *Proteus* spp., which together with *H. influenzae* and Gram positives such as methicillin-sensitive *Staph. aureus* and *Strep. pneumoniae* may be regarded as 'core organisms' to be anticipated and covered empirically in *all* patients with hospital-acquired pneumonia [139,141].

The chance of *Staph. aureus* being implicated in hospital-acquired pneumonia is increased if patients are admitted comatose, whereas Gram-negative enteric bacilli are more likely if patients become comatose *after* admission [142]. The reason for this is subject to speculation but it has been suggested that the first group have a tendency to aspirate earlier in their admission, when their oropharynx was more likely to be colonized by *Staph. aureus*, whereas the second group tend to aspirate later in their hospital stay, by which time oropharyngeal colonization with Gram-negative enteric bacilli would be more likely to have taken place [143]. The chance of *Staph. aureus* infection in hospital-acquired pneumonia is also increased by coexisting diabetes mellitus and renal failure [144].

### Further predictive situations

In addition to these core organisms, other pathogens in hospital-acquired pneumonia may be anticipated when certain predictive situations arise, in which case consideration can be given to further broadening the empirical antimicrobial spectrum to include these groups.

1 Highly resistant Gram-negative organisms such as *Ps. aeruginosa* and *Acinetobacter* spp. may be found especially in patients with severe illness who have required prolonged endotracheal intubation and mechanical ventilation in an intensive care environment, particularly if they have been treated previously with antibiotics or systemic corticosteroids [145,146]. *Ps. aeruginosa* is also a common

colonist in patients with underlying bronchiectasis or cystic fibrosis.

2 Anaerobic organisms should be covered if there has been a witnessed episode of overt aspiration of gastric contents, particularly if the patient has poor dentition, although it should be noted in these circumstances that anaerobes are not always responsible since:

- (a) the pneumonia could be chemical rather than infective; and
- (b) patients susceptible to hospital-acquired pneumonia have often had their gastric contents neutralized by  $H_2$  blockers or by gastric feeding, with the effect that their stomachs may be colonized by Gram-negative enteric bacilli and *Staph. aureus* so that these may be responsible for the pneumonia [147]. Anaerobes are also more likely to be causal pathogens if hospital-acquired pneumonia follows recent abdominal surgery.

3 It should be borne in mind that *Legionella* spp. may be important pathogens in some locations according to North American reports [148]. It is predisposed by concomitant high-dose systemic corticosteroid therapy [139].

#### Assessment of severity in hospital-acquired pneumonia

It has been recommended that the same criteria applied to community-acquired pneumonia may also be applied to cases of hospital-acquired pneumonia in order to assess its severity (see Table 13.4) and that this has a bearing on the choice of empirical antimicrobial therapy [139]. However, in contrast with community-acquired pneumonia the age of the patient is no longer a major determinant of antibiotic choice. There are therefore three important considerations that have a bearing on the choice of antimicrobial agents: (i) whether the patient's pneumonia is severe or not; (ii) the length of time that the patient has been in hospital prior to developing pneumonia; and (iii) whether predictive situations for certain organisms or groups of organisms exist.

#### Antibiotic regimens in non-severe hospital-acquired pneumonia

Patients with non-severe hospital-acquired pneumonia (mild to moderate) may be reasonably treated with a single agent that covers the 'core organisms' mentioned above, including the non-pseudomonal Gram-negative enteric bacilli, *H. influenzae*, *Strep. pneumoniae* and *Staph. aureus* (methicillin-sensitive). The options include:

- 1 a second-generation cephalosporin (such as cefuroxime);
- 2 a non-pseudomonal third-generation cephalosporin (such as cefotaxime);
- 3 a  $\beta$ -lactam/ $\beta$ -lactamase inhibitor, e.g. amoxicillin/clavulanate (co-amoxiclav in the UK) or ampicillin/sulbactam (in the USA);

4 a fluoroquinolone (e.g. ciprofloxacin or ofloxacin) might be equally effective (except for *Strep. pneumoniae*) in penicillin-allergic patients;

5 clindamycin and aztreonam (effectiveness of aztreonam limited to Gram-negative enteric bacilli) may be used as alternative combination chemotherapy unlikely to cause problems in penicillin-allergic patients [139].

Initial treatment is usually intravenous, being stepped down to an oral agent with a similar spectrum (e.g. co-amoxiclav, ciprofloxacin) once a response has occurred.

In the predictive situation of overt aspiration, anaerobes may be covered by adding clindamycin or metronidazole or by using a  $\beta$ -lactam/ $\beta$ -lactamase (e.g. co-amoxiclav) alone. The more virulent and resistant Gram-negative organisms *Ps. aeruginosa* and *Acinetobacter* spp. may need to be targeted (as below) in certain predictive circumstances, such as in the presence of coexisting bronchiectasis or during a prolonged stay on an intensive care unit for whatever reason, even if the pneumonia is not severe. Treatment may need to include vancomycin in institutions where MRSA is endemic until this organism has been excluded.

#### Antibiotic regimens in severe hospital-acquired pneumonia

In patients with severe hospital-acquired pneumonia, intravenous antimicrobial treatment should usually be extended to cover *Ps. aeruginosa* and *Acinetobacter* spp. unless the pneumonia has occurred less than 5 days after admission, in which case infection with the 'core organisms' is more likely. The options include:

- 1 an antipseudomonal penicillin and an aminoglycoside, e.g. piperacillin and gentamicin;
- 2 an antipseudomonal third-generation cephalosporin and an aminoglycoside, e.g. ceftazidime and gentamicin;
- 3 the  $\beta$ -lactam carbapenem imipenem/cilastin or meropenem (also covers anaerobes) and an aminoglycoside;
- 4 an antipseudomonal penicillin/ $\beta$ -lactamase inhibitor combination and aminoglycoside, e.g. piperacillin/tazobactam (covers  $\beta$ -lactamase producers resistant to ureidopenicillins) and gentamicin.

Blood levels of the aminoglycoside should be monitored to both avoid renal toxicity and achieve the optimal bactericidal effect [149]. Ciprofloxacin may be used as an alternative to the aminoglycoside in any of the foregoing combinations and has less potential for toxicity [139]. It may be combined with gentamicin as an alternative treatment regimen in the penicillin-allergic patient. There is experimental evidence to support the use of more than one antibiotic active against Gram-negative bacilli, the combination of two such antibiotics acting synergistically [150]. Treatment may need to include vancomycin in institutions

where MRSA is endemic until this organism has been excluded.

### Supportive treatment in pneumonia

#### Respiratory support

Patients who are in obvious respiratory distress with tachypnoea are at increased risk of dying and need close monitoring, particularly if they are beginning to show evidence of exhaustion with drowsiness or confusion. Clearly such a patient is likely to be desaturated, with arterial hypoxaemia. The finding of a  $P_{aO_2}$  of less than 8 kPa (60 mmHg) when breathing room air indicates a serious situation, as does hypercarbia. Many patients are already receiving supplemental oxygen, in which case the ratio of arterial oxygen tension to fractional inspired oxygen concentration can be used, a  $P_{aO_2}/F_{IO_2}$  ratio equal to or less than 40 kPa (300 mmHg) having the same significance [60]. A  $P_{aO_2}$  of 6.7 kPa (50 mmHg) or less in the presence of a rising  $P_{CO_2}$  and acidosis are clear indications that mechanical ventilation may be necessary. Overcorrection of hypoxaemia should be avoided (see Chapter 55). Sometimes improvement in oxygenation can be achieved by postural change so that the 'good lung' is dependent [151,152]. Occasional patients may tolerate high-flow oxygen via a nasal continuous positive airway pressure system or nasal ventilation if they are sufficiently cooperative, not too tachypnoeic and untroubled by cough and sputum production.

#### Fluid and electrolyte replacement

Patients with severe pneumonia may become dehydrated so that their depleted intravascular volume requires par-enteral replacement. The situation may be further complicated if an intrapulmonary capillary leak develops, with resultant pulmonary oedema or adult respiratory distress syndrome (ARDS; see Chapter 27); such cases usually require mechanical ventilation with measurements of central venous or pulmonary capillary wedge pressure and meticulous attention to all aspects of fluid and electrolyte balance. Hypophosphataemia should be corrected if this arises [153].

#### Total parenteral nutrition

Total parenteral nutrition is best instituted early in severe cases of pneumonia in whom mechanical ventilation is likely to be prolonged. Intravenous feeding cannulae should be placed with great care in order to avoid their colonization by pathogenic organisms with consequent bacteraemia.

### Other considerations

#### Pleuritic pain

Pleuritic pain is usually easily relieved by simple non-sedative analgesics; care is taken to avoid narcotic analgesics with respiratory depressant properties in all but the mildest of cases.

#### Physiotherapy

Physiotherapy is of no benefit in an acutely ill patient who finds cooperation difficult and who may easily become exhausted, but it may assist expectoration of sputum in less ill patients and in those who are recovering [154].

#### Corticosteroids

Corticosteroids are not usually of convincing benefit either in patients with severe pneumonia or in those with systemic sepsis, although their use has caused debate [155,156]. They may be given in immunosuppressed patients with *Pneumocystis carinii* infection, when their use is thought to 'buy time' by suppressing the inflammatory response while the antimicrobial effect builds up (see Chapter 52).

#### Inotropic agents

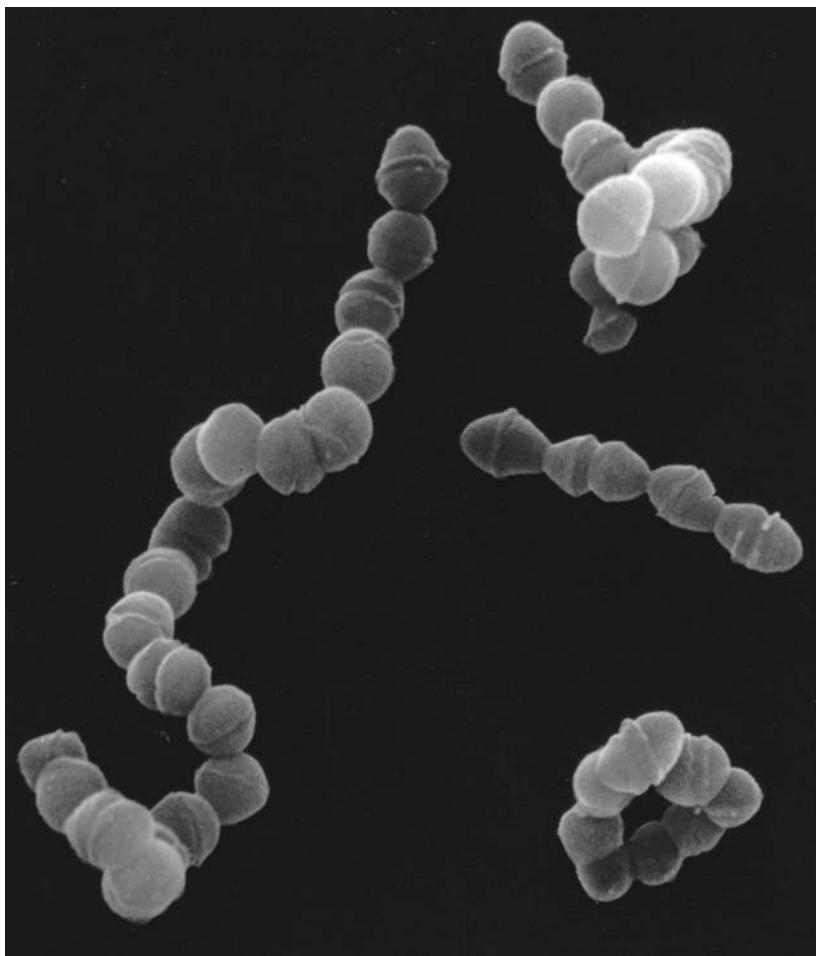
Inotropic agents such as dopamine or dobutamine may be required when severe pneumonia is complicated by hypotension; indeed the requirement for vasopressors for more than 4 h was one of a number of features of severe pneumonia defined by the American Thoracic Society, as was a systolic blood pressure below 90 mmHg (12 kPa) or a diastolic blood pressure below 60 mmHg (8 kPa) [60].

## Specific microbiological types of pneumonia

### Pneumococcal pneumonia

#### Prevalence

Pneumococcal pneumonia is caused by *Strep. pneumoniae*, often referred to as the pneumococcus and classified in old literature as *Diplococcus pneumoniae* (Fig. 13.5). These Gram-positive diplococci are of extreme importance, being the most common cause of bacterial pneumonia. As the disease is not notifiable in either the UK or USA, data regarding its frequency in whole populations rely on estimation. In the USA an incidence of 1–5 cases per 1000 per year has been reported [158]. Other sources estimate a total of 150 000–570 000 cases per year in the USA, of which about 5% die [159]. Pneumococcal bacteraemia is also a



**Fig. 13.5** The ubiquitous Gram-positive pathogen, *Streptococcus pneumoniae* often appears in a diplococcal form ( $\times 14\,520$ ). (After Philips [157].)

serious problem in children worldwide, having been estimated to cause over 1 million deaths per year in those aged under 5 years [160].

The frequency with which evidence of pneumococcal infection is found in cases of pneumonia varies according to the methods used to detect infection and whether the patient has been treated with an antibiotic. Thus in the pre-antibiotic era, *Strep. pneumoniae* was found to be responsible for 96% of over 3000 cases of lobar pneumonia reported in one survey and in another to account for almost 80% of 350 cases of pneumonia [161,162]. In more recent studies the failure to isolate the pneumococcus (or indeed any organism) has become commonplace, leading to microbiological complacency and inertia on the part of clinicians that has been condoned in the literature [163]. Thus a paper published in 1974 found no organism in 37% of 203 cases of lobar pneumonia and isolated *Strep. pneumoniae* in only 8% [164]. A district general hospital survey from Bristol in 1981 found evidence of a specific infective organism in only 46% of cases and *Strep. pneumoniae* in only 11%, previous antibiotics having been given 'blind' in 75% of cases [165]. The view that this apparent reduction in prevalence is in part due to prior antibiotic suppression

of growth is supported by a serological study using CIE, which found evidence of pneumococcal infection in 72% of cases of pneumonia against a culture isolation rate of only 9% [166]. Further support for this view was provided by a painstaking hospital study from Nottingham that claimed to identify the causative organism in 97% of 127 patients, pneumococcal infection accounting for 76% of cases [167]. A multicentre British Thoracic Society study has also confirmed that *Strep. pneumoniae* is the most frequent causative organism in cases of pneumonia admitted to hospital from the community [35]; a similar experience has been reported from some North American centres [168].

#### *Pathological anatomy and pathogenesis*

A micrococcus was described postmortem by Friedländer in cases of pneumonia over a century ago and was thought to be a probable aetiological factor. The pathological anatomy of lobar pneumonia has also been admirably described since Lænnec's day [29]. Three stages were then recognized. The first stage is one of inflammatory congestion, in which the affected part of the lung is coloured dark

red due to hyperaemia; the air in it is diminished but not absent, affected alveoli and bronchi beginning to fill with a fluid and haemorrhagic exudation. In the second stage (red hepatization), the exudate coagulates so that the lung assumes the consistency of liver (Fig. 13.6). In the third stage, the red appearance of the cut surface of lung changes to become yellowish-grey (grey hepatization), the numbers of red cells in the exudate diminishing and being replaced by neutrophils (Fig. 13.7). When resolution takes place, the exudate liquefies and is coughed up or otherwise absorbed, the neutrophils phagocytosing the pneumococci and monocytes clearing up the fibrinous debris so that the lung is restored to its former state. A case of lobar pneumonia need not go through all three classical stages and different stages of the process may occur at the same time in an individual case. The entire cycle is relatively short, running its course in 7–10 days. If resolution is incomplete, the fibrinous exudate organizes so that aveoli become filled with a mass of fibroblasts that may result in permanent scarring.

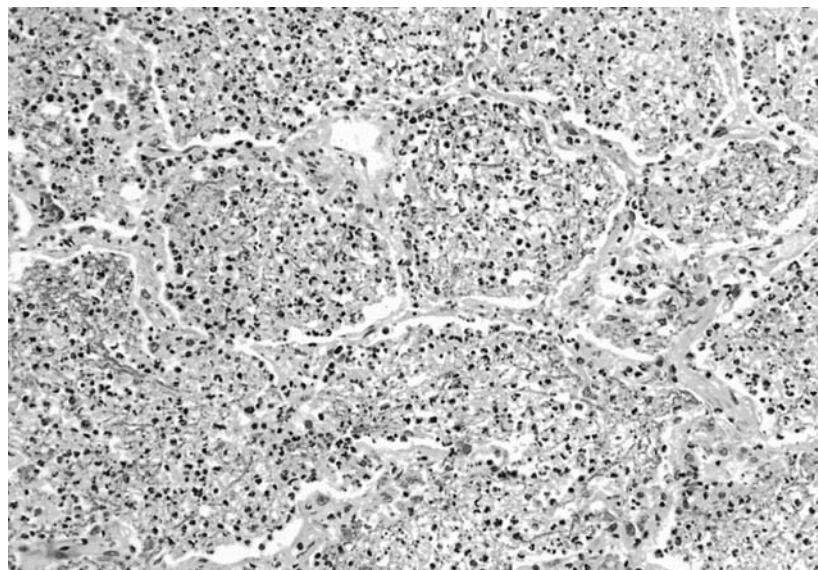
Classically, pneumococcal pneumonia produces diffuse involvement of most of a lobe and more than one lobe may be involved in 10–25% of cases but spread of consolidation throughout an entire lung is unusual, occurring in less than 1% of patients [169]. Segmental or subsegmental involvement may also occur, these types being more common in children, the elderly and in those with underlying chronic pulmonary disease.

There are at least 84 distinct serotypes of pneumococci, their identification being based on antigenic differences in their polysaccharide capsules. The variable pathogenicity of these individual pneumococcal subtypes is incompletely understood but the chemical composition of the capsule is important in determining the virulence of the organisms. This is partly related to the degree of inhibition

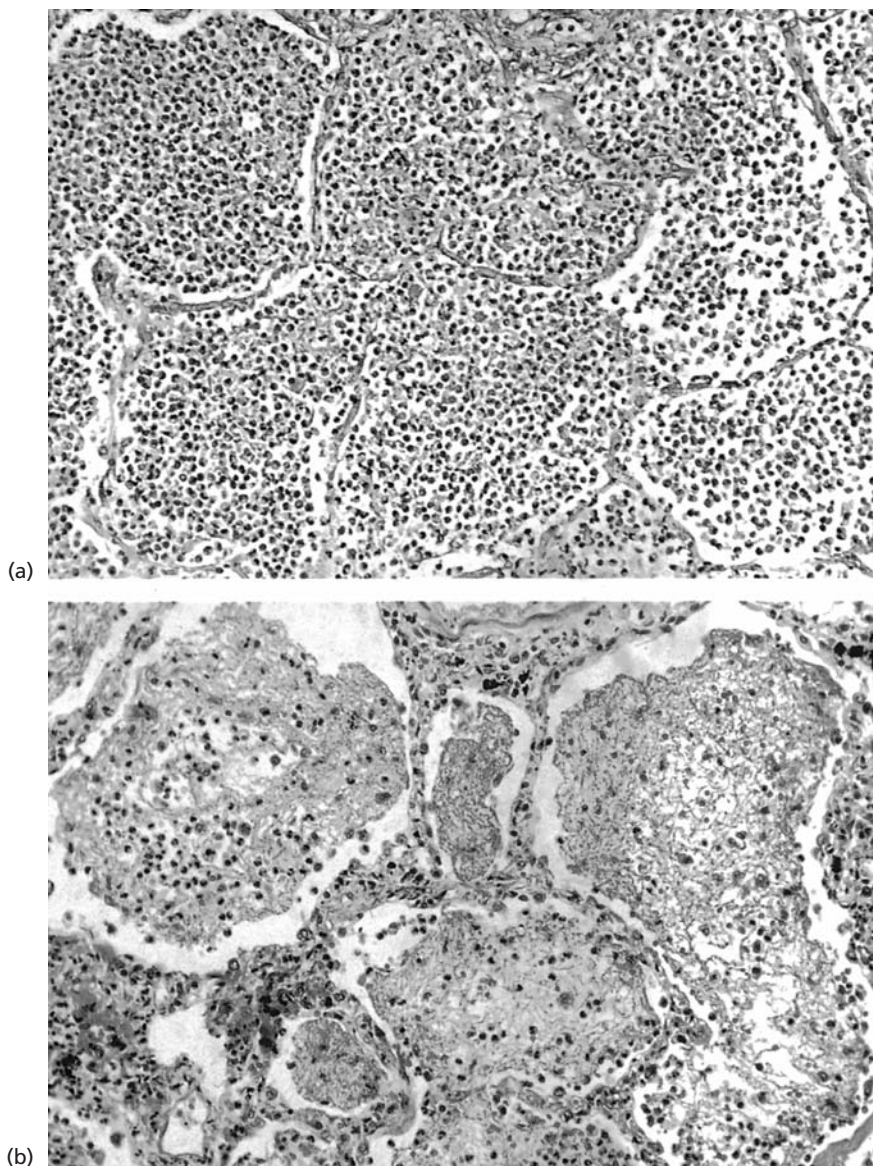
of phagocytosis afforded by the type-specific capsular polysaccharides, which do not themselves appear to stimulate an inflammatory response; however, the sub-capsular cell wall is able to stimulate considerable inflammation, with the alveolar exudation of fluid in which the organisms multiply and are spread throughout a lobe [170–172]. *Strep. pneumoniae* is an extracellular pathogen and in order for it to be removed it has to be phagocytosed. The whole process is complex, involving opsonization with serotype-specific capsular antibodies, complement and C-reactive protein with the participation of alveolar macrophages and neutrophils [173]. The molecular events that transform a tranquil pharyngeal colonist into the seemingly aggressive pathogen that causes rapidly progressing pneumococcal pneumonia are incompletely understood but it is known that pneumolysin, and other components, including cell-wall material are released as neutrophils destroy the invading organisms and that these act as toxins, leading paradoxically to increased inflammation and cellular damage in the lung [172].

### Epidemiology

Pneumococcal pneumonia is slightly more common in males than females throughout life, for reasons that are unclear. It also becomes more common with increasing age, so that an attack rate of about 46 cases per 1000 over the age of 40 years has been noted [44] compared to 1–5 per 1000 per year for the population overall [174]. It has been estimated that it is responsible for 30–50% of all cases of community-acquired pneumonia in the UK [175]. Pneumococcal bacteraemia shows a bimodal age distribution, 50% occurring in patients over the age of 65 years, with another large peak in infants under the age of 1 year,



**Fig. 13.6** Necropsy specimen showing early stage lobar pneumonia, with alveoli containing a fibrinous coagulum and relatively few leucocytes (haematoxylin & eosin  $\times 12$ ).



**Fig. 13.7** (a) Lobar pneumonia at a later stage than Fig. 13.6 showing normal alveolar architecture and dense confluent polymorphonuclear intra-alveolar infiltrate (haematoxylin & eosin  $\times 112$ ). (b) Later stage of lobar pneumonia showing degenerating leucocytes in fibrinous coagulum (haematoxylin & eosin  $\times 112$ ).

in whom pneumococcal meningitis is mainly reported [176].

Pneumococcal pneumonia occurs more frequently in the winter months in temperate climates and at the end of the dry season in the tropics [177]. Each year the number of reports of bacteraemic pneumococcal infection in England and Wales increase sharply in the first quarter and are at their lowest in the third quarter [178]. It is possible that an individual patient's defences against the pathogenicity of *Strep. pneumoniae* may be compromised by a preceding viral upper respiratory tract infection [179]. This would accord with the observation that coryzal symptoms frequently precede the onset of pneumococcal pneumonia and also with the observed increased seasonal incidence of common cold virus infections in winter [180]. Furthermore, pneumococcal pneumonia is the most common serious bacterial complication of influenza and

measles, both of which show an increased winter prevalence; indeed the advent of an influenza epidemic may be heralded by a rise in the number of cases of pneumonia in the community [21]. In order to induce pneumococcal pneumonia experimentally in monkeys, it is necessary to inoculate the pneumococcus into the trachea rather than the nasopharynx [181]. Similarly in humans, infection in the nasopharynx is commonplace, this being the organism's usual ecological niche, up to 70% of the population acting as asymptomatic carriers of *Strep. pneumoniae* at some time or other. In view of this it is remarkable that pneumococcal pneumonia does not occur more frequently. It is thought that pneumonia is unlikely to occur in the absence of microaspiration of infected mucus from the nasopharynx in a subject whose defences are compromised by some other factor such as viral infection.

At least 84 distinct types of *Strep. pneumoniae* have been



identified according to the antigenicity of their polysaccharide capsules (see p. 380) [172]. Although all these types may be carried asymptotically, some have greater pathogenicity than others and it is microaspiration of the more virulent strains that causes trouble for humans. The majority of the pneumococcal types carried by the normal population are not commonly associated with pneumonia, although they may rarely cause it, and are sometimes referred to as 'carrier types'. About two dozen of the more pathogenic or 'infective types' of pneumococcus are responsible for 80% of cases of pneumococcal pneumonia, type 3 being particularly virulent [22,182,183]. Carrier rates for the various antigenic types have been noted to be higher in closed communities such as schools and barracks and high attack rates have been recorded in encampments of military personnel and South African gold miners [184,185].

Epidemics have been unusual since the introduction of antibiotics. When they do occur, several serotypes are usually implicated in a population with a high carrier rate that is attacked by predisposing viral infection [184,186]. During such epidemics the asymptomatic nasopharyngeal pneumococcal carrier rate goes up and carriers may develop pneumonia themselves or transmit the organism by droplet spread to others, who then become similarly susceptible. One such epidemic was recently reported in an overcrowded and poorly ventilated prison, caused on this occasion by a single serotype (12F), with a carriage rate of 7% within the prison population and with no evidence of any predisposing respiratory viral infection [187]. Cell blocks with the worst combination of crowding and poor ventilation had the highest rates of disease. Another such outbreak was reported in relation to two shelters for homeless men [188], and a third outbreak caused by a single multidrug-resistant strain (23F) was reported in unvaccinated nursing home residents [189]. In general, asymptomatic carriage of the pneumococcus decreases as age increases, except in relatively closed communities where rates may be disproportionately high. Although asymptomatic pneumococcal carriers are firmly implicated in the spread of infection, cases of direct patient-to-patient spread of disease are recorded [190–192].

### *Predisposing factors*

Pneumococci that enter the bloodstream are dealt with by the reticuloendothelial system. The spleen clears bacteria from the blood and also acts as a store for B lymphocytes that respond to capsular polysaccharide antigens by producing the appropriate antibodies. Subjects who have had a splenectomy, either for the treatment of abdominal trauma or for haematological disorders such as thrombocytopenia or lymphoma staging, have a small but well-documented lifelong increase in susceptibility to

pneumococcal infection that is probably greatest in the first two postoperative years [193]. Such patients (over the age of 2 years) should be offered pneumococcal vaccination (see p. 381) 2 weeks before elective splenectomy or before discharge from hospital if the spleen has been removed as an emergency [195]. Patients with functional asplenia due to various causes are also more susceptible. These include homozygous sickle cell disease (in which the risk of pneumococcal sepsis is increased several hundred fold), thalassaemia and adult coeliac disease [195–197]. Pneumococcal bacteraemia in asplenic patients is often overwhelming, with no obvious focus of infection, and may be associated with disseminated intravascular coagulation (DIC) and multiple organ failure [198–200]. Susceptible asplenic patients should be educated about the risks they face and encouraged to wear a medical warning (e.g. 'Medic Alert') bracelet. They should also be immunized against *H. influenzae* type b and *Neisseria meningitidis*. Local audits of such measures have shown them to be effective in achieving uptake of vaccination [201]. There are a number of other groups who are more susceptible to pneumococcal pneumonia or in whom the mortality from pneumococcal pneumonia is higher, including those patients, many of whom are elderly, with chronic lung disease, congestive heart failure, chronic renal disease (including nephrotic syndrome), chronic liver disease (including cirrhosis), diabetes mellitus and inherited or acquired immunodeficiency states including hypogammaglobulinaemia, IgG subset and complement deficiencies, neutropenia, leukaemia, lymphoma and amyloidosis [173].

Immunosuppressed HIV-positive patients are at increased risk of developing bacterial pneumonia and *Strep. pneumoniae* is the most commonly isolated pathogen in such cases, having been reported to precede the onset of AIDS in approximately 60–80% of this population [202]. The clinical presentation in such cases is generally indistinguishable from that occurring in normal hosts but bacteraemia is more common and the mortality somewhat higher in HIV-positive cases [203]. HIV testing should be considered in patients who are younger than 40 years of age and who present with pneumococcal pneumonia, as this may be the first manifestation of their compromised immunity [204,205].

### *Clinical features*

Classical lobar pneumonia in a previously healthy subject results in an acute febrile illness. The onset of the illness is frequently preceded by mild coryza or other upper respiratory tract symptoms of presumed viral origin. Symptoms may begin abruptly with a high fever often heralded by a rigor or 'shaking chill' (Fig. 13.8). Before the availability of antibiotics a patient would remain febrile with a continuous fever, typically 38.5–39.5°C, for between 5 and 10



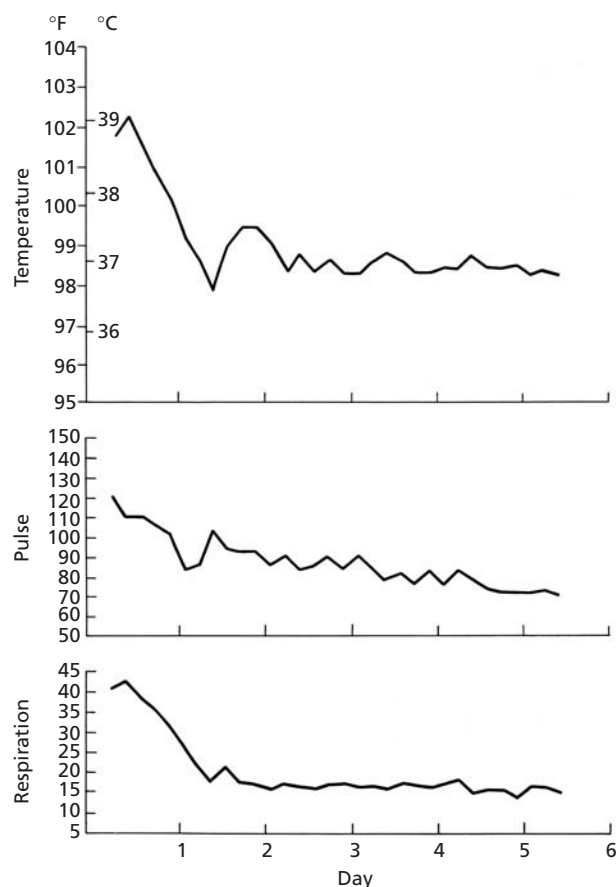


Fig. 13.8 Temperature, pulse and respiration chart of patient with pneumococcal pneumonia showing typical response to intravenous penicillin.

days. If recovery occurred it was characteristically abrupt, with a sudden fall in temperature, the so-called 'crisis'. Pleuritic pain over the affected lobe is common and when present makes coughing painful. The cough may be dry initially but is later productive of sputum. This is classically described as being a rusty-brown colour as a result of the release of red blood cells into the alveolar exudate in the phase of red hepatization. Nowadays this is a less common finding, presumably because of the modifying effect of antibiotics on the pathological process, and the sputum is usually a non-specific yellow or greenish colour, sometimes containing small flecks of blood.

On physical examination the patient may be sweating, flushed and ill-looking. Cyanosis is uncommon in a previously healthy patient and when present indicates extensive pneumonia with a sizable shunt effect. A fever and concomitant tachycardia are present. Tachypnoea is usually present and breathing may be limited in depth by pleuritic pain. An impaired percussion note may be elicited over the affected lobe. The breath sounds are usually bronchial in quality over the same area; when this is the case the other signs of consolidation, namely

increased vocal fremitus and resonance, aegophony and whispering pectoriloquy, are also elicitable. Localized crackles may be heard. Herpes labialis (herpes simplex infection of the lips) is a common finding within a few days of the onset of infection.

Although the foregoing clinical features are well recognized in relation to lobar pneumonia, in a microbiological sense they are entirely non-specific and it is impossible to conclude with certainty that the infective organism is *Strep. pneumoniae* without supporting evidence from the laboratory. Furthermore, the classical presentation in modern-day practice is often modified by (i) the early use of antibiotic therapy, (ii) the presence of pre-existing lower respiratory tract disease such as chronic bronchitis, emphysema and bronchiectasis, and (iii) the age of the patient. Thus although fever may be present in the elderly, this is by no means always the case, even in the presence of bacteraemia [206,207]. Rigors, cough and pleuritic pain may also be absent [208]. Loss of mental clarity, somnolence or frank confusion are also found commonly in elderly patients with pneumonia of any type [209], and may be a manifestation of the pneumonia itself or of deterioration in a coexisting illness such as renal insufficiency or congestive heart failure [4,44]. As with the elderly, so symptoms in young children may be non-specific and misleading. Fever and delirium are common. Respirations may be rapid and grunting. Meningism is sometimes present and abdominal pain may occur in lower lobe pneumonia. The usual auscultatory findings of consolidation may be absent or difficult to detect, making a chest radiograph essential for diagnosis.

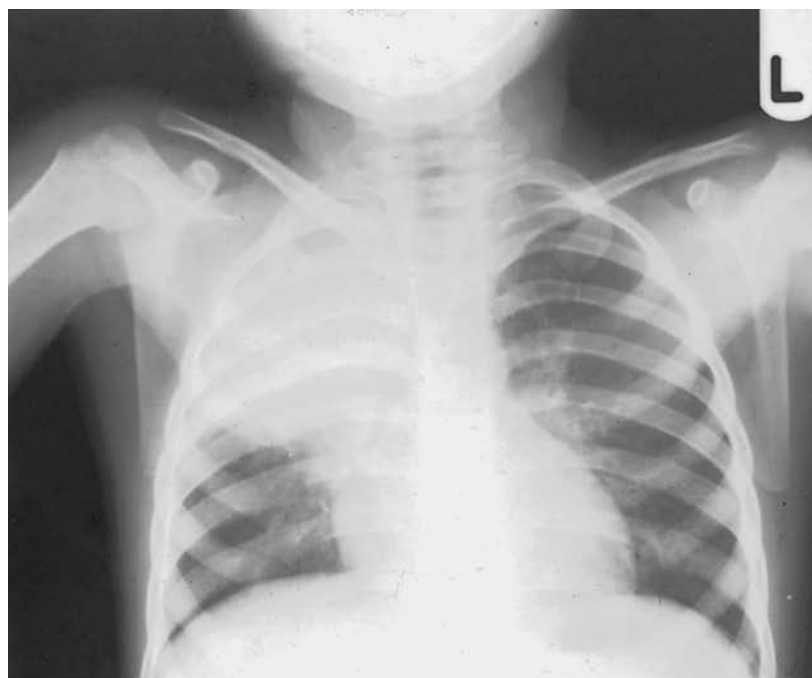
## Investigations

### Haematology and biochemistry

The blood count usually shows a polymorphonuclear leucocytosis. In the elderly and where the infection is overwhelming, the white cell count may be normal or there may be leucopenia [206]. A marked leucocytosis (exceeding  $30 \times 10^9/L$ ) or leucopenia ( $<4 \times 10^9/L$ ) have also been found to be associated with a poor prognosis [4]. Severe infection is occasionally accompanied by DIC and the syndrome of inappropriate ADH secretion may occur. The erythrocyte sedimentation rate is usually raised and it falls as clinical improvement occurs. If it remains raised, then another disease or other complicating factors should be considered.

### Chest radiography

The chest radiograph classically shows homogeneous hazy shadowing occupying the anatomical distribution of a lobe (Fig. 13.9). Shadowing need not involve the whole lobe, but if most of it is included then it is conventionally



(a)



(b)

**Fig. 13.9** (a) Right upper lobe pneumococcal pneumonia in a child following influenza showing classical lobar consolidation. The radiograph cleared within 2 weeks of starting penicillin. (b) Right lower lobe consolidation of more patchy distribution in a patient with emphysema. Pneumococcus was cultured from blood.

classified as lobar. Any part of the lung may be involved, although the lower lobes are most commonly affected. The density of the shadowing varies according to the intensity of the pneumonic exudation. Although pneumonic shadowing in *Strep. pneumoniae* infection is more commonly homogeneous than patchy [210], this feature does not reliably serve to distinguish it from other pneumonias such as *Mycoplasma*, *Legionella* and psittacosis. *Klebsiella*

pneumonia is also classically lobar in distribution. In patients admitted to hospital with pneumonia, cases with radiographic evidence of lobar consolidation are less common than those in whom consolidation is radiographically confined to one or more segments or subsegments, sometimes in different lobes [211]. Radiographic clearing usually occurs over 3–6 weeks and is nearly always complete. This radiographic delay contrasts with the generally

rapid clinical response to treatment with antibiotics, which is measured within hours or days.

#### *Blood gases*

Arterial blood gas analysis is an important gauge of severity (see Table 13.4, p. 360) and may show hypoxia and hypocarbia, with a respiratory alkalosis due to shunting of blood through consolidated lung [212]. Hypercarbia may occur if there is coexisting chronic bronchitis and emphysema or in severe cases if the patient is becoming exhausted.

#### *Microbiological tests*

Blood culture is normally carried out routinely and is positive in about 30% of cases. Sputum examination is best carried out expeditiously but antibiotics should not be delayed if a specimen is not readily obtainable. Gram staining of expectorated sputum in pneumococcal pneumonia is reported to have a sensitivity and specificity of 62 and 85% respectively [213]. The characteristic sputum finding in pneumococcal pneumonia is the presence of Gram-positive diplococci, some of which may be contained within polymorphs. If standard pneumococcal antisera are available (obtained by immunizing rabbits with pneumococci), then *Strep. pneumoniae* can be rapidly identified and typed using the Quellung (Neufeld's capsular precipitin) reaction, in which specific antibodies in the standard antisera react with capsular antigens on the surface of the pneumococci being tested. The Quellung reaction can be applied to sputum or other clinical specimens.

Since it is not uncommon for patients admitted to hospital with pneumonia to have received an antibiotic beforehand, positive cultures in these subjects are unusual. A positive diagnosis may be made from sputum microscopy and culture in about 50% of patients with pneumococcal pneumonia, although this figure may be reduced by half in the elderly [66,206]. It must be remembered that expectorated sputum may contain contaminants that colonize the nasopharynx commensally and these may include *Strep. pneumoniae*, staphylococci, *H. influenzae* and *Moraxella catarrhalis* [214].

Pneumococcal (polysaccharide capsular) antigen detection is carried out routinely in some centres usually using latex agglutination or, less commonly, CIE. Pneumococcal antigen detection has been found to be less sensitive when applied to blood (<25%) than urine (about 40%), being most sensitive when used on mucopurulent sputum (about 80%) [94,95]. This compares with a sensitivity of about 50% when the Gram stain is applied to sputum for the same purpose. The investigation can also be applied to pleural fluid and to lung secretions that have been obtained invasively using percutaneous ultra-thin needle aspiration and bronchoalveolar lavage (see p. 362), so that

the sensitivity of these tests may be increased [96–98]. The specificity of sputum pneumococcal antigen for detecting cases of pneumococcal pneumonia is reduced to about 70% because *Strep. pneumoniae* is often isolated from the sputum of patients with chronic bronchitis who do not have pneumonia. A positive sputum pneumococcal antigen test may also not differentiate between oropharyngeal colonization and pulmonary infection; furthermore some capsular antigens are difficult to detect by these methods. Pneumococcal antigen testing has been useful in research to establish the relative frequencies with which different organisms are found in population studies of pneumonia, since it has the particular advantage that its sensitivity is unaffected by prior antibiotic treatment, unlike the various culture techniques. Despite this, it has not established itself as a routine test in most general hospital laboratories. Although the routine use of pneumococcal antigen testing is expensive and requires technical expertise, it does have the advantage of providing rapid information and might be usefully applied in the sicker patient in whom routine cultures are likely to have been suppressed by previous treatment with a broad-spectrum antibiotic. Pneumococcal antigen may be detected in the serum or urine of 50% of patients with pneumococcal pneumonia who are non-bacteraemic in terms of negative blood cultures. The antigen remains detectable for 7–14 days after bacteraemic pneumococcal pneumonia.

Pleural fluid, if present in sufficient quantity, should be aspirated and submitted for Gram stain and culture and the usual chemistry as referred to above. If pus is not found and the patient is on an antibiotic, the fluid is frequently sterile but may still be submitted for pneumococcal antigen testing if this is available.

#### *Treatment*

In many parts of the world penicillin-insensitive pneumococci are still uncommon, although in general protocols for treating *Strep. pneumoniae* infections do have to take into account the local prevalence of penicillin resistance, particularly in the case of pneumococcal meningitis. Benzylpenicillin (penicillin G) is still the antibiotic of choice for bacteriologically confirmed pneumococcal pneumonia, having greater activity against this organism (MIC usually <0.06 mg/L) than amoxicillin or ampicillin. Despite this, the aminopenicillins ampicillin or amoxicillin, with or without a  $\beta$ -lactamase inhibitor, are often prescribed to good effect by clinicians concerned about using a narrow-spectrum penicillin without positive identification of the organism, particularly in older patients with comorbidity. The first 2 days of treatment in hospital is often given parenterally, although the need for this in all cases is debatable. A benzylpenicillin dose of 1.2 g (2 megaunits) i.v. 6-hourly is usual, although the intramuscular route is feasible and higher doses may be

used in severe infection. Parenteral penicillin may also be continued for longer than 2 days according to the clinical response, although this is not often necessary with uncomplicated pneumonia. Parenteral therapy may be followed by oral amoxicillin at a dose of 500 mg orally 8-hourly, or if ampicillin is chosen 500 mg orally 6-hourly. Phenoxymethylpenicillin (penicillin V) 500 mg 6-hourly for 7 days can be used as an alternative to an oral aminopenicillin but is less well absorbed. When a patient is allergic to penicillin, a macrolide such as erythromycin may be used instead, 0.5–1 g being given intravenously every 6 h for 48 h (commonly causing phlebitis and therefore not given in bolus form) to be followed by 250–500 mg orally 6-hourly for 7 days. It should be borne in mind that the Central Public Health Laboratory in England reported pneumococcal resistance to erythromycin in 8.6% of strains that it tested [115]. This resistance extends to those newer macrolides such as clarithromycin that may be used in place of erythromycin. These cause less nausea and need less frequent dosing but are more costly. Resistance rates to macrolides of 6–19% are reported in the USA, these rates being significantly higher for penicillin-resistant strains of pneumococci [121]. Cefuroxime 1.5 g i.v. 8-hourly may be used as an alternative to parenteral erythromycin in patients who report rashes in response to penicillin, although cross-allergenicity between penicillins and cephalosporins may occur in about 10% of patients. Alternatives that might be preferred in the presence of pulmonary comorbidity are cefotaxime 1 g i.v. 8-hourly or ceftriaxone 2 g i.v. once daily. Some cephalosporins (e.g. ceftazidime and cefoxitin) are significantly less active against the pneumococcus than penicillin and are best avoided where this is the known pathogen. Newer fluoroquinolones such as sparflaxacin, which have much greater efficacy against the pneumococcus than ciprofloxacin and ofloxacin, offer an alternative but further published data on their clinical efficacy in this situation are awaited.

Where much higher levels of penicillin are required for adequate penetration, as for example in rare cases of complicating meningitis or endocarditis or in septic arthritis or empyema, then much higher doses of benzylpenicillin of up to 24 g (40 megaunits) i.v. daily in divided 4–6-hourly doses have been given.

Penicillin-resistant forms of *Strep. pneumoniae* (see below) were well described in the 1970s [215]. Although at that time rare in Europe and North America, penicillin resistance has now become a global problem, being no longer confined to certain parts of the world such as South Africa and New Guinea where epidemics of pneumococcal pneumonia led to the widespread use of prophylactic penicillin in certain locations [215,216]. Because of potential or real problems with penicillin insensitivity, a careful watch has to be kept for possible clinical treatment failures and closer attention has to be paid to patterns of antibiotic

sensitivity when pneumococci are isolated so that treatment may be changed if necessary. Benzylpenicillin is still usually effective for pneumococcal pneumonia even in areas where the prevalence of penicillin-resistant organisms is high and can still overcome organisms with an intermediate or even high level of resistance. However, treatment failures may occur in pneumococcal meningitis because penicillin may not achieve adequate cerebrospinal fluid (CSF) levels to deal with insensitive organisms and the best way of dealing with this situation is still a matter of debate. One suggested approach is to use a combination of an extended-spectrum third-generation cephalosporin such as cefotaxime or ceftriaxone and vancomycin in children or adults with suspected pneumococcal meningitis in areas where penicillin resistance is known to be a significant problem, treatment being continued with a single drug when the results of sensitivities are available [217,218]. Vancomycin is currently regarded as the single most effective antibiotic for treating meningitis caused by penicillin-resistant pneumococci.

The temperature in patients with pneumococcal pneumonia usually starts to fall within 24–48 h of commencement of an appropriate antibiotic (Fig. 13.8). If it does not, then the possibility of another infecting organism, a resistant pneumococcus, allergy to the antibiotic, a collection of pus or a diagnosis other than pneumonia should be considered. Response to treatment in meningitis is usually slower but improvement should be detected within 5 days, treatment being continued for 10–14 days. Complicating endocarditis, septic arthritis or pleural empyema may well require treatment for 6 weeks.

General supportive therapy is discussed above, and includes the provision of oxygen at sufficient concentration to correct hypoxaemia. The usual constraints to oxygen therapy apply when the patient has coexisting chronic obstructive pulmonary disease, with possible respiratory centre dependency on hypoxic drive (see Chapter 23). Pleuritic pain is treated with appropriate analgesia. Narcotic analgesics are not usually required but may be given in the absence of serious hypoxaemia, alveolar hypoventilation or obstructive pulmonary disease.

## Prevention

### Vaccination

Pneumococcal pneumonia remains the most common form of community-acquired pneumonia and it causes large numbers of deaths. A significant proportion of these deaths occur in association with bacteraemia despite early treatment with appropriate antibiotics and, peculiarly, the mortality has remained fairly constant over the last four decades at around 25% in such bacteraemic cases [217,219]. For these reasons attention has been focused on prevention by means of vaccination [158]. Efforts in this

direction are not new and the first trial of such a vaccine was carried out during the Second World War [220]. Interest rapidly faded, however, following the advent of penicillin in 1944 and did not reawaken until the 1960s, the vaccine only becoming available in the UK in 1979.

Immunization against *Strep. pneumoniae* is desirable in those groups of the population most likely to develop the infection and in those who, if they do develop it, have a greater risk of dying as a result. Pneumococcal infection is more common in the elderly [44] and in patients who have had a splenectomy or who have splenic dysfunction, such as occurs in sickle cell anaemia as a consequence of multiple small infarcts and in coeliac disease [221–223]. Groups in whom the mortality from pneumococcal pneumonia is higher include the elderly and those with chronic pulmonary or cardiac disease, chronic renal insufficiency, chronic liver disease or alcoholism and diabetes mellitus [224].

The vaccines at present commercially available in the UK and USA are complex polyvalent preparations currently based on the capsular polysaccharide antigens of 23 pneumococcal types that are responsible for over 80% of episodes of bacteraemic pneumococcal infection in the USA, the distribution of serotypes in the UK being broadly similar [225,226]. The vaccines (Pneumovax II and Pnu-Imune) may be given subcutaneously or intramuscularly. Local tenderness is a common side-effect but fever occurs in less than 5% of subjects [227].

Although it is agreed that pneumococcal pneumonia is well worth preventing, there is no shortage of controversy about the ability of the vaccine to provide adequate immunity in those patients at special risk. It does not apparently influence nasopharyngeal carriage rate in normal subjects but has been shown to be effective in preventing pneumonia in controlled trials involving immunocompetent young men and in relatively isolated or crowded populations, such as South African gold miners, highland town dwellers in Papua New Guinea and military recruits, all of whom were susceptible to epidemic pneumococcal pneumonia [220,228–231]. Unfortunately the evidence of benefit in elderly populations and those with chronic disease who are at particular risk from sporadic disease has been more conflicting. It has been estimated that a large, prospective, randomized, placebo-controlled trial involving 100 000 subjects would be required to remove doubts about whether vaccination is effective in these subjects and a project of such a size would not receive funding or even ethical approval, in view of the fact that government health agencies already recommend widespread use of the vaccine [232]. In the mean time the evidence is conflicting. One well-designed, placebo-controlled, randomised, double-blind study of 2295 high-risk patients aged over 55 years was unable to demonstrate the efficacy of pneumococcal vaccine in preventing pneumonia or bronchitis [233]. Another study of only 43 patients with

chronic bronchitis and emphysema showed that pneumococcal vaccine did not diminish the frequency of isolation of *Strep. pneumoniae* from the sputum and also found that the levels of antibody to the various vaccine strains of pneumococcus were high before vaccination [234]. These findings raised doubts about the recommendations of the US Centers for Disease Control, which have been based on retrospective analyses and have been taken to indicate that the vaccine is useful in preventing bacteraemic complications in elderly patients, a hypothesis supported by an earlier case-control study [159,235,236]. It has been suggested that elderly patients at risk from pneumococcal bacteraemia should be vaccinated before hospital discharge, since a high proportion of patients with pneumococcal bacteraemia were found to have been in hospital within the preceeding 5 years [237–239]. A large and more recent case-control study claimed to show an overall efficacy for the vaccine of 56%, patients with severe pneumococcal infection being less likely to have been vaccinated than a control group [240]. In immunocompetent persons the protective efficacy was 61% but it varied a good deal with age, from 93% in those aged less than 55 years to 46% for those aged 85 years or more. It is possible that relative immune incompetence may be a reason for the vaccine's diminished efficacy in some elderly or chronically sick patients. This has led to the suggestion by some that any vaccination programme would be more likely to be successful were the vaccine to be administered at an earlier age [241]. An uncontrolled indirect cohort study took 2837 patients in whom the pneumococcus had been isolated from blood or CSF and then investigated their vaccination history, finding that those who had been vaccinated were less likely to have been infected by a serotype contained in that particular vaccine than by a serotype not in the vaccine. Using this method, these workers claimed to demonstrate an overall vaccination efficacy of 57% and an efficacy of 75% in those aged over 65 years [242]. The vaccine's efficacy in non-bacteraemic pneumonia is less easy to evaluate because of the lack of non-invasive methods for reliably diagnosing this type of illness. A single-blind trial of 2837 subjects over the age of 60 years, who were randomized so that half received both 14-valent pneumococcal vaccine and influenza vaccine and half influenza vaccine alone, found no significant difference in the overall frequency of pneumococcal pneumonia over 3 years, although there was a statistically significant preventive efficacy of 59% in a subgroup with chronic disease risk factors [243].

The efficacy of pneumococcal vaccination was found to be only 21% in patients who were immunocompromised for reasons other than HIV infection [240,244]. This group includes patients with acute leukaemia, chronic lymphocytic leukaemia, Hodgkin's disease and multiple myeloma. This has led to doubts about whether it confers significant protection in patients who are serologically

HIV positive, although both North American and British agencies recommend its use in this patient group [245,246]. The concern is that at least some HIV-positive patients may not be able to mount an effective antibody response to the vaccine [247]. This may well be the case as HIV infection progresses so that a pragmatic but unproven policy is to vaccinate seropositive HIV patients as early as possible, while the CD4<sup>+</sup> (T-helper) lymphocyte count is greater than  $0.2 \times 10^9/L$ , or even to vaccinate HIV-negative subjects who belong to groups that are at high risk of subsequently becoming positive [248]. In HIV-positive patients about to start antiretroviral therapy, it has been argued that pneumococcal vaccination should be delayed for a few weeks in the hope that their ability to mount an immune response improves [249].

It can be stated with conviction that pneumococcal vaccination is safe and, whether it is applied to the elderly and those with chronic disease or not, it can be used effectively in younger immunocompetent subjects who may be at risk in geographically localized outbreaks or in outbreaks caused by resistant organisms. In addition, vaccination can be strongly recommended in subjects at risk (see Table 13.5, p. 385), such as those about to undergo elective splenectomy, those who have undergone emergency splenectomy and those with splenic dysfunction as occurs in sickle cell anaemia and coeliac disease. Children under the age of 2 years (who cannot mount an adequate antibody response to unconjugated polysaccharides) should not be vaccinated but those at risk may be protected by twice-daily oral penicillin.

Antibody levels following immunization may wane to low levels after about 5 years; as the antibody response tends to be weaker and of shorter duration in asplenic patients than in those with normal immunity, it is suggested that such patients should be revaccinated after 5–10 years [193,241]. Protection may last for an even shorter time in some patients known to have a particularly rapid antibody decline, such as those with the nephrotic syndrome, renal failure and also organ transplant recipients, prompting some to suggest that such patients should have their antipneumococcal antibody levels monitored annually following immunization so that a more informed decision might be made about the most appropriate time to revaccinate [173]. However, it remains somewhat unclear as to what antibody level is protective and most immunology laboratories only measure a selected few of the 23 serotypes in use. Revaccination within 5 years in subjects who still have significant antibody levels may give rise to an unpleasant local reaction. The vaccine should not be given during pregnancy or to those who are acutely ill.

Research into the efficacy of new protein-conjugate pneumococcal vaccines is underway in the hope that these will offer better protection, as well as being protective in infants under the age of 2 years. The pneumococcal poly-

saccharide capsules in these conjugated vaccines are attached to a protein carrier in a similar manner to that used in the successful conjugated *H. influenzae* type b vaccine, in order to attain a higher degree of immunogenicity with a better concentration of circulating capsular antibodies. One current drawback with these vaccines is that they are pentavalent, it being possible to conjugate only seven capsular polysaccharides to the protein carrier.

Asplenic patients should also be vaccinated against *H. influenzae* type b and *Neisseria meningitidis* groups A and C. Although two-thirds of isolates in the UK are group B and therefore not covered by the existing meningococcal vaccines, a B vaccine is under development. These patients are also at increased risk of malaria.

### *Antibiotic prophylaxis*

Antibiotic prophylaxis is considered essential in patients following splenectomy, although the optimal duration of therapy is undetermined and the subject of conjecture [194]. The first 2 years after splenectomy is considered to be the time of greatest risk, although a lesser risk of serious pneumococcal infection is lifelong. The Department of Health recommends that all children should receive penicillin prophylaxis after splenectomy and it would seem reasonable to continue this up to the age of 16 years or as long as the child remains in the care of their parents, after which problems with compliance often increase [193]. A reasonable policy in adults is to discuss the risks and to treat with prophylactic penicillin for 2 years and thereafter, in patients judged to be compliant, to ensure that a small supply of antibiotic is available so that self-treatment can start promptly at the first sign of a febrile illness, after which medical advice can be taken [250–253]. Some authorities have recommended lifelong antibiotic prophylaxis but the drawbacks of this include the likelihood of poor compliance as well as the potential for encouraging the emergence of antibiotic-resistant bacterial strains [254]. Prophylactic penicillin has also been shown to prevent pneumococcal infection in functionally asplenic Jamaican children with homozygous sickle cell anaemia and should be given to such children from the age of 3 months at least until the age of 2 years, when they should be vaccinated (see above) [255].

Usual prophylactic dosages are phenoxymethylpenicillin 500 mg for adults, 250 mg for children aged 6–12 years and 125 mg for children aged less than 6 years, all taken twice daily. Others have recommended amoxicillin 500 mg daily for adults and 250 mg daily for children in order to extend cover to *H. influenzae* as well [253]. Penicillin-allergic subjects may take erythromycin 250 mg twice daily for adults and children over 2 years of age, the dose being reduced to 125 mg twice daily in younger infants.

### Problems with penicillin resistance

Penicillin-resistant pneumococci were unheard of before 1967 when the first isolates were cultured in patients living in remote parts of Papua New Guinea. The problem was subsequently reported in Australia and South Africa and by the 1990s had become global. Over 40% of isolates in Spain, Iceland and some eastern European countries such as Hungary show reduced susceptibility to penicillin. High prevalence rates have also been reported in parts of South America and South Africa and recent data have shown a rate of 25% in the USA, over 40% of isolates from white children under the age of 6 years in Atlanta being resistant to penicillin [256]. The prevalence in the UK is 5–10% and that in Australia reportedly about 7%. It is not uncommon for quite wide geographical variations in the prevalence of resistant pneumococci to be reported within a single country and thus it is important for clinicians to have some knowledge of the microbiological resistance patterns in their own locality.

Resistance is likely to have arisen largely because of the heavy and indiscriminate use of penicillin, sometimes as prophylaxis in crowded communities prone to epidemics of pneumococcal infection; clearly, a fortuitously resistant clone of organisms is provided with a powerful Darwinian advantage if its competitors are conveniently destroyed by penicillin [257]. This is supported by the recent observation in Atlanta that drug-resistant pneumococcal infection was more commonly found among suburban-dwelling whites who would, as a group, have had readier access to antimicrobial drugs than poorer people living in other less affluent parts of the same city [215,258]. The mechanism of penicillin resistance is *not* due to  $\beta$ -lactamase production but to subtle changes in the penicillin-binding proteins on the cell wall of the pneumococcus, these 'new' proteins having a lower affinity for the penicillin molecule. Once these molecular changes in the penicillin-binding proteins have taken place by genetic remodelling or point mutation, the altered genes may spread horizontally among pneumococcal strains and also geographically as a result of modern modes of world travel. Thus resistant pneumococci are known to spread among small children in daycare centres, this being considered of major epidemiological importance in the dissemination of resistant forms in Iceland where 80% of children attend such centres [259,260].

Decreased susceptibility to penicillin may be defined as 'intermediate' (or low-level resistance) with an MIC of 0.1–1.0 mg/L and 'resistant' (or high-level resistance) with an MIC equal to or greater than 2.0 mg/L. Pneumococci with an MIC of 0.06 mg/L or less are defined as fully susceptible. Thus pneumococcal resistance to penicillin is relative rather than absolute, a recent study in Spain finding that the levels of penicillin resistance that were then current were not associated with increased mortality in

pneumococcal pneumonia, the implication being that this relative resistance can be overcome by usual therapeutic doses [217]. There is thus little evidence linking clinical failure in pneumococcal pneumonia with conventional doses of parenteral penicillin. Unfortunately this is not the case when pneumococci cause infection in less accessible sites such as the meninges, so that the mortality in pneumococcal meningitis is increased by resistant strains [261]. Penicillin-resistant pneumococci also tend to show cross-resistance to other  $\beta$ -lactam antibiotics such as imipenem and third-generation cephalosporins (e.g. cefotaxime and ceftriaxone), which also have reduced activity, pneumococcal resistance to cefotaxime being about 9% in both Spain and the USA [217]. Pneumococcal resistance may also extend to classes of antibiotic beyond the  $\beta$ -lactams. These organisms are sometimes described as multidrug resistant and may display the presence of at least an intermediate level of resistance (as above) to two or more of the following drugs or classes:  $\beta$ -lactams and carbapenems, macrolides, tetracycline, fluoroquinolones, chloramphenicol and trimethoprim, so that vancomycin may be required in the case of meningitis complicating bacteraemic disease caused by resistant pneumococci, all strains having remained susceptible to this drug. *Strep. pneumoniae* resistant to erythromycin are also resistant to the newer macrolides.

### Mortality

The overall mortality from pneumococcal pneumonia in hospital is 5–19% [167,262,263], having been approximately 30% before the advent of antibiotic therapy. The death rate is about twice as high in patients who are found to have bacteraemia and has remained disappointingly static for about four decades, bacteraemia itself occurring in 15–25% of patients [209,263]. Thus the overall mortality from pneumococcal bacteraemia is 18–40% [22,167,209,263–266]. The largest prospective UK study of pneumococcal bacteraemia from the 1980s found the overall mortality to be 28.6% in 325 episodes, falling to 11.8% in those who received antibiotics for at least 24 h [219].

Mortality is related to the antigenic type of *Strep. pneumoniae* responsible for the infection, the type 3 pneumococcus having a sinister reputation. This serotype has been found to have an 18% mortality without bacteraemia, rising to 51% in the presence of bacteraemia (see section on complications) [169]. This accords with a 37% overall mortality rate for the same type in the series of Macfarlane *et al.* [167]. In contrast, the overall mortality for serotypes 1 and 7 was 17 and 10% respectively, whereas no mortality has been reported for non-bacteraemic type 2 infection compared with 10% when this type was associated with bacteraemia [167,169]. These differences are clearly important as the large study of Gransden *et al.* [219] found that type 3



**Table 13.5** Conditions increasing susceptibility to pneumococcal infection and its attendant mortality (see text).

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Splenectomized state
Functional asplenia or hyposplenia (as in homozygous sickle cell disease, thalassaemia, adult sickle cell disease)
Chronic lung disease
Chronic heart failure
Chronic renal disease (including nephrotic syndrome)
Chronic liver disease (including alcoholism)
Diabetes mellitus
Immunodeficiency states arising as a result of disease or its treatment (including lymphoma, acute leukaemia, chronic lymphocytic leukaemia, multiple myeloma, HIV infection)
Cerebrospinal fluid leaks
Old age (>65 years) and extreme youth (<2 years)

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was the commonest serotype in adult pneumococcal bacteraemia.

The age of the patient has also been related to mortality, death being more likely to occur in elderly patients [168,263]. Wide age-linked variations have been reported, from 18% mortality for patients in their fifth decade to 83% in patients aged over 90 years [44,209]. Increasing age seems to be an independent risk factor in bacteraemic disease, although this may be accounted for partly by delayed diagnosis and treatment as a result of atypical presentations in the elderly [208,266]. Certainly some physicians have reported the same low mortality rates in those aged over 65 as in those who are younger, provided that antibiotic treatment has been commenced promptly [209]. When death does occur in the elderly, it is usually within 24 h of admission compared with 4–5 days for younger age groups [208]. Other factors that increase the likelihood of mortality include the presence of serious coexisting disease, such as chronic bronchitis and emphysema, congestive heart failure and diabetes mellitus, etc. (Table 13.5). Patients with renal or hepatic insufficiency may suffer a mortality of almost 70% should they develop bacteraemic pneumococcal pneumonia and patients who are immunosuppressed, have associated malignancy or have extrapulmonary infection also have a higher mortality [219,266].

The total number of deaths from pneumococcal pneumonia in a given period of time is a function of the prevalence of influenza during the same period, epidemics of influenza being associated with increased mortality from bacterial pneumonia, of which pneumococcal pneumonia is the most common type [267].

### Complications

Complications of pneumococcal pneumonia include pleural effusion, which may occur in up to 25% of cases. Aspiration should be performed to exclude empyema but the fluid is usually found to be a sterile exudate. Shock and

DIC may occur with serotype 3. Empyema (see Chapter 14) used to occur in 5–8% of patients before antibiotic availability but is now unusual, being found in only 1% overall and in 10% of those with pleural effusions. Lung abscess (see Chapter 15) is rare and when it does occur is usually associated with serotype 3 infection. Purulent pericarditis is also rare and may occur as a result of the direct extension of infection from an empyema [268]. More widely disseminated infection may occur and includes meningitis, peritonitis, endocarditis and septic arthritis. These complications are unusual or rare but may result from the delayed institution of antibiotic therapy. Occasional cases of rhabdomyolysis with myoglobinuric renal failure have been reported, as has massive pulmonary gangrene [269,270].

### *Legionella pneumonia*

*Legionella pneumonia* (Legionnaires' disease) is usually caused by the aquatic organism *Legionella pneumophila*. This first came to light after a serious outbreak of pneumonia affecting over 100 of the delegates attending the 1976 American Legion convention at a hotel in Philadelphia. The circumstances of this outbreak and the deaths that arose from it led to the description of a previously unidentified small aerobic Gram-negative flagellated coccobacillus that was obtained postmortem from the consolidated lungs of four victims [271]. Material from this lung tissue had been inoculated intraperitoneally into guinea-pigs and thence to chick embryo yolk sacs, a procedure usually followed in order to isolate rickettsiae, which were under consideration as a possible cause of the outbreak. The illness became popularly known as Legionnaires' disease and the organism was similarly termed '*Legionella*' [272]. Previously unclassified organisms were subsequently recognized as belonging to the same Legionellaceae family and to have been responsible for undiagnosed febrile illnesses dating back to 1947 [273]. *L. pneumophila* is the most important species in the genus *Legionella* in terms of human pathogenicity, but more than 40 different species have been identified, of which less than half have been shown to be pathogenic in humans. *L. pneumophila* itself has at least 11 serotypes of which group 1 is the predominant cause of human illness, being thought to be responsible for over 80% of all cases of human *Legionella* infection [274,275]. *L. pneumophila* and at least one other species may also cause a benign non-pneumonic influenza-like illness known as Pontiac fever, after the town in Michigan where this epidemic illness was first described [276].

*L. pneumophila* is a small organism and takes up Gram stain poorly, so that it is easily overlooked on microscopy. It is fastidious in its culture medium requirements but can nevertheless be readily grown if these requirements are met. It is possible to identify the *Legionella* sp.

microscopically by fluorescein-tagged monoclonal antibody against a common bacterial membrane protein [277]. *Legionella* spp. live in water, in which medium they are ubiquitous. They are able to multiply extracellularly but may also invade and multiply in aquatic organisms such as amoebae or protozoa [278]. They are able to colonize the water and air-conditioning systems of public buildings such as hotels and hospitals. These sources may be responsible for the sporadic epidemics that continue to attract the popular media, although the majority of cases of pneumonia are sporadic and community-acquired from unknown sources. *L. pneumophila* has been shown to be transmissible to animals by droplet aerosols [279]. *L. pneumophila* is the most pathogenic of the species and accounts for about 90% of reported cases of Legionnaires' disease, a few being attributed to *L. micdadei* (the Pittsburgh pneumonia agent) and *L. bozemanii*.

### Incidence

*Legionella* pneumonia occurs both sporadically in the community at large and less commonly but more dramatically in epidemics clustered about some particular physical location in which the water supply has become contaminated by the organism. A community study carried out retrospectively in the USA found serological evidence of previous *Legionella* pneumonia in 1–2% of the population, giving an estimated incidence of 12 cases per 100 000 per year [280]. These figures may be an underestimate, as only serotype 1 was tested for and as hospital-acquired cases were excluded. A multicentre study carried out under the auspices of the British Thoracic Society found that *L. pneumophila* was responsible for 2% of 453 adult cases of community-acquired pneumonia [281]. Other prospective studies have found higher rates of infection in certain locations. Thus a Nottingham survey of community-acquired pneumonia found *L. pneumophila* to be responsible for 15% of 127 cases during the study period, this organism being the second most common pathogen isolated, whereas a New Zealand study found *Legionella* sp. to be the cause in 11% of 255 cases [126,167]. Legionellosis has been reportedly responsible for even higher proportions of pneumonic infections at some centres in North America [282,283], particularly among severe cases of community-acquired pneumonia needing intensive care [121]. Although it is likely that regional differences in prevalence exist, the enthusiasm with which evidence of *Legionella* infection is pursued is bound to influence the reported infection rate in any centre; thus in the Nottingham study half the patients were not severely ill and the diagnosis of *L. pneumophila* pneumonia would have been missed if a convalescent serum sample had not been tested routinely [284], a retrospective procedure frequently omitted in general hospital practice.

Fluctuations in the number of cases have also been

observed to occur from year to year and seasonally [285]. A follow-up study in Nottingham, carried out 3 years after the original report, found that the proportion of cases had fallen from 15 to 5% [286]. The most consistently reported figure is about 6% [276].

The epidemic form of *Legionella* pneumonia is dependent upon a combination of circumstances that result in the exposure of a sufficiently large number of people to a contaminated source of water. Epidemics occur in buildings such as hotels or hospitals; Wadsworth Veterans Administration Hospital, Los Angeles, experienced over 175 cases during a period of 3 years, at one time over 20 cases occurring within a month. The number of cases declined sharply when the hospital's water supply was chlorinated [287]. It is possible that the wider availability of urinary antigen testing may also result in an apparent increase in the frequency of hospital-acquired cases.

### Epidemiology

*Legionella* pneumonia is most likely to be caused by the inhalation of droplets of contaminated water. There is some evidence to suggest that seasonal factors play a role in sporadic cases of *Legionella* pneumonia, infection having been noted to be more common in the summer and autumn months [167,283,288]. Cases commonly occur in relation to travel on holiday or away from home but this alone is not thought to explain the seasonal pattern. The incubation period is 2–10 days [289]. There is no evidence that any of the *Legionella* spp. can be transmitted from person to person, so that isolation of a case is not necessary. When clustering of cases or epidemics of *Legionella* infection have been investigated thoroughly and to a successful conclusion, the origin of the organism has invariably been tracked down to a source of contaminated warm water that has acted as a reservoir of infection. Such outbreaks may occur in hotels, hospitals and elsewhere [290]. Sources of infection include domestic hot and cold water systems, wet cooling systems (including cooling towers and evaporative condensers), whirlpool and natural spas, humidifiers, ultrasonic mist machines, respiratory therapy equipment and fountains or sprinkler systems [291–296]. Considering that most hot water systems in large buildings are colonized by *L. pneumophila* [297] and that clinical outbreaks are relatively uncommon, it is likely that situations arise in which relative overgrowth of the organism occurs. It is also likely that a significant degree of immunity to *Legionella* infection exists in the community [298], although no test exists for separating those who are immune from those who are not and it appears that cellular rather than humoral immunity is the main defence against infection. Certainly previously healthy individuals may be infected by virulent organisms. However, the attack rate is higher in the elderly, tobacco smokers and those with chronic lung disease, alcoholism and

diabetes mellitus. Patients who are immunocompromised, such as those taking corticosteroids and other immunosuppressive or cytotoxic drugs, are at greater risk of infection and this group particularly includes the recipients of organ transplants [299–302]. *Legionella* pneumonia may occur in patients with HIV infection but there does not seem to be an excess of cases in this group and co-trimoxazole prophylaxis taken for *Pneumocystis carinii* may help to suppress *L. pneumophila* as well [303]. When the disease does occur in this group, however, it tends to be more severe. It is unresolved whether *Legionella* spp. are distributed in mud, soil and horticultural potting media in sufficient quantities to cause sporadic infection [304,305].

Successful epidemiological studies of large outbreaks of *Legionella* pneumonia or Pontiac fever have incriminated either the piped hot water system or vapour from the water coolant of the air conditioning [297]. In the case of hot water systems, *L. pneumophila* has been retrieved more frequently from shower fittings in hospital rooms where infection occurred compared with shower fittings where it had not [306]. Patients who developed infection in a Spanish hotel outbreak were found to have bathed earlier in the morning than those who did not develop infection, suggesting that multiplication of the organism in relatively stagnant water might be an important factor [307]. The organism may also have a predilection for the bases of hot water cylinders [308]. Sudden pressure shocks to a hot water system may also release increased numbers of organisms into free-flowing parts of the supply [287]. Intervention in such cases by either raising the hot water temperature or by introducing chlorination have been successful in controlling outbreaks [307]. It has also been documented that the organism may be transmitted by microaspiration of contaminated water, which may occur with the use of nasogastric tubes and in other situations [285].

The heat exchanger in air conditioning systems of large buildings is cooled by water. The water vapour resulting from this process is usually expelled by fans through a cooling tower, gaining egress through an opening on the roof of the building. Overcontamination of this coolant water with *Legionella* spp. may occur during periods of stagnation, and outbreaks of *Legionella* pneumonia or Pontiac fever have occurred when *Legionella* organisms have been drawn from the plume of water vapour into air conditioning ducts or other ventilation channels [276,309,310].

Occasional cases of legionellosis have been described in connection with bathing in so-called 'spa-whirlpools' and following exposure to lightly oiled water friction coolants in industry [311,312]. No cases have been connected with the large concrete 'natural draught' cooling towers seen in industrial areas and used widely by electricity-generating companies [313].

Species of *Legionella* other than *L. pneumophila* have been

identified as causes of pneumonia in clustered outbreaks acquired in hospitals in which the water supplies have been found to be contaminated. They include *L. micdadei* (the Pittsburgh pneumonia agent) and *L. bozemanii* [314,315].

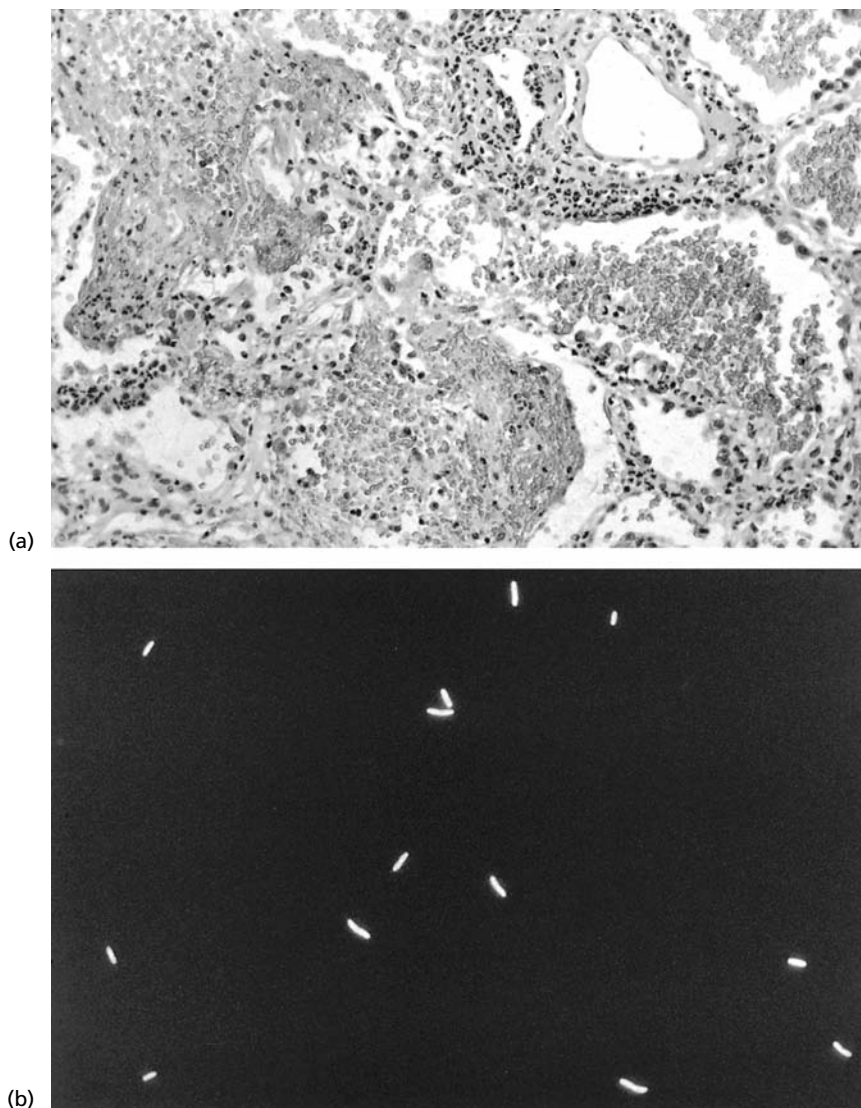
### Pathology

*Legionella* pneumonia produces gross appearances that resemble those of other severe lower respiratory tract infections. It may develop as areas of bronchopneumonia that cause adjacent lobules to coalesce resulting in lobar consolidation. Consolidation need not be confined to a lobe and is often bilateral in fatal cases. There may be evidence of a fibrinous pleurisy but empyema is rare. Small multiple abscesses may be found in up to 25% of cases coming to postmortem examination [316], and are more common in cases occurring in association with HIV infection. Microscopy shows that areas of consolidation contain an inflammatory cellular exudate within which there are areas of focal haemorrhage and loss of alveolar epithelium [317]. These features do not serve to differentiate pneumonia caused by *Legionella* from that caused by other microorganisms. However, *L. pneumophila* may be demonstrated in areas of inflammation particularly by silver staining, and fluorescent antibody techniques enable the organism to be identified specifically in lung tissue [318] (Fig. 13.10). Electron microscopic studies suggest that the organism divides intracellularly [319]. Resolution of pneumonia may be incomplete in patients who recover, as evidenced by the presence of persistent 'fibrotic' radiographic shadowing [210].

### Clinical features

*Legionella* pneumonia may occur in any age group but is rare in children and the median age of infection is 55 years [288]. It occurs more frequently in men than women, the ratio approaching 3:1. As with pneumococcal pneumonia, it may occur in the previously healthy but also appears to be predisposed to by coexisting illness such as chronic bronchitis, emphysema, diabetes mellitus and immunosuppression. Most paediatric cases of Legionnaires' disease occur in immunosuppressed patients.

It is likely that infection with *L. pneumophila* and other *Legionella* spp. can produce a wide spectrum of illness, much of which doubtless goes undiagnosed. Such infection may range from very mild or subclinical infection with seroconversion to so-called Pontiac fever to pneumonia. Pontiac fever is a supposedly uncommon, self-limiting febrile 'flu-like' illness associated with mild upper respiratory tract symptoms that last for 2–5 days [276]. *Legionella* pneumonia also produces a febrile illness associated with the usual constitutional symptoms, such as malaise, anorexia, myalgia and headache. This is



**Fig. 13.10** (a) Lung biopsy from patient with *Legionella* pneumonia complicating Wegener's granulomatosis showing intra-alveolar inflammatory cells, a mixed inflammatory interstitial infiltrate and hyperplasia of type II cells (haematoxylin & eosin  $\times 110$ ). (b) Smear from the same patient showing positive immunofluorescence for *Legionella pneumophila*. (Courtesy of Mr Michael Croughan.)

followed by a cough that may be initially dry but which is often later productive of faintly mucopurulent sputum, which may be flecked with blood. Dyspnoea may occur depending upon the extent of the pneumonia and the presence or absence of pleuritic pain. A relative bradycardia has been reported, especially in the elderly patient. Mental confusion and delirium may be impressive and the pyrexia may exceed  $40^{\circ}\text{C}$ . Diarrhoea has also often been recorded as a feature of the illness, occurring in over 20% of cases. Despite this, prospective studies have shown no particular clinical features that serve to reliably distinguish *Legionella* pneumonia from other pneumonic infection [282]. Extrapulmonary legionellosis is well documented but rare (see section on complications, p. 391).

Similar pneumonic illness may be caused by other *Legionella* spp., although *L. pneumophila* serotype 1 is by far the most common (80%). *L. micdadei*, originally known as the Pittsburgh pneumonia agent, is the most common of

the other pathogenic species, accounting for 8% of infections [320], usually occurring in hospital patients who are immunocompromised [321].

### Investigations

Haematological and biochemical measurements in *Legionella* pneumonia are of low specificity. The white cell count is usually raised but exceeds  $20 \times 10^9/\text{L}$  in fewer than 15% of cases [322,323]. The erythrocyte sedimentation rate and plasma viscosity are usually raised. DIC is reported in common with many other severe infections, but is unusual. Mild abnormalities of liver and renal function including proteinuria and microscopic haematuria are not uncommon [324,325] but have been reported with equal frequency in pneumonia caused by other organisms [282]. Similarly, raised lactate dehydrogenase and creatine kinase levels have also been recorded. However, hypona-

traemia (serum sodium  $<130$  mmol/L), possibly caused by inappropriate secretion of ADH, is more common in *Legionella* pneumonia than in other types, occurring in up to 50% of cases [282].

### Chest radiography

The diagnosis of *Legionella* pneumonia cannot be made on the basis of the chest radiographic appearances as these are very variable and entirely non-specific [210,282]; 90% of patients have a chest radiographic abnormality when first seen [326,327]. Infiltrates may be diffusely distributed, patchy and non-homogeneous, although with increasing consolidation the shadowing may become confluent (Fig. 13.11). Involvement of both lungs may occur in about one-quarter of patients and small pleural effusions have been reported with variable frequency [210,326]. Two further characteristic features are described: the first is that the shadowing may become more extensive despite adequate antibiotic therapy [210], and the second that resolution may be delayed or incomplete, with only one-third of patients having clear lung fields at 1 month and a further proportion having persistent areas of fibrotic scarring [327–329]. Bilateral nodular opacities that may expand and cavitate have been described in immunosuppressed patients, such as those taking systemic corticosteroids [285].

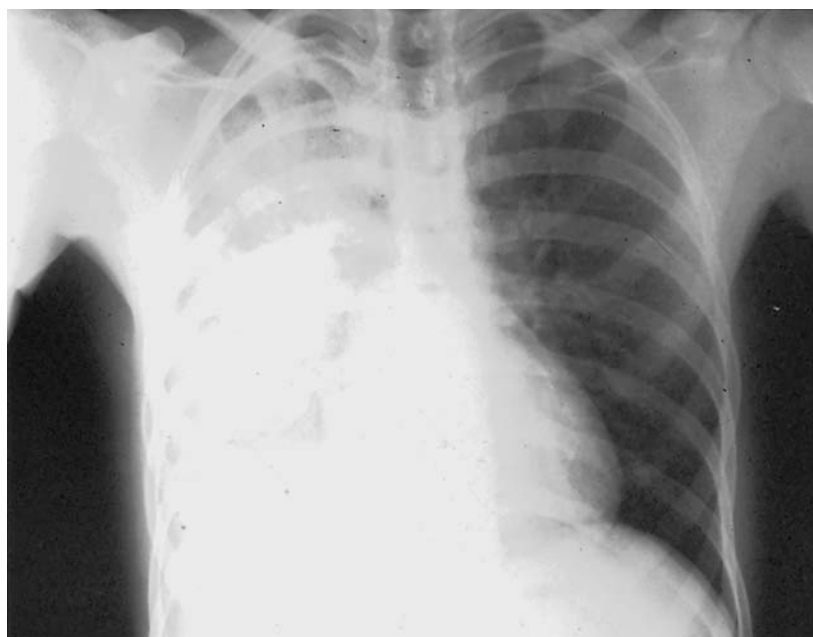
### Microbiological identification

*Legionella* spp. may be very easily missed unless the organisms are specifically sought in patients with pneumonia. This is unlikely to happen unless a knowledgeable person

in the laboratory is persuaded that there is a genuine clinical need, as in the case of a patient with microbiologically undiagnosed severe pneumonia. An adequate sample of sputum that shows few Gram-stained organisms despite the presence of neutrophils should raise the possibility of *Legionella* pneumonia. Morphologically the organisms are small coccobacilli. They take up stain poorly but if staining time is prolonged and basic fuchsin used as a counterstain, they can be demonstrated as Gram-negative coccobacillary rods. However, this is not a productive way of searching for this shy organism.

The usual methods include (i) the determination of antibody level in serum, (ii) the direct demonstration of the organism in body fluids or tissues under the microscope by using immunofluorescent techniques, (iii) the isolation of the organism on special culture media, (iv) the demonstration of antigen in the urine and (v) the detection of the organism using DNA probes and PCR.

The diagnosis in published series is commonly based on retrospective serological information. Most laboratories that have the capability use the microscopic immunofluorescent antibody test (IFAT) on blood to determine the antibody titre, testing for the most common *L. pneumophila* serogroup 1 and often first using the rapid microagglutination test (RMAT) as a screen. An initial blood sample should be taken as soon as possible after the onset of the illness, while the second 'convalescent' sample may be obtained 2–3 weeks later, a fourfold rise in antibody titre to 1/128 or more being diagnostic. Antibody production is commonly delayed, seroconversion at the second week having been found in about 55% of cases [330], so that a third sample at 6–9 weeks may be necessary in epidemiological work. However, a single titre of 1/256 (heat-fixed



**Fig. 13.11** Chest film of a young man who presented with hallucinations, hyponatraemia, fever, cough and diarrhoea showing dense consolidation of the right lung. Sputum smear showed *Legionella pneumophila*.

antigen) or greater for IFAT during convalescence is very suggestive of recent infection in a patient with a compatible illness. A single titre of 1/128 is less sure, as 5–30% of the normal populations have shown this level [331]. Similarly, a single titre of greater than 1/32 for RMAT is very suggestive of infection. Both RMAT and IFAT have a sensitivity of about 80% [332]. A few culture-positive proven cases fail to convert serologically [275].

The specific identification of *Legionella* bacilli in sputum, tracheal aspirates, BAL or lung biopsy tissue (Fig. 13.10) may be carried out rapidly using a monoclonal direct immuno-fluorescent antibody test (DFAT) and can give an answer in 3–4 h. The test is highly specific, false positives rarely occurring, although sensitivity is lower (25–75% for respiratory secretions, 80–90% for lung tissue) since large numbers of organisms need to be present before they can be seen, so that a negative result does not rule out the diagnosis [331]. A monoclonal antibody against a bacterial membrane protein common to all *L. pneumophila* subgroups has been developed for this purpose [277]. Interpretation of DFAT slides under the microscope requires a good deal of skill. This test is less likely to be positive if the radiographic changes are less extensive or if appropriate antimicrobial therapy has been started more than 2–4 days previously.

*Legionella* spp. are fastidious organisms and do not grow on the ordinary media used to process respiratory specimens. It is now possible to attempt routine culture of *L. pneumophila* and the organism can be grown from sputum, tracheal or bronchial aspirates and from lung tissue itself [333]. The choice of medium is important and a commercially produced charcoal yeast extract agar, containing antibiotics to suppress the growth of other organisms, may be used [334]. The reported sensitivity of culture on such selective media using samples from respiratory secretions or lung is better than with DFAT and exceeds 80% [331]. However, relatively few practical workaday laboratories have both the inclination and expertise to carry these cultures out satisfactorily. Isolation from blood cultures is unusual and has been achieved only rarely when blood taken at the onset of the illness is subcultured on to an appropriate solid medium [335].

*Legionella* antigen may also be detected in urine by various methods including radioimmunoassay. The test is specific for *L. pneumophila* serogroup 1, which is somewhat limiting for those in pursuit of excellence. The specificity is very high so that false positives are rare [331]. The sensitivity approaches 80% in serologically confirmed disease with a specificity of greater than 98% and it is a rapid, relatively inexpensive and valuable tool [336] that every properly developed clinical microbiology laboratory should have; those that do not have to rely on empiricism and fast motor cyclists. It has been reported that urine positivity may persist for weeks or months after acute *Legionella* infection [275].

Gene probes based on PCR and using radiolabelled DNA are commercially available to facilitate the rapid identification of *Legionella pneumophila* in clinical specimens such as urine, serum and BAL fluid. The sensitivity is less than with culture of respiratory secretions or lung tissue but of a similar order to that found with DFAT. Less technical skill is required than for DFAT and the gene probe test may remain positive for a few days longer after commencement of treatment. Such testing may also detect species other than *L. pneumophila* [285].

### Treatment

The management of *Legionella* pneumonia should include the usual supportive measures, such as correction of hypoxia, the relief of pain, the maintenance of blood pressure and the correction of fluid and electrolyte balance. Empirical treatment of severe community-acquired pneumonia must cover the possibility of legionellosis.

Antimicrobial therapy for *Legionella* cannot be based on laboratory sensitivities alone because these tend to mislead—effectiveness *in vitro* need not translate into efficacy in patients so that some drugs that appear effective when tested *in vitro*, such as co-amoxiclav and imipenem, are ineffective *in vivo*. This presumably reflects the propensity of the organisms, once engulfed by polymorphs or alveolar macrophages, to multiply intracellularly before disrupting these cells and being released in even greater numbers. The ability to penetrate cells is therefore an essential prerequisite for antibiotics if these are to be successful in destroying or at least limiting the growth of *Legionella* organisms (as is also the case with both *Mycoplasma* and *Chlamydia* infection).

Because of the difficulties and delays in the diagnosis, most of the information on the relative success or failure of antibiotics in treating this disease has been obtained from the interpretation of case fatality reports and there are no controlled trials. Most clinical experience points to erythromycin as the drug of choice [337] but increasing experience with the newer macrolides suggest that they may be as effective [338–340]. Whereas clarithromycin is available for parenteral use, this is not yet universally the case with azithromycin, which has greater intracellular penetration and a long half-life so that 5–10 days of therapy should be sufficient [285]. Tetracyclines and ciprofloxacin have been found to be equally effective and experience with their use is increasing [341,342]. Rifampicin has been shown to be highly active against *Legionella in vivo* and in animal models [343], and experience has accumulated with regard to its use in human *Legionella* pneumonia so that it is used as an ‘add on’ to a macrolide, quinolone or tetracycline in patients with severe microbiologically confirmed Legionnaires’ disease.

An effective dose of erythromycin is 500 mg i.v. 6-hourly (in all but mild infections) for 2 days, continuing with

500 mg orally every 6 h if clinical response is satisfactory. It is recommended that treatment is continued for 2–3 weeks for fear that shorter periods may result in delayed resolution or relapse, particularly in those who are immunosuppressed or who have extensive disease. If infection is judged to be severe or if clinical response is not occurring to erythromycin alone, rifampicin 600 mg 12-hourly either intravenously or orally should be added. The author's own experience and that recorded in the literature suggests that this combination is effective [344]. The use of rifampicin alone is *not* recommended for fear of inducing resistant strains. Parenteral erythromycin tends to cause local phlebitis so that cannulae have to be resited and at high dosage it may cause transient neural deafness. It also commonly produces nausea. If for some reason erythromycin cannot be used, a tetracycline such as doxycycline may be used instead at a dose of 200 mg i.v. for the first dose, followed by 100 mg i.v. 12-hourly for 2 days or until response, and thereafter orally. Alternatively a quinolone such as ciprofloxacin 400 mg i.v. 8-hourly followed 750 mg orally every 12 h may also be used. Ciprofloxacin does not interfere significantly with cyclosporin metabolism, whereas interactions do occur with macrolides and rifampicin, necessitating closer monitoring of cyclosporin levels in organ transplant recipients [338] and thus a quinolone may therefore be preferable in this situation [285].

Other Legionellaceae including *L. micdadei* (Pittsburgh pneumonia agent) can be similarly treated with erythromycin [345] with the addition of rifampicin in severe cases.

### Mortality

Statistics compiled from case fatality reports indicate that mortality in *Legionella* pneumonia is mainly influenced by the choice of antimicrobial therapy and by the previous state of health of the patient. The mortality rate is lowest for those who were previously healthy and who received erythromycin (about 5% mortality) and highest for patients who were immunocompromised and who did not receive erythromycin (about 80% mortality) [346]. The importance of accurate microbiological diagnosis or appropriate empiricism is illustrated by the observation that correct treatment lowers the mortality in immunocompetent patients from 25% to 7% and in immunocompromised patients from 80% to 25% [330]. When data recording the efficacy of different antibiotics are pooled, the overall mortalities with the use of erythromycin and tetracycline are comparable at 5–10% but for inappropriate antibiotics, including ampicillin, other penicillins, cephalosporins and aminoglycosides, mortality is high at 22–34% [337]. The crude mortality rate in a group of 84 patients sufficiently unwell to be admitted to an intensive care unit in Barcelona was 30% [347].

### Complications

Numerous complications have been described in association with *Legionella* pneumonia. These have often taken the form of individual case reports of rare associations and have been well reviewed [323,348].

Intrathoracic complications include respiratory failure, which may occur in 20–40% of cases so that ventilatory mechanical support may become necessary [121,330]. The prognosis in such cases is by no means hopeless [349]. Pleural effusions may occur but empyema is uncommon [350], as is cavitation [351].

Extrapulmonary legionellosis is rare and may occur as a result of bacteraemia. Cardiac involvement with pericarditis, myocarditis and prosthetic valve endocarditis have all been described [285,352,353], possibly as a result of nosocomial sternotomy wound infection with contaminated water, in which case there may be no evidence of pneumonia. Neurological sequelae may include confusion, memory impairment, cerebellar ataxia and peripheral neuropathy including Guillain-Barré syndrome [354,355]. Other extrathoracic complications have included pancreatitis and cellulitis [285]. Renal failure is usually due to associated hypotension in severe infections but interstitial nephritis [356], glomerulonephritis [357] and myoglobinuria [358] have also been reported.

### Prevention

At present, prevention of *Legionella* infections is limited to the identification of the sources where epidemics or case clustering have occurred. Expert advice should be sought when a point source of infection is suggested by the close temporal and spatial association of two or more cases [359]. In many such small clusters no source is in fact positively identified [290]. Hot water supplies are usually decontaminated by hyperchlorination, or by superheating water supplies to 70–80°C, and by the removal of rubber washers from shower fittings [360–362]. When cooling towers in large buildings have been shown to be the source, they are either shut down, modified or the water that they use treated with appropriate biocides [309].

### Pneumonia caused by species other than *Legionella pneumophila*

Over 40 different species of *Legionella* have been identified environmentally and a number of these may cause pneumonia. However, such infection is uncommon and when it does arise the host is not infrequently on immunosuppressive therapy [363–366]. The non-*pneumophila* species detected most frequently in these circumstances is *L. micdadei* (previously known as the Pittsburgh pneumonia agent). A number of *L. micdadei* pneumonia reports describe a more nodular pulmonary infiltrate than seen in



*L. pneumophila* pneumonia, the appearance having been likened to that of septic pulmonary emboli. *L. bozemanii* also tends to occur in immunocompromised patients and this species also seems to have a propensity towards progression and cavitation despite treatment with a macrolide, so that combined treatment including rifampicin is appropriate [367]. Other species may cause pneumonia infrequently [368–372]. Although good data on antimicrobial responsiveness is lacking, cases should probably be managed as for *Legionella pneumophila*.

### ***Mycoplasma pneumonia***

Mycoplasmas are the smallest free-living organisms [373]. They are quite unlike viruses and are able to grow and multiply extracellularly on artificial media, probably dividing by binary fission. They are nearest in their behaviour to bacteria but differ principally from these by their lack of a cell wall, being bounded by a deformable membrane, a characteristic that has resulted in their inclusion in a class of organism known as mollicute which means 'soft skinned'. Ten subgroups of human mycoplasmas are described and until recently only one, *Mycoplasma pneumoniae*, was known to cause respiratory infection in humans. *M. pneumoniae* is an important respiratory pathogen in the community [374], mainly affecting children and younger adults in whom it may produce pharyngitis, tracheobronchitis and, in a minority of cases, pneumonia. This is usually relatively mild but nevertheless accounts for a significant number of hospital admissions, occasional cases of which have been fatal.

The first mycoplasma to be isolated was obtained from cattle with 'pleuropneumonia' in 1898 [375] but the isolation of *M. pneumoniae* in humans had to wait until 1962 [376]. In the mean time it had been recognized that 'atypical pneumonia' could occur in humans in the absence of any recognizable pathogenic cause [377]. During the Second World War and subsequently, a relatively mild form of 'recruit pneumonia' was noticed to afflict troops in camps and barracks, and Eaton was able to pass on pneumonia to experimental animals from the filtered nasal washings of human cases, indicating a small pathogen that was termed the 'Eaton agent'. This agent was later grown on agar, identified as a mycoplasma and renamed *M. pneumoniae* [376,378].

There are a number of more recent publications indicating that some genital mycoplasmas may cause systemic disease outside the urogenital tract. One such organism is *M. hominis*, which has been isolated from lung tissue in young Australian Aboriginal adult males dying of pneumonia [379].

### ***Incidence***

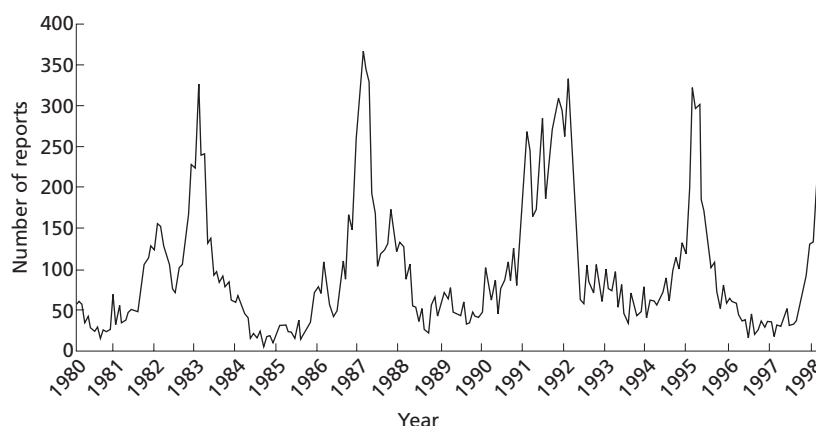
Reported estimates of the relative incidence of *Mycoplasma pneumoniae* are bound to vary according to the nature of

the population surveyed and the diagnostic approach in individual studies. A multicentre British Thoracic Society study of patients with community-acquired pneumonia admitted to hospital found evidence of *M. pneumoniae* infection in 18% of 453 adult cases [281]. Individual hospital series have reported that *M. pneumoniae* constituted from 2% of 124 microbiologically confirmed cases over 1 year [167] to 14% of 210 cases, in whom infective agents were detected in 103 patients, over 3 years [165]. In the latter series, *M. pneumoniae* infection accounted for 25% of cases under the age of 50 years. This incidence of *Mycoplasma pneumoniae* was found to be higher than in other series, possibly because of two extended UK epidemics of *M. pneumoniae* infection that occurred during the period of the study [165]. The organism has accounted for about 4% of cases of community-acquired pneumonia requiring hospital admission in North American series [373,380], but it has been noted that in selected groups such as military personnel it may account for up to 44% of all cases of pneumonia [381]. *M. pneumoniae* was found to be the second commonest agent (after *Strep. pneumoniae*) causing hospital admission with pneumonia in young adult US military personnel over a 10-year period [382]. A large community survey in Seattle found that 15% of cases of pneumonia were caused by *M. pneumoniae* but also that it was a mild infection, only 2% of these patients requiring hospital admission [374]. Although predominantly affecting younger age groups, *M. pneumoniae* also causes pneumonia in old people. A large prospective study of community-acquired pneumonia admitted to hospital in Nova Scotia found evidence of *M. pneumoniae* infection in 4.9% of 1300 cases; of these 64 cases, only six occurred in patients aged 65 years or older [383].

### ***Epidemiology***

Sporadic cases of *Mycoplasma pneumoniae* occur in the population throughout the year [384]. Epidemics in the community at large tend to be prolonged rather than sharp, being spread over many months, peaks in incidence occurring every 4–5 years (Fig. 13.12), this being the case worldwide [373,385]. It may become relatively more common in the later summer months due at least partly to a decline in other causes of pneumonia such as pneumococcal infection. The organism is spread by droplet aerosol [386,387] and the infection is not highly contagious, transmission depending upon relatively close contact such as might occur between pupils at school and thence between family members in the home [388,389]. Localized epidemics of *Mycoplasma* infection may sometimes occur when large numbers of susceptible individuals are in relatively close contact, as is the case in schools or military establishments [388,390]. Shedding declines within a few days of the onset of the illness but may continue at a low level for weeks unless cut short by appropriate antibiotic therapy [391,392]. The chance of developing clinical infec-

**Fig. 13.12** Four-weekly reports of *Mycoplasma pneumoniae* infections in England and Wales showing prolonged pattern of epidemics spread over many months with cyclical peaks in incidence occurring every 3–5 years. (Data courtesy of the Communicable Diseases Surveillance Centre of the Public Health Laboratory Service.)



tion is reduced by pre-existing immunity, which is associated with the presence of circulating antibodies to the organism [373], so that attack rates within the family range from approximately 60–70% for children to 20–50% for adults [388]. Such infection need not manifest itself clinically as pneumonia. The duration of immunity is unknown and second infections have been recorded but are probably unusual [393,394]. Infection with *M. pneumoniae* may occur in immunocompromised individuals [395].

### Pathology

Respiratory disease in *M. pneumoniae* infection occurs as a result of the growth of the organism on the surface of respiratory epithelial cells, to which attachment may occur via a terminal receptor. Extrapulmonary spread of the organism is rare and disease at distant sites probably occurs as a result of immunological phenomena, circulating immune complexes having been detected in *M. pneumoniae* infection [396]. Fortunately few cases of *Mycoplasma pneumoniae* come to postmortem examination, and those that do may show pulmonary oedema and intra-alveolar haemorrhage with patchy areas of consolidation. Microscopic examination suggests that the primary process is bronchitis and bronchiolitis, with the presence of intraluminal neutrophils and macrophages and a submucosal and peribronchial infiltrate containing inflammatory cells with a predominance of lymphocytes and plasma cells. Progression to produce patchy or more confluent pneumonic changes, with diffuse alveolar destruction, hyaline membrane formation and fibrosis, may occur [397–399]. Postmortem diagnosis may be established from lung tissue using an *M. pneumoniae* DNA probe [399]. Ciliary motility may be impaired in common with other lower respiratory tract infections [400].

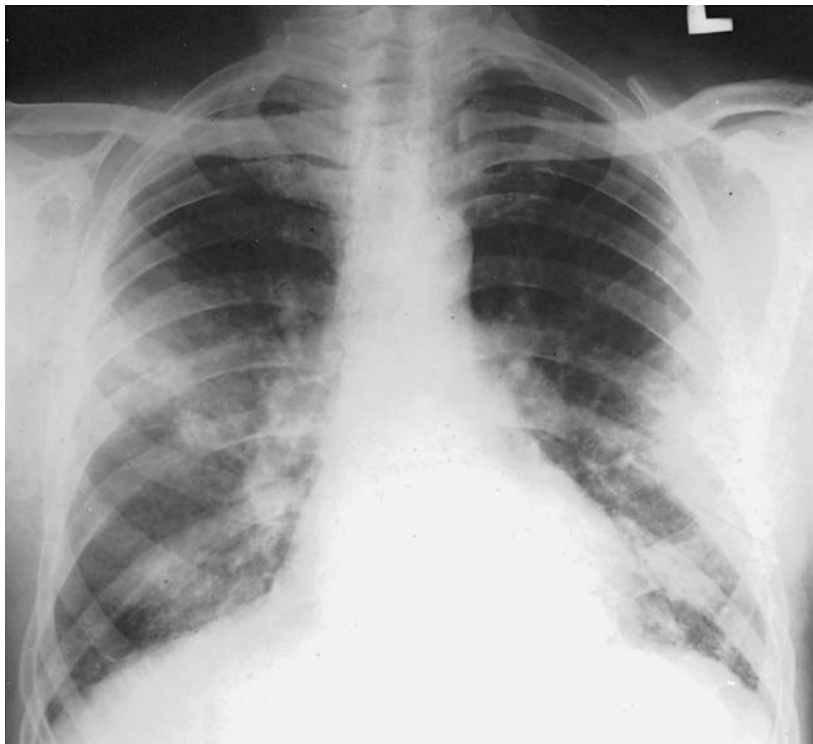
### Clinical features

Although *M. pneumoniae* may be an important cause of infection throughout life, it most commonly affects children aged 5–15 years in whom symptoms of coryza and

tracheobronchitis are the rule [401,402]. Pneumonic illness may occur in this age group but is usually mild and seldom requires hospital admission. Infection tends to be more serious when it affects older children and adults under the age of 50 years, in whom it is one of the more common pathogens identified as a cause of community-acquired pneumonia [165,402]. The incubation period is 2–3 weeks [403], after which clinical illness comes on gradually over the space of 2–4 days, with malaise, headache, myalgia and pyrexia. A sore throat and coryza are sometimes present. The cough may be dry at first, becoming productive of small amounts of mucoid or mucopurulent sputum sometimes flecked with blood. There may be substernal discomfort on coughing suggestive of tracheitis. Fever is usually sustained for several days unless modified by appropriate antibiotics or antipyretics, but rigors are unusual as is pleuritic pain. Patients may be prostrated but are seldom severely ill in the sense of being tachypnoeic or cyanosed. Cough, malaise and tiredness may persist for over a month. Examination of the chest may reveal crackles or wheezes over an affected area and there may or may not be local signs of consolidation. Bullous myringitis (painful haemorrhagic blisters on the ear-drum and external auditory canal) is said to occur in 5% of cases. Generalized lymphadenopathy and splenomegaly are occasionally elicited. There is a wide variety of other non-respiratory complications that are dealt with below.

### Investigations

The chest radiographic appearances are too variable for this investigation to be useful in establishing the likely microbial cause of the pneumonia. Thus the shadowing may be patchy and widespread or more confluent and confined to one or two lobes (Fig. 13.13). Involvement has been found to be unilateral in 65% and a lower lobe may be involved in three-quarters of cases [404]. Pleural effusions may occur in 7% or more of cases but are usually small [404,405]. Nodular shadowing may occur but is unusual [404]. Hilar gland enlargement is also an occasional but



**Fig. 13.13** Bilateral patches of micronodular shadowing in a patient with systemic illness but few respiratory symptoms other than cough. The clinical suspicion of *Mycoplasma pneumoniae* pneumonia was confirmed by serology.

inconsistent finding [210,404]. Radiographic shadowing usually resolves within 4–6 weeks, residual fibrosis being rare [406].

Gram stain of sputum may show some polymorphs and mononuclear cells but no predominant organism, mycoplasmas being too small to be seen by light microscopy, and sputum culture is frequently negative for pathogens as indeed is blood culture.

The white cell count is normal in about one-third of cases and the erythrocyte sedimentation rate and plasma viscosity usually raised, often markedly so. The coulter count may sometimes spuriously suggest a macrocytosis, this being the result of red cell agglutination. IgM cold agglutinins specific for the I antigen of red blood cells may be found at a titre of 1/32 or greater, or show a fourfold increase in about 50% of cases [407]. This test is usually done by combining the patient's serum with type O red cells in the laboratory. If clumping is noted, the serum is serially diluted and the test repeated, the titre reported being the highest dilution at which clumping occurs at 4°C. Cold agglutinins usually develop in the first week and a half of infection. This test tends to be more sensitive in iller patients, who have *M. pneumoniae* titres that exceed 1/128. A modified test may be carried out at the bedside by placing 1–2 mL of the patient's blood in a standard laboratory clotting (i.e. citrated) tube and placing it in iced water (or on the shelf of the ward refrigerator) for a few minutes [408]. Clumping of red cells is observed after about 3 min if cold agglutinins are present, the specimen reverting to its original appearance when rewarmed in the

doctor's pocket. The specificity of the cold agglutinin test for *Mycoplasma pneumoniae* is only in the order of 50% but a positive test is nevertheless suggestive of *Mycoplasma* infection when taken in the right clinical setting [409]. Cold agglutinins usually reach a peak 2–4 weeks after the onset of cough and fever and if they are not found early in the illness the test should be repeated after an interval [410].

About 30% of patients develop an antibody to *Streptococcus* MG that can form the basis of a serological test. As this test is less sensitive than the cold agglutinin test and as cold agglutinins are also detectable when it is positive, it is not usually carried out.

*M. pneumoniae* infection may occasionally be associated with antinuclear antibody production and the organism may also produce a phospholipid capable of giving false-positive serological tests for syphilis. However, neither of these characteristics are diagnostically useful.

There is at present no rapid, readily available means of making a diagnosis in cases of *Mycoplasma pneumoniae*, as the organism can only be cultured with difficulty in enriched artificial media containing antibiotics to suppress bacterial overgrowth. Even then culture takes 1–2 weeks before pinpoint colonies become visible [411] and very few clinical laboratories therefore offer this service. Diagnosis often relies on clinical suspicion in the acute stage of the illness and subsequent retrospective serological information to demonstrate a fourfold rise in specific antibody titres between the acute and convalescent blood samples. The CFT is still most commonly used, detecting

rising titres of antibody during the second week that peak at about the fourth [412]. A single titre of 1/128 or greater is also suggestive of infection within the previous few weeks or months. Such a test does not provide a sufficiently rapid answer to influence management and its chief usefulness is in epidemiological work. The sensitivity of the CFT may be as low as 54% [413]. This is improved by a more modern ELISA [414], which gives a specificity of 99% and sensitivity of 98% in patients with positive CFTs. The ELISA is designed to detect *Mycoplasma*-specific IgM and IgG, the IgM being most useful as its presence is more likely to indicate recent infection, the IgG being included as well because some patients display only an IgG response. Unfortunately this test too may not read positive until a week or so into the illness so that the result is unlikely to influence therapy.

The development of genetic probes for *Mycoplasma* nucleic acids has led to the commercial production of a rapid diagnostic test that detects *Mycoplasma* nucleotide sequences directly in clinical samples within 2 h by the attachment of radiolabelled DNA to *Mycoplasma* RNA (Gen-probe). A sensitivity of 95% and specificity of 85% was found on sputum from young adults with confirmed *Mycoplasma* pneumonia but the test was of limited value when applied to throat swabs [415]. Further tests that have been developed for rapid diagnosis include enzyme immunoassays for *Mycoplasma* antigen detection in sputum and nasopharyngeal aspirates, the reported sensitivity and specificity of which has ranged from good to indifferent [416,417]. PCR gives a reportedly high sensitivity and specificity and has the potential to give a rapid result but is a practicable proposition in very few centres [418].

### Treatment

Untreated *Mycoplasma* infection usually resolves gradually over the space of about 2 weeks and those cases of pharyngitis or tracheobronchitis are clinically indistinguishable from many viral upper respiratory tract infections. Most cases of pneumonia remain ambulatory and an antibiotic is started empirically; indeed in the present state of knowledge treatment is almost invariably started and often finished before diagnostic confirmation is available.

Cases of pneumonia in which *Mycoplasma* infection is suspected should be treated with an antibiotic that inhibits protein synthesis, erythromycin or tetracycline 250–500 mg 6-hourly in adults having been established as first-line therapy. Both these drugs have been shown to be effective in controlled trials in terms of diminishing the clinical manifestations of disease and in hastening radiographic clearing [419,420]. Tetracycline should be avoided in pregnant women as well as in children under the age of 9 years because of its effect on developing teeth. Doxycycline is similarly effective and may be adminis-

tered at a dose of 100 mg twice daily but the same constraints apply. The newer macrolides such as clarithromycin and azithromycin have been shown to be equally effective *in vitro*; indeed azithromycin has greater *in vitro* activity against *Mycoplasma* than either erythromycin or tetracycline [421,422]. Azithromycin and clarithromycin also appear to be as effective as erythromycin in a comparative clinical setting, with fewer adverse effects [423,424]. Another newer macrolide, roxithromycin, has also been shown to be clinically effective in treating *Mycoplasma* pneumonia [425]. Quinolones such as ciprofloxacin are also effective [426], whereas antibiotics that have their effect by disrupting cell walls such as the penicillins and cephalosporins are, not surprisingly, ineffective against *M. pneumoniae* which lacks a cell wall for them to attack. One disadvantage of the newer oral macrolides and quinolones is that they are presently 20–30 times more expensive than erythromycin and tetracycline.

Interestingly, the organism may remain culturable in sputum for several weeks after apparently effective antimicrobial therapy [391,392]. The reasons for this are unclear but it is possible to speculate that as well as attaching itself to the surface of cells *Mycoplasma* may also behave as an intracellular parasite or that the antimicrobials inhibit multiplication rather than killing the organisms. The ability of the organism to persist in the respiratory tract in this manner is presumably the cause of the observed tendency for the disease to relapse in a small but significant number of cases unless treatment is continued for 2–3 weeks. Thus, when *Mycoplasma* is strongly suspected or confirmed, treatment should, in the author's opinion, be continued for at least 2 weeks.

Anything but complete recovery in *M. pneumoniae* infection is exceptional, persistent respiratory symptoms occurring only rarely [394,427]. Clinical experience suggests that corticosteroids may be beneficial in cases of severe *Mycoplasma* pneumonia, but as such cases are rare there are no controlled trials to support this impression. It is not known whether treatment prevents the non-respiratory complications listed below. No effective vaccine against *Mycoplasma* infection has so far been developed.

### Complications

Although the majority of *M. pneumoniae* infections are sub-clinical or limited to the upper respiratory tract [428,429] and even those that cause pneumonia are generally benign [430], nevertheless occasional complications occur, sometimes with fatality [399,431,432].

All pulmonary complications are rare. They include massive pneumonic infiltration leading to respiratory failure [398], ARDS [399], large pleural effusions [433], lung abscess or cavities that usually resolve [434,435], unilateral hyperlucent lung (Swyer-James and MacLeod's

syndrome) [436] and diffuse interstitial fibrosis [437]. *Mycoplasma pneumoniae* may be complicated by secondary bacterial infection [438]. Chronic obliterative bronchiolitis (which may lead to organizing pneumonia) and bronchiectasis have also been described as complications [394,432,439–442].

The literature contains numerous case reports of extrapulmonary complications affecting every system of the body and usually occurring within 3 weeks of the onset of the illness. As *Mycoplasma* infection is common, some of these reports may be chance associations. Arthralgia, myalgia, diarrhoea and transient maculopapular erythematous rashes or urticaria are not uncommonly associated. Cold agglutinin-associated autoimmune haemolytic anaemia is well recognized; although usually mild, with a positive Coombs' test and increased reticulocyte count, it may occasionally be more severe, requiring blood transfusion and treatment with corticosteroids [428,443,444]. The production of cold agglutinins in *Mycoplasma* infection may be associated with Raynaud's phenomenon, presumably due to the agglutination of erythrocytes in the peripheral circulation when exposed to cold. An extreme form of this, with digital necrosis, may occur in patients with sickling haemoglobinopathies such as sickle cell anaemia. Other haematological associations that have been described include thrombocytopenia, thrombocytosis and DIC [383,399]. Other extrapulmonary complications range from the unusual to the extremely rare. The most serious are neurological and are said to occur in about 1 in 1000 cases [445]. These include meningoencephalitis, cerebellar ataxia, brainstem dysfunction, transverse myelitis, Guillain-Barré syndrome, cranial (including optic) neuritis and peripheral neuropathies; 10% of these patients may die and one-third may be left with some neurological deficit [397]. Direct invasion of nervous tissue by the organism has not been demonstrated (although it has been demonstrated in the CSF), leading to the supposition that there may be an immune basis for these and other extrapulmonary complications. Immune complex-related interstitial nephritis or glomerulonephritis may occur [446,447]. Cardiac complications include pericarditis and myocarditis with associated conduction defects, dysrhythmias and heart failure [448–450]. In addition to the rather common transient rashes referred to above, erythema multiforme, sometimes occurring as Stevens-Johnson syndrome (bullous eruption of the skin and mucous membranes with variable systemic manifestations), is described with *Mycoplasma* infection, as is erythema nodosum [428,440,451]. The cutaneous lesions usually clear within a week or two. Corticosteroids are sometimes used to settle the symptoms of Stevens-Johnson syndrome, although evidence of benefit is thin. Aside from transient diarrhoea, other possible gastrointestinal associations include anicteric hepatitis, acute pancreatitis and sialoadenitis [428]. Apart from myalgia

and arthralgia (which may be protracted), migrating polyarthritis affecting large joints may unusually occur and the organism has occasionally been isolated from synovial fluid [452]. Direct extension of infection from the pharynx to the tympanic membrane via the eustachian tube may cause bullous myringitis.

### ***Chlamydia pneumoniae***

*Chlamydia* is a genus of small obligate intracellular coccoid Gram-negative bacteria containing three species, *C. pneumoniae*, *C. psittaci* and *C. trachomatis*. The following sections are mainly concerned with infection caused by the first two organisms. *C. trachomatis* is almost exclusively a parasite of humans and although it may unusually cause respiratory illness, in adult practice it is more familiar as a major cause of blindness in endemic areas and of genitourinary disease. About 300 cases of respiratory chlamydial disease are reported to the Communicable Diseases Surveillance Centre every year, most cases occurring in patients aged 15–44 years [453]. It is thought that about three-quarters of these infections are due to *C. psittaci* [453].

#### ***C. psittaci pneumoniae (psittacosis)***

*C. psittaci*, being filterable, was once thought to be a virus but is now recognized as a special type of intracellular bacterium that possesses a cell wall and both DNA and RNA. It divides by binary fission and is susceptible to certain antibiotics [454]. *C. psittaci* infection is distributed widely among various members of the animal kingdom [455], particularly avian species, an outbreak of respiratory infection in humans having been linked with imported parrots in the 1890s, hence the term 'psittacosis' from the Greek word *psittakos* meaning parrot [454–456]. The more general term 'ornithosis' is sometimes used following the recognition that the same disease can be contracted from other birds including budgerigars and other parakeets, cockateels, pigeons, doves, ducks and turkeys. Although both words are entrenched in common useage, it can be seen that other modes of transmission may occur and *C. psittaci pneumoniae* is therefore a more accurate term.

#### **Epidemiology**

*C. psittaci* may be hosted by many avian species, both wild and caged, including domestic poultry such as ducks and turkeys. All are susceptible and disease is occasionally transmitted to humans [456]. However, a history of contact with birds in human *C. psittaci* infection is recorded in less than one-third of cases [457], and when it does occur it need not be prolonged. This observation raises the possibility of other methods of transmission, such as animal to human or human to human [455].

Psittacine infection is an occupational hazard of veteri-

narians, pet-shop workers, taxidermists, zoo staff and poultry workers, apart from those who handle only dressed fowl [458,459]. Bird fanciers are therefore not only at risk of extrinsic allergic alveolitis (see Chapter 31) but also of *C. psittaci* pneumonia, and in the UK budgerigars are thought to account for half of all sporadic cases in which a source is identified [460]. A similar proportion of the much smaller total number of cases reported in the USA is related to the ownership of pet birds. When a caged bird is responsible for transmitting infection it may appear ill, although this is not always the case as asymptomatic carriage can occur. *C. psittaci* can be recovered from the tissues, feathers and excreta of infected birds and the organism is generally assumed to reach the human respiratory tract as a result of the inhalation of small particles of dried excreta or other organic material. Some of those human cases in whom no avian source is evident may arise from other animals, such as sheep, newborn lambs, cattle and cats [461–466]. Person-to-person spread, though formerly regarded as rare, may be more common than is thought and presumably occurs by droplet aerosol. Two putative episodes have been recorded in the literature in which the index case has passed infection to 11 and 25 contacts respectively, with fatal results in 13 of them [467,468]. A mild outbreak of *C. psittaci* infection has also been reported in an English boys' boarding school, where 24 cases occurred with no obvious point source [469]. It is possible that such cases may have been caused by serological cross-reactivity with *C. pneumoniae*, which was at the time unknown. The vast majority of cases reported are sporadic rather than epidemic, with no apparent pattern of seasonal variation [470,471]. Food-borne transmission occurring as a result of the ingestion of infected poultry has not been described.

### Incidence

The true incidence of *C. psittaci* pneumonia in the community is unknown, as published figures reflect the diligence with which the diagnosis is pursued. The number of cases reported annually in the UK (through the Public Health Laboratory Service) has exceeded 300 [470] and two English hospital series of community-acquired pneumonia have found that *C. psittaci* accounts for 1.5% and 5.5% of cases [165,167]. The figure obtained by a British Thoracic Society multicentre study was 3% [35]. A survey carried out in a population of about 30 000 based around Cambridge, England detected 18 cases between 1975 and 1983, giving an annual incidence of 1 in 2000. The rate in one rural practice of under 5000 patients within this same area was as high as 1 in 200 [471]. An avian source of infection was detected in only 17% of cases. It seems probable that all these foregoing reporting rates are overestimates of *C. psittaci* infection as the studies were carried out before *C. pneumoniae* was recognized, the CFTs that were

used having been genus specific but not species specific. Only 40–60 cases are reported annually in the USA despite the much larger population in that country. It has been suggested that this discrepancy may be explained by measures such as the medication of imported cage birds and the treatment of poultry feed with tetracycline [472].

### Pathology

*C. psittaci* most commonly has a two-stage developmental cycle, the organism entering the respiratory tract and being transported via the blood to the reticuloendothelial cells of the liver and spleen, where replication takes place intracellularly. Large numbers of organisms then cause a secondary bacteraemia, invading the lungs and other organs haematogenously. It is now thought that in some cases immediate infection of the respiratory epithelial cells may progress directly to pneumonia without the bacteraemic phase, these patients having a short incubation period of up to 3 days [473]. Those cases coming to post-mortem examination show areas of consolidation that are more common in the lower lobes. The bronchiolar and bronchial epithelium shows desquamative and necrotic changes and the alveoli and bronchioles contain a fibrinous exudate. A variable degree of lymphocytic infiltration is found in the interstitium. Small areas of haemorrhage are present and macrophages contain inclusion bodies. The liver and spleen may be enlarged and may contain areas of focal necrosis. The hilar lymph nodes may be enlarged [474].

### Clinical features

Symptomatic *C. psittaci* infection typically occurs in adults of working age and is unusual in children [470,475]. The incubation period is usually 1–2 weeks but may vary from a few days to as long as 4 weeks (see above). In some individuals infection is subclinical [471], while in others symptoms may range from a mild 'flu-like' illness to chlamydial bronchitis or pneumonia, which in the severest cases may be fulminant with multiple organ involvement.

The onset of illness may be abrupt with rigors or there may be a gradual onset of malaise, chills and fever. Systemic symptoms are usual and may include myalgia, arthralgia and headache, which may be severe. A sore throat is sometimes present. Cough may occur from the onset or after a few days, and may be either dry or productive of mucoid sputum sometimes flecked with blood. Pleuritic pain may occur. Some patients experience nausea, vomiting and abdominal pain. Epistaxis may occur. Hepatitis, endocarditis, acute renal failure (in an unspiciated case), Stevens–Johnson syndrome, erythema nodosum and other vasculitic rashes have been described [475–479].

Physical examination of the chest may reveal crackles

over infected areas of lung but most patients do not have impressive signs of consolidation [472,475,480]. Palpable splenomegaly may be present.

### Investigation

The white count is frequently normal. An eosinophilia is sometimes seen during recovery. Non-specific findings may include mild anaemia and proteinuria. Liver function tests are commonly abnormal, sometimes showing mild cholestasis. As with other acute pneumonias, the chest radiographic appearances are highly variable and non-discriminatory [210,475]. The infiltrate is most commonly described as 'patchy', but is not infrequently confluent to the extent of being lobar. Shadowing is bilateral in about 12% of cases. Pleural effusions may occur but are usually small. Radiographic changes in *Chlamydia* pneumonia are relatively slow to clear, complete resolution having been recorded in about 50% of cases by 7 weeks [210,475]; 28% of serologically positive and symptomatic patients have been found to have normal chest radiographs, implying the presence of chlamydial bronchitis rather than pneumonia [475]. Many of these cases are likely to have been caused by unrecognized *C. pneumoniae* infection.

Routine blood cultures are negative. If sputum is obtained, it is often found to contain no pathogens on routine Gram stain and culture and a firm diagnosis relies upon serological confirmation. The most widely used test is the CFT. Unfortunately this uses chlamydial lipopolysaccharide antigen, which is genus specific but which does not distinguish between the three different *Chlamydia* species, so that many patients diagnosed in the past as having psittacosis on the basis of a positive CFT in fact had *C. pneumoniae* infection [481]. Both acute and convalescent serum samples should be taken. Complement-fixing antibodies start to rise by the end of the second week of illness and a fourfold rise in titre is confirmatory. Some have accepted a single high titre (1/256) as confirmatory; although others would regard a single titre of greater than 1/32 as sufficient grounds for a presumptive diagnosis when taken in conjunction with a compatible illness, false positives do occur and the significance of single raised titres may be problematical. It should be noted that early treatment with an appropriate antibiotic may delay the rise in antibody titre, which is only detected some weeks later at follow-up.

Species-specific microimmunofluorescence (MIF) is available in some laboratories and detects *C. psittaci* IgM and IgG. IgM is used to detect current or recent infection, a titre of greater than 1/8 being taken as indicative and falling in the convalescent sample. However, problems may arise because the organism is antigenically diverse with at least 11 serotypes (or 'serovars'), not all of which may be included in the test. One practical method of arriving at a serological diagnosis is to use CFT to detect the

genus and MIF to detect *C. pneumoniae* (see below), or *C. psittaci*, depending upon the availability of the test, so that the other species can be identified by a process of exclusion.

Techniques for chlamydial antigen detection using an ELISA or direct immunofluorescence have been developed but are not yet readily applicable for respiratory diagnostic purposes [482,483]. PCR has been used to detect *Chlamydia* species antigen but is not generally available.

*C. psittaci* can be grown on cell monolayers; however, its culture presents a considerable potential hazard to laboratory personnel in whom deaths have occurred as a result of infection [456,484]. Attempts to culture it are therefore carried out infrequently and then only with stringent precautions and in laboratories with special expertise [485].

PCR techniques have been used in research settings to detect *C. psittaci* and *C. pneumoniae* in sputum but are not generally available [486].

False-positive serological tests for syphilis may occur as with *Mycoplasma pneumoniae*.

### Treatment

Tetracycline or doxycycline are equally effective, the dose of tetracycline being 500 mg 6-hourly and that of doxycycline 100 mg twice daily. Gradual improvement after 2–3 days is the rule but relapses may occur [487] so that it is sensible practice to treat for 3 weeks. Cases in childhood are rare but when they do occur they may be treated with erythromycin, which is probably as effective as tetracycline, although there are no controlled trials. Penicillin is relatively ineffective. Rifampicin has been successfully used in the treatment of *C. psittaci* endocarditis [488]. Supportive measures are applied as necessary.

### Prognosis

The mortality from *Chlamydia* pneumonia before the availability of antibiotics was in the order of 20–40%. Milder cases of *C. psittaci* infection often settle spontaneously at 1–2 weeks or might enter a more chronic phase lasting for some months. Mortality following appropriate treatment is low, at around 1%.

### Complications

As with any acute pneumonia, occasional fulminant cases may occur that can result in death due to hypoxia or overwhelming sepsis [489]. Neurological involvement with meningoencephalitis may result in lethargy, confusion or delirium progressing to stupor and coma [490]. Other complications have included myocarditis, pericarditis and endocarditis, which should be considered in cases of valvular disease where, despite the suspicion of this diag-



nosis, blood cultures are repeatedly negative [488,490–493]. The author has seen inappropriate secretion of ADH in a severe case of *C. psittaci* pneumonia.

### *C. pneumoniae* pneumonia

*C. pneumoniae* is not a new organism but a relatively newly recognized one. The first isolate was obtained from a conjunctival culture of a Taiwanese child (hence the laboratory designation TW-183) in 1965. It was subsequently recognized as a respiratory pathogen by Marrie *et al.* [494] who isolated it from adults with acute respiratory symptoms in 1986 and at first referred to it as *C. psittaci* strain TWAR (from TaiWan Acute Respiratory). It was subsequently declared the third *Chlamydia* species and renamed *C. pneumoniae*. Apart from TWAR, one further serological variant, IOL-207, has been described. Studies on banked serum have shown that infections by this organism were as common 35 years ago as they are today.

### Epidemiology

Infection by *C. pneumoniae* is very common worldwide, about 50% of the population having serologically detectable antibodies to this organism by early adult life. As with other potential pathogens, carriage of the organism in the throat may be unaccompanied by symptoms so that its relevance as a cause of infection has sometimes been questioned. Humans are the only known reservoir of infection, which is probably spread from person to person by aerosolized droplets, although direct evidence is lacking. A subject may be culture positive in the absence of serological evidence of infection, and it is possible that asymptomatic carriers may play a role in the spread of infection although this is also speculative. Infection is endemic and common from school age onwards. Reinfection is also thought to be common and epidemics have been described in closed communities [495]. It is likely that some of these may have been attributed to psittacosis in the past.

### Incidence

It is now thought that *C. pneumoniae* infection causes 6–9% of cases of community-acquired pneumonia admitted to hospital [494,496,497]. These form only a small minority of all cases of infection, 70–90% of which are estimated to be subclinical [498]. A population survey carried out in the Seattle area by Grayston [499] found the incidence of *C. pneumoniae* pneumonia to be 1 per 1000 per year compared with a rate for *M. pneumoniae* of 1.8 per 1000 per year. The highest incidence of pneumonia caused by the former organism was in the elderly, whereas by contrast the latter organism was a more frequent cause of pneumonia in chil-

dren. Infection commonly causes acute bronchitis rather than pneumonia.

### Clinical features

There are no reliable clinical features to distinguish infection caused by *C. pneumoniae* from that caused by *M. pneumoniae* or indeed from other pyogenic bacterial pneumonias. The illness is generally mild and self-limiting. Prolonged subacute bronchitis, lasting days or weeks, or a mild pneumonic illness is often preceded by a sore throat and the patient does not usually require admission to hospital [500,501]. However, more serious illness may occur and fatalities have been reported, especially in the presence of serious coexisting disease [494,502]. It has not always been clear in such cases whether *C. pneumoniae* has been the main cause of the illness or a co-pathogen such as *Strep. pneumoniae* or *H. influenzae* [503]. Episodes of reinfection may occur and tend to cause milder illness. Sinusitis, otitis media, tonsillitis and laryngitis may also result from *C. pneumoniae* infection. Exacerbations of asthma have been described following *C. pneumoniae* infection and it has been suggested that this might be causal in some cases, although this is doubtful [504]. Serological evidence of recent *C. pneumoniae* infection in exacerbations of chronic obstructive pulmonary disease has been described but is unusual [505].

### Investigations

The white cell count is often normal and the erythrocyte sedimentation rate raised. The chest radiograph commonly shows a segmental infiltrate, although more extensive bilateral radiological change may be seen in patients with severe illness and pleural effusions may uncommonly occur [506,507].

There are several laboratory tests for diagnosing *Chlamydia* infection. The comments on the CFT made for *C. psittaci* infection also apply to *C. pneumoniae*. Other tests that can distinguish between species are often only carried out in specialist laboratories. One such species-specific test is MIF, which can also use *C. pneumoniae*-specific antibodies [508]. This test separately measures IgM and IgG antibodies, the IgM antibodies developing within a few weeks of primary infection and falling off on recovery, and the IgG antibody developing by 2 months and remaining detectable for years, so that it may be used to estimate the prevalence of infection in a population. In repeat infections IgM does not develop and IgG develops faster and to a higher level. The usual criteria for acute infection by *C. pneumoniae* on paired samples are a fourfold or greater rise in IgG antibody, and on a single sample an IgM antibody titre equal to or greater than 1/16 and/or IgG equal to or greater than 1/512 [509]. However, treatment with an appropriate antibiotic may suppress antibody responses

and the presence of rheumatoid factor may cause a false-positive result. MIF remains the most sensitive method for diagnosing *C. pneumoniae* infections. Chlamydial antigen detection methods include an ELISA and a direct immunofluorescent test as mentioned under *C. psittaci*.

*C. pneumoniae* may be cultured from throat swabs on to an established cell line such as HEp-2 over the space of about 3 days, these specialized techniques being available to laboratories with cell culture capability.

PCR has been developed to detect minute amounts of *C. pneumoniae* DNA. This is still largely a research tool but has been shown to have a high degree of sensitivity and specificity.

### Treatment

Early recommendations for the treatment of *C. pneumoniae* was with a 2-week course of tetracycline or doxycycline, clinical relapses being thought to be somewhat more common with erythromycin if this was given for less than 3 weeks [498]. However, the newer macrolides such as clarithromycin and azithromycin have also been shown to be effective, clarithromycin being particularly active *in vitro*, although controlled clinical trials are lacking [510,511]. Fluoroquinolones are also effective.

### Complications

A number of extrapulmonary complications of *C. pneumoniae* have been described. These include Guillain-Barré syndrome [512], encephalitis [502,513], erythema nodosum, thyroiditis [509], reactive arthritis [514], myocarditis [515] and possible endocarditis [516]. It has been proposed, mainly on the basis of serological evidence in case-control studies, that *C. pneumoniae* infection is associated with coronary artery disease. However, it cannot be assumed that this association is causal, as some authors found that tobacco smoking was an independent risk factor for *C. pneumoniae* infection, which tended to negate the statistical significance of the association [517,518]. Others have disputed this, pointing out that the organism has been recovered from atheromatous plaques and suggesting that it may be responsible for low-grade inflammation and increased plasma fibrinogen concentrations [519].

### Other chlamydial infection

It is unusual for the other species, *C. trachomatis*, to cause pneumonia in adults, although isolated cases have occurred in immunocompromised patients [520]. However, non-lymphogranuloma venereum strains of this organism may produce pneumonia in infants, infection presumably being communicated to the child from the mother's genital tract [521,522]. These strains belong to

the serotypes D-K and are also responsible for non-gonococcal urethritis, cervicitis, endometritis and inclusion conjunctivitis [523]. Lymphogranuloma venereum strains ordinarily produce inguinal buboes but have on rare occasions been described as causes of pneumonia, pleural effusion and mediastinal lymphadenitis, five cases of which have occurred in laboratory researchers exposed to the organism [523]. Treatment is with tetracycline (in adults) or a macrolide [523,524]. The general prevalence and significance of a 'new' organism known as *Chlamydia*-like microorganism Z, which has been described as a possible aetiological agent in 2.6% of 308 patients with community-acquired pneumonia in Israel, remains uncertain. These patients appeared to respond to erythromycin [525].

### *Coxiella pneumoniae* (Q fever)

Q fever is an infectious zoonosis that is an unusual cause of pneumonia but one that needs to be considered in the differential diagnosis when another infective agent is not readily identifiable. It is caused by a rickettsial organism that has been assigned its own genus because it differs from other rickettsiae in several respects, including both its ability to survive outside the host and its transmissibility to humans by inhalation rather than the bite of an insect vector. It was originally known as *Rickettsia burnetii* after Burnet, who identified the organism from the blood of patients with Q fever [526], a febrile illness noted to afflict abattoir workers in Queensland, Australia [527]. 'Q' stands for 'query', as the term Q fever was originally used at a time when the cause was unknown and its usage continues today. The present name of the organism is *Coxiella burnetii* after Cox who independently found it in ticks in Montana, USA. *C. burnetii* is a small bacterium that is an obligate intracellular parasite. It divides by binary fission and is fastidious in its growth requirements, so that diagnosis is usually by serological testing.

### Epidemiology

*C. burnetii* is distributed worldwide in mammals, both domestic and wild. The main reservoir of infection in the UK and North America is cattle and sheep [528]. Humans are an incidental host of no particular value to the organism, which is mainly transmitted to humans by inhalation, probably in the form of spores that can withstand desiccation [529,530]. Infection in cattle and sheep is subclinical, so there is no commercial reason for farmers to eradicate it. Infected animals may excrete large numbers of *C. burnetii* in milk, urine, faeces and in the products of parturition. Humans are highly susceptible to infection if they inhale dried particles from any of these sources. Ingestion of milk is another potential source, although infection does not occur if pasteurization has been carried out [531]. Q fever

is an occupational hazard of farmers, slaughter-house workers, veterinarians, hide handlers, butchers and indeed all who come into contact with cattle, sheep and goats, including personnel at medical research institutions [532,533]. It may also occur in laboratory workers [534]. The illness may occur both sporadically and in sudden outbreaks and it is important to realize that it may occur in patients from whom no history of animal contact can be obtained. An outbreak has been reported in town-dwellers in Wales in whom infection was supposed to have been disseminated by straw and other debris falling from farm vehicles as they passed through the locality [535]. The largest UK outbreak occurred in the urban West Midlands, possibly as a result of the wind-borne spread of infection from adjacent farmland [536]. Person-to-person transmission of Q fever has been described but is probably exceedingly rare [537].

### ***Incidence***

Q fever is almost certainly underdiagnosed as a result of the mild nature of the infection in the majority of cases, which are probably often attributed to influenza [538,539]. Thus of 111 cases diagnosed in a Melbourne abattoir only eight had pneumonia [532]. About 50–100 cases are confirmed serologically each year in the UK [540]. *Coxiella* pneumonia probably accounts for approximately 1% of cases of community-acquired pneumonia admitted to hospital in the UK [167,281]. It appears to be more common in spring and early summer in England and Wales, possibly reflecting lambing and the movement of livestock to market [540].

### ***Pathology***

Few cases have come to postmortem examination and those that have show non-specific pneumonic changes [541]. The inflammatory response is mainly mononuclear [474,542]. A detailed microscopic description has been made of a *C. burnetii* inflammatory pseudotumour that was resected on the radiological suspicion of carcinoma of the lung [542].

### ***Clinical features***

The manifestations of Q fever can be very varied but typically the illness is characterized by the sudden onset of high fever with rigors, headache (often severe) and myalgia after an incubation period of 2–5 weeks [532]. Nausea, vomiting and diarrhoea occur less commonly. There may be no cough or other respiratory symptoms, pneumonia occurring in less than 8% of an Australian series containing over 100 cases [532]. Admission to hospital with pneumonia was required in 8 of 29 cases of Q fever detected in an outbreak in South Wales [535]. A recent

Spanish study of 164 cases showed that about half had no respiratory symptoms. Cough was common in those that did have respiratory symptoms and about one-third of patients had pleuritic pain [543]. Most cases with lung involvement have single or multiple pulmonary infiltrates on the chest radiograph and a minority has a more rapidly progressive pneumonia. The physical signs are similar to those described for viral pneumonias (see below) but in addition hepatosplenomegaly occasionally occurs [532,544].

### ***Investigations***

The white blood cell count is often normal. Thrombocytopenia has been described in about 25% of cases and a reactive thrombocytosis may occur during the recovery phase [545]. Hepatic transaminases are commonly slightly raised and it is worth considering the diagnosis when this finding occurs in the absence of positive hepatitis serology. The diagnosis is confirmed retrospectively in most laboratories and relies on a clinical index of suspicion high enough to lead to appropriate serological testing (usually CFT). *C. burnetii* undergoes an antigenic change that produces two antigenic polysaccharides at different stages of infection. Paradoxically, phase II antibody can be detected first; phase I antibody remains at a low titre unless the disease enters a chronic stage (see below), in which case it exceeds the titre of phase II antibody. Antibodies may take 1–2 weeks to become detectable, a fourfold rise in titre of phase II antibody between acute and convalescent samples being diagnostic of acute infection. Titres fall gradually thereafter but may persist for years [546]. Apart from CFT, more recent serological developments include indirect immunofluorescent antibody tests, an ELISA and microagglutination tests [547]. PCR has also been used.

The chest radiograph is not discriminatory. Patients with Q fever pneumonia tend to show predominantly homogeneous unilateral or bilateral lower lobe shadowing of segmental or subsegmental distribution but the appearances are variable [548,549]. Pleural effusions may occur [550].

*C. burnetii* can be cultured from blood and other specimens but the technique requires guinea-pig inoculation and is hazardous to technical staff, necessitating special laboratory techniques and precautions, so that it is rarely carried out.

The Weil–Felix reaction, which is positive in other rickettsial infections, gives a negative reaction in Q fever.

### ***Treatment***

Q fever, whether associated with pneumonia or not, may be self-limiting and it is not entirely clear that therapy with antibiotics shortens its course, although the impression is that it does [532,551]. Q fever pneumonia may be fatal in

rare instances or may be associated with serious complications [541]. As the organism is sensitive to tetracycline *in vitro*, it is logical to treat with this antibiotic at a dose of 500 mg 6-hourly for about 3 weeks. Doxycycline 100 mg 12-hourly may also be used and may be more effective than erythromycin 500 mg 6-hourly, which is another alternative [551,552]. Rifampicin has been added in sicker patients with apparent good effect [547]. Untreated, the fever usually settles in 2–14 days but convalescence may be protracted [532,553]. Isolation is not ordinarily required as person-to-person spread of infection is rare, although immunocompromised patients may be more susceptible. A vaccine has been developed for those at risk such as abattoir workers but is not generally available [554].

### Complications

These are unusual and when they do occur are the result of the infection entering a chronic phase. The most serious manifestation is endocarditis, which usually affects a diseased native aortic or prosthetic valve [555,556]; 11% of 839 cases of confirmed Q fever reported between 1975 and 1981 developed this complication of culture-negative endocarditis, which is sometimes associated with a vasculitic rash. There are no controlled trials but successful treatment may require the use of combinations of antibiotics for months or years and valve replacement may be required [547,557]. Endocarditis may occur several years after the acute infection and the diagnosis is confirmed by a phase II antibody titre exceeding that of the phase I titre in the presence of negative blood cultures. It is not clear whether adequate treatment of acute Q fever infection prevents this sequel, which probably occurs as the result of latent hepatic infection.

Other complications include intravascular graft infections, meningoencephalitis, myocarditis, pericarditis, hepatitis with granulomas on liver biopsy, uveitis, osteomyelitis, haemolytic anaemia and epididymo-orchitis [540,557–559].

### Staphylococcal pneumonia

*Staph. aureus* is one of the less common causes of pneumonia acquired in the community but is nevertheless of great interest to clinicians because it may cause sudden and devastating illness. The same organism is an important cause of hospital-acquired infection and should be one of the foremost considerations when treatment of any severe case of pneumonia is planned. Treatment of infection with this organism has become more difficult because of the emergence of multidrug-resistant strains.

Staphylococci are members of the family Micrococcaceae and the specific name '*aureus*' has been given because most colonies of *Staph. aureus* appear golden-yellow when growing on agar. *Staph. aureus* grows well

both aerobically and anaerobically and is the only member of the genus that produces coagulase, a plasma-clotting enzyme, hence the term 'coagulase-positive staphylococcus'. It is a highly adaptable, non-spore-forming, non-motile pathogen, able to colonize rapidly and to penetrate damaged skin or mucosal surfaces. It has a specialized cell wall and can elaborate numerous toxins that contribute to its pathogenicity [560]. Most strains are surrounded by an antiphagocytic polysaccharide capsule or slime layer that affords it protection from polymorph attack, thereby increasing its virulence [561]. These encapsulated forms are better able to gain access to the bloodstream and to produce bacteraemia, unencapsulated forms being more likely to be contained locally in tissues. Paradoxically, if unencapsulated forms do gain access to the blood, e.g. via a contaminated intravenous line or from a drug addict's needle, they are more likely to produce the symptoms of septic shock or DIC, in the same way that DIC occurs with Gram-negative sepsis [562,563]. *Staph. aureus* has proved itself to be a frighteningly adaptive organism over the years, well able to develop resistance to antibiotics as the emergence of first penicillin-resistant *Staph. aureus* and now MRSA has shown only too well.

### Epidemiology

The main reservoir for *Staph. aureus* is humans, 30–50% of healthy adults being colonized, 10–20% persistently so [564]. Large numbers of these organisms may be carried asymptomatically, particularly in the anterior part of the nose. It is unknown why some should be carriers and others not, but higher carriage rates have been noted in type 1 diabetics, intravenous drug users, those on haemodialysis, surgical patients and those with AIDS [564–566]. *Staph. aureus* is an extremely hardy organism that can survive for some months outside its host and can be transferred from person to person both in particles suspended in air and by direct contact with skin or inanimate objects. Most hospital transmission is probably from the hands of healthcare workers who are transiently colonized by contact with infected patients or from their own reservoirs. Given these circumstances, it is unsurprising that outbreaks of *Staph. aureus* infection sometimes sweep through hospital wards [567].

In order that *Staph. aureus* may cause pneumonia it has to reach the lungs either via the trachea or by haematogenous spread in all cases other than those in which direct spread results from chest trauma or surgery. Nosocomial *Staph. aureus* pneumonia is favoured by tracheal intubation [568] and by conditions producing an impaired cough reflex, so that it has been found to be a common microbial isolate in cases of hospital-acquired pneumonia, coming second only to *Ps. aeruginosa*, and being particularly associated with diseases that impair conscious level [142,569]. Cases of staphylococcal pneumonia in the community may occur

in previously healthy people and are usually the sequel to a viral upper respiratory tract infection, therefore tending to be most common in the first few months of the year; indeed an association with influenza is well recognized so that the admission of a few cases of staphylococcal pneumonia to hospital may herald the onset of an influenza epidemic [570]. This was true in the large 1957 epidemic in which staphylococcal pneumonia was a significant cause of death and it continues to be so, a review of 61 community-acquired cases showing an association with influenza in about half [571]. At times when influenza is not epidemic, community-acquired staphylococcal pneumonia is uncommon in adult practice. *Staph. aureus*, in company with *Ps. aeruginosa*, is one of the major pathogens of the lower respiratory tract in cystic fibrosis (see Chapter 30).

*Staph. aureus* pneumonia may also result from bacteraemia. This may arise following direct invasion through breaks in the skin or at sites of pyogenic soft tissue infection, particularly where levels of hygiene are low as may be the case in developing countries or in communities where parenteral narcotic abuse is prevalent. The organisms may also gain access through prolonged intravenous cannulation or instrumentation sites or as a result of haemodialysis; having gained entry, they may be disseminated to various organs and structures including the lungs [572–574]. In all these cases, septic and thrombotic material may reach the lungs directly from a peripheral vein or sometimes from endocarditis involving the tricuspid valve (see Fig. 15.1) [19]. Although the source may be obvious, such as an infected wound, a burn, an eczematous skin lesion or marks of self-injection, at other times it may be inapparent, in which case the bacteraemia may be termed 'primary'.

The defence mechanisms in staphylococcal infection include not only complement-associated polymorphonuclear attack but also the phagocytic capacity of pulmonary alveolar macrophages, so that patients whose immune systems are compromised are more susceptible to *Staph. aureus* infection as they are to other pathogenic organisms [575]. One study of patients infected with HIV who were being investigated for lower respiratory tract infection found evidence of *Staph. aureus* pneumonia in 6%, AIDS having been diagnosed in most of these patients [576]. *Staph. aureus* pneumonia has been found to be more likely in HIV-infected patients who are drug abusers or who give a previous history of *Pneumocystis carinii* pneumonia [577]. Patients recovering in hospital following solid organ transplant are also more liable to *Staph. aureus* and other bacterial infections [578].

### Incidence

*Staph. aureus* has been estimated to be responsible for 1–2.4% of cases of community-acquired pneumonia requiring hospital admission [35,167]. *Staph. aureus* is

second only to *E. coli* in terms of causation of hospital-acquired infection as a whole and it more or less shares the honours with this pathogen as the commonest cause of hospital-acquired bacteraemia [566,579]. *Staph. aureus* may be a responsible pathogen in 10–16% of cases of nosocomial pneumonia [34,569].

### Pathology

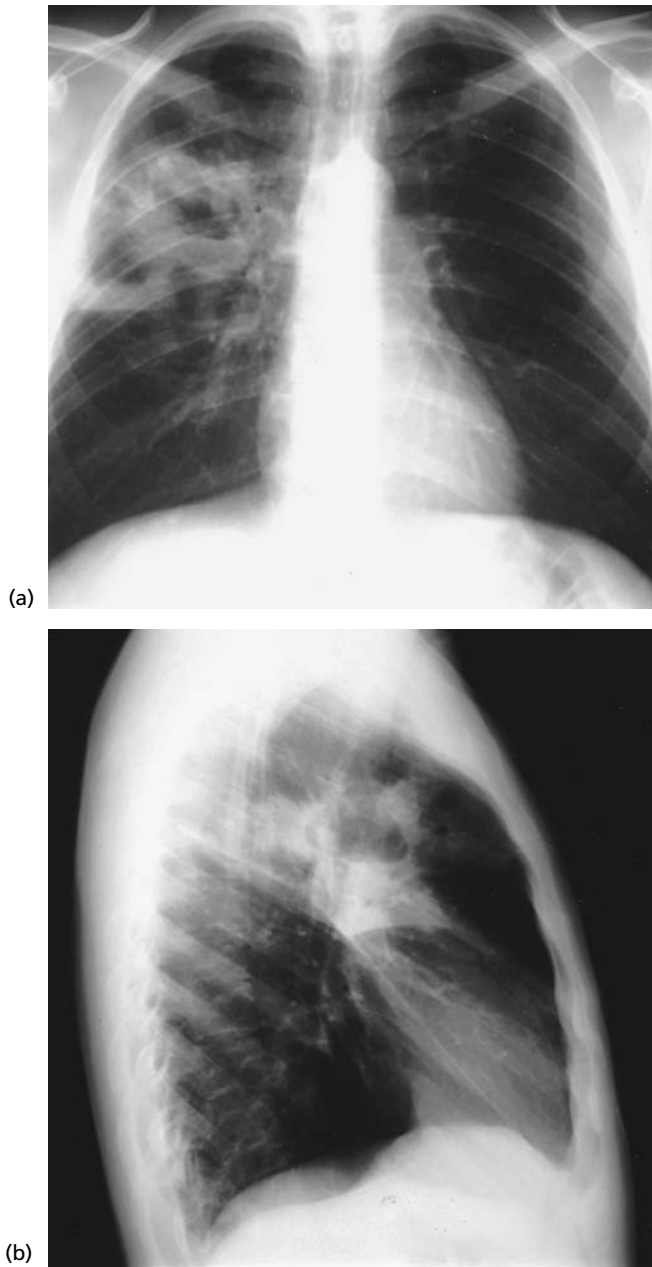
In cases where infection has been fulminating, the lungs are heavy and waterlogged with oedema fluid that may be haemorrhagic and the bronchial mucosa is very inflamed. In those where the illness has been more protracted, there are features to suggest that the infection progresses from an acute necrotic bronchitis or bronchiolitis to produce focal areas of consolidation. These may break down to form ill-defined abscess cavities and, if extensive, may result in honeycombing of the lungs [474].

### Clinical features

Community-acquired staphylococcal pneumonia in its severest form usually occurs within a few days of influenzal symptoms and, if appropriate treatment is withheld, results in a prostrating illness with rising fever, cough, breathlessness and bacteraemic shock that can result in death within a few hours. Less severe cases may differ little in their presentation from pneumococcal pneumonia, except that abscess formation is more common and may be the dominant feature. *Staph. aureus* pneumonia should be suspected in any severe pneumonia and in less severe cases if response to antipneumococcal antibiotics is unsatisfactory or if cavitation or other evidence of progressive sepsis becomes apparent. The complications of staphylococcal pneumonia are discussed below. Unsurprisingly, adult hospital-acquired *Staph. aureus* pneumonia tends to occur in an older population with pre-existing illness that is commonly pulmonary and this complication is often first diagnosed in intubated patients on intensive care units [580]. Occasionally the painless desquamating rash otherwise associated with toxic shock syndrome may be found [581,582].

### Investigations

The chest radiograph may show a wide spectrum of change. Infiltrates may be localized to a single lobe and the shadowing may be confluent. Multiple more patchy shadows may also occur and these are sometimes rounded. These appearances may be associated with cavitation, which may also be multiple and bilateral. The development of cavities always raises the possibility of staphylococcal pneumonia (Fig. 13.14). Sometimes thin-walled, air-containing cavities known as pneumatoceles appear [583]. These are more common in young adults and



**Fig. 13.14** Cavitating staphylococcal pneumonia in the right upper lobe of a previously healthy 41-year-old man who developed fever and cough productive of mucopurulent sputum following influenza.

children. They sometimes reach enormous size, causing respiratory embarrassment in their own right. It is likely that they arise from small cavitating abscesses, the surrounding consolidation allowing air to enter the space on inspiration but preventing its escape on expiration [584]. When treatment of pneumonia is successful, these pneumatoceles may disappear with surprising rapidity. Complicating effusions and pneumothoraces may be seen but

the absence of so-called typical changes does not exclude the diagnosis [585].

There is usually a neutrophil leucocytosis but sometimes low white cell counts are found and anaemia often develops when bacteraemia is present. A low platelet count may indicate the development of DIC, in which case the prothrombin time and clotting time are prolonged.

Microscopic examination of the sputum may show grape-like (*staphyle* is ancient Greek for 'bunch of grapes') clusters of Gram-positive cocci mixed with neutrophils and inflammatory debris, these appearances being highly suggestive of staphylococcal pneumonia. However, interpretation may be difficult as the cocci can be relatively isolated, sometimes occurring singly, in pairs or in chains.

The organism is frequently isolated from both sputum and blood cultures and standard methods exist to enable microbiology laboratories to differentiate between staphylococci that are coagulase positive (i.e. *Staph. aureus*) and those that are coagulase negative (e.g. *Staph. epidermidis*) on the first day of isolation [586–588]. Although false-positive sputum cultures may occur as a result of nasopharyngeal colonization, false negatives are unusual in the presence of pneumonia [589]. *Staph. aureus* can often be isolated from blood in bacteraemic cases despite the prior commencement of an appropriate antibiotic, particularly if there is a septic focus. High spikes of fever, such as may occur during rigors, are particularly good times to draw blood for culture, this being positive in one-quarter to one-third of cases of *Staph. aureus* pneumonia [589]. The organism may also be grown from associated pleural effusions.

#### **Treatment of methicillin-sensitive *Staph. aureus* pneumonia**

Most strains of *Staph. aureus* produce  $\beta$ -lactamases so that it has long been the exception for these organisms to be sensitive to penicillins, such as benzylpenicillin, phenoxymethylpenicillin and the aminopenicillins (ampicillin, amoxicillin), even if the infection is acquired in the community. This is the case on both sides of the Atlantic, a figure of only about 5% being commonly quoted for penicillin sensitivity [564]. Over a decade ago Lacey [590] noted that 80% of hospital- and community-acquired *Staph. aureus* were penicillin resistant in the health district in which he worked. Intravenous benzylpenicillin may be used in those relatively few cases that are sensitive at a dose of 2.4 g (4 megaunits) 4–6 hourly but for the most part it is normal practice when *Staph. aureus* is suspected as a cause of pneumonia to treat with a  $\beta$ -lactamase-resistant antibiotic, of which flucloxacillin is preferred as drug of first choice in UK at a dose of 1–2 g i.v. 4–6 hourly for 48 h, thereafter continuing either parenterally or orally according to response. Treatment for 2 weeks is usually sufficient in uncomplicated cases but a minimum of 4 weeks of treatment is usually needed if an intravascular source of infec-

tion, such as right-sided endocarditis, is suspected (initial gentamicin being added in this circumstance). Flucloxacillin is unavailable in the USA, where options include intravenous oxacillin or nafcillin followed by dicloxacillin orally. Treatment for 2 weeks usually suffices, although this may need to be prolonged in severe or complicated infections, in which case other antistaphylococcal antibiotics may also need to be added. Options include rifampicin, which is a very potent antistaphylococcal drug that can be prescribed either orally or parenterally at a dose of 600 mg 12-hourly [591]. It must not be used alone or resistance will develop and its use in conjunction with other antistaphylococcal antibiotics is required [592].

For the patient with a history of delayed-type non-severe penicillin allergy a first-generation cephalosporin (e.g. intravenous cefradine or cefazolin) may be used; in cases of severe infection, one of these may be backed up by rifampicin as above.

Vancomycin 1 g i.v. 12-hourly is the most effective substitute for patients who are seriously allergic to penicillins (anaphylaxis or other accelerated reactions) but it is potentially toxic (see below) so that blood levels have to be assayed and the dose adjusted accordingly. Teicoplanin is a less toxic alternative (see below).

Other 'reserve drugs' whose spectra include useful antistaphylococcal activity so that they may be 'added on' in certain circumstances include fusidic acid and aminoglycosides.

### *Treatment of MRSA pneumonia*

The problem of *Staph. aureus* strains no longer susceptible to  $\beta$ -lactamase-resistant antibiotics has become very important. These MRSA strains have appeared in many parts of the world, including Australia, the UK and the USA and are resistant to all  $\beta$ -lactam antimicrobial agents [593]. In the USA they are sufficiently common for intravenous vancomycin to be used as a drug of first choice in any suspected serious staphylococcal infections until the susceptibility of the isolate is known, the dose being 1 g 12-hourly. In the UK the drug may be used 'first off' if the patient with staphylococcal pneumonia is already known to be a carrier of MRSA or if admission has been from a nursing home where MRSA is known to be endemic.

Vancomycin is a glycopeptide that has been clinically available for over 30 years but its use has been limited by toxicity, which is probably one reason why it remains effective. Full MRSA resistance to vancomycin has not been reported thus far. Unfortunately the emergence of intermediate resistance is already taking place [592] as the frequency of this drug's usage increases. Vancomycin-resistant enterococci have also emerged and have spread from intensive care units across hospitals. This is relevant to *Staph. aureus* infection because enterococci may act as a reservoir for vancomycin-resistant genes and this resis-

tance has been shown to be potentially transferable from enterococci to other genera such as staphylococci [594]. Adverse effects to vancomycin include allergic reactions, local phlebitis, flushing ('red man syndrome'), ototoxicity with tinnitus and hearing loss, nephrotoxicity (less common with the purer preparations now available and if other nephrotoxic drugs are avoided) and neutropenia. Dose-related effects may be limited by keeping serum concentrations below 30 mg/L and by using a nomogram in the presence of renal insufficiency. Teicoplanin is a newer glycopeptide antibiotic that may be used instead of vancomycin. It is easier to administer and probably less toxic than vancomycin, with a longer half-life leading to once-daily dosage. It can be used in serious infections as an alternative to vancomycin when allergic reactions or neutropenia have occurred but is expensive. It is usual to add rifampicin to vancomycin or teicoplanin in severe infections, as above.

Tolerance to glycopeptides may occur so that combination therapy may sometimes be required. The choice of combination may be guided by sensitivities and sometimes by microbiological back-titrations of the patient's serum against cultures of the organism [595]. Possible additions include fusidic acid, fluoroquinolones such as ciprofloxacin, minocycline or co-trimoxazole (trimethoprim-sulfamethoxazole) [564,580,596,597].

The management of colonization by MRSA and the prevention of spread within or between institutions is a specialized infection-control area that has been well reviewed [596].

### *Mortality*

The mortality of staphylococcal pneumonia depends upon the virulence of the strain, the age of the patient, the extent of consolidation, the provision of appropriate antibiotics and whether complications such as bacteraemia occur. Before the availability of antibiotics the mortality from staphylococcal bacteraemia stood at about 80% [598]. Even though antistaphylococcal antibiotics are now available, the mortality from this form of pneumonia is still 25–50% overall [165,264,571]. A mortality figure of 75% has been recorded for patients aged over 70 years, higher figures being recorded in bacteraemic cases, compared with 25% for patients aged under 40 years [168,599]. Such younger patients usually fall into the category of postinfluenzal staphylococcal pneumonia of whom an alarming proportion still die despite appropriate antibiotic treatment.

### *Complications*

Staphylococcal pneumonia can itself be a complication of a bacteraemic illness that may become manifest in many ways [566,600]. Some intrathoracic complications have



already been mentioned and include lung abscesses, which occur in 25% of cases (see Chapter 15) and related pneumatoceles. Pneumothorax (see Chapter 44) may occur as a result of focal sepsis rupturing through the visceral pleura. This complication is more likely if mechanical ventilation is required and if the patient is taking corticosteroids for some other reason [601]. When it does occur it is liable to become complicated by infection in the pleural space with resultant pyopneumothorax. Treatment is with continued antibiotics and tube drainage. Empyema may occur in its own right in about 10% of cases [568,570]. Residual pulmonary or pleural shadowing is not uncommon after successful treatment of the pneumonia and its intrathoracic complications.

*Staph. aureus* bacteraemia may be complicated by left-sided endocarditis in about 10% of cases and if this is suspected clinically, treatment should be continued for 4–6 weeks [566]. Patients with known valvular heart disease who develop staphylococcal bacteraemia from any source have a higher risk of developing endocarditis and should be treated as such. Right-sided endocarditis has a lower mortality and usually results from the introduction of venous sepsis such as may occur in heroin abusers. Metastatic abscesses may occur at any site in a bacteraemic case [564]. Profound hypotension (endotoxin shock) may occur in bacteraemia as a consequence of a generalized capillary leak [563]. It may also be complicated by DIC [602]. Cutaneous desquamation or exfoliation is sometimes seen and has already been alluded to [581,582,600]. Rhabdomyolysis has been reported but is seemingly extremely rare [603].

### Prevention

Prevention of all *Staph. aureus* infections in the hospital setting is reduced by simple measures such as handwashing. Infection-control measures include, where possible, the separate nursing of patients who are carriers of MRSA and their treatment with topical agents to eliminate colonization. The same applies to patients with MRSA infection [564,596,597].

### ***Klebsiella pneumonia* (Friedländer's pneumonia)**

The genus *Klebsiella* contains four species, all of which are large, aerobic, non-motile, Gram-negative enteric bacilli. Like *E. coli* they belong to the family Enterobacteriaceae. They have a prominent polysaccharide capsule that is believed to be important in enhancing virulence [604]. Two of these species have been associated with Gram-negative pneumonia, namely *Klebsiella pneumoniae* (Friedländer's bacillus) and less commonly *Klebsiella oxytoca*. These two microbes used to be considered as one species but have been separated in terms of the ability of

the former organism to give an indole-positive reaction and to liquefy gelatin.

### Epidemiology

*Klebsiella* are found in soil, water and in the human faecal flora. *K. pneumoniae* occurs commensally in the oropharynx of 1–6% of healthy people and may be more common in the oropharynx of subjects with carious teeth or periodontal disease [605]. It becomes more prevalent in hospital patients, particularly if they have received antibiotics. It is believed to reach the lungs by aspiration from the oropharynx and certain groups of patients are particularly predisposed. These include alcoholics, diabetics, those who have been endotracheally intubated and those who are elderly or otherwise debilitated by disease [44,606].

### Incidence

*Klebsiella* spp. is the most common group of enteric Gram-negative bacilli to cause community-acquired pneumonia and is also commonly implicated in nosocomial pneumonia [607]. Some series have reported that it accounts for 1–2% of pathogenic organisms isolated in acute pneumonia and for about 8% of those found in more elderly and debilitated patients [165,177,608,609]. *K. oxytoca* is much less commonly cultured from sputum than *K. pneumoniae*, accounting for only 10 of 110 *Klebsiella* isolates in one series [610]. A high incidence of concurrent bronchopulmonary disease has also been reported in *K. oxytoca* infections [610].

### Pathology

*K. pneumoniae* and *K. oxytoca* are unusual among the Gram-negative bacteria in that they may cause a confluent pneumonia of lobar distribution. This led Friedländer in 1882 to suppose that it was a common cause of lobar pneumonia before it was realized that *Strep. pneumoniae* accounted for the majority of these cases.

It is notable that *Klebsiella pneumoniae* tends to involve the posterior segments of the upper lobes and the apical segments of the lower lobes, the majority of cases being unilateral and the right side being affected more frequently than the left. These observations are consistent with the supposition that it is generally caused by the aspiration of the organism from the oropharynx, presumably by patients in the supine position. The affected area of lung becomes distended by viscid oedema fluid that may produce a characteristic radiographic sign (see below). The lung contains an acute inflammatory infiltrate that may result in tissue necrosis and cavitation [474,609]. This necrotizing pneumonia may occasionally cause major vascular compromise resulting in pulmonary gangrene [474].

### Clinical features

The clinical syndrome produced in *Klebsiella* pneumonia may be indistinguishable from that produced by many other acute bacterial pneumonias, except that the infection tends to be severe and, in contrast to other Gram-negative bacteria, may cause a confluent pneumonia of lobar distribution. As with staphylococcal pneumonia, cavitation and abscess formation may occur, although these tend to be less widespread. The sputum is viscid and may be blood-stained, sometimes being fancifully likened to redcurrant jelly.

### Investigations

The Gram stain may be difficult to interpret as *Klebsiella* spp. may be oropharyngeal commensals and irrelevant to any lower respiratory tract infection that may be present. Discussion with the reporting microbiologist may be valuable, as the association of large numbers of organisms with many pus cells is more likely to be significant.

The radiographic features may be variable. A so-called typical case shows confluent shadowing that affects an upper lobe with downward displacement of the fissure, resulting from distension of the lobe with oedema fluid (bowed or bulging fissure sign) [44,611–613]. In reality such classic signs are often absent [614]. Cavitation and necrotizing pneumonia tend to be more evident if the patient undergoes CT [615].

### Treatment

The antibiotic sensitivities of *Klebsiella* spp. are highly variable but resistance to ampicillin is usual. A synergistic combination of an aminoglycoside such as gentamicin with either a third-generation cephalosporin (e.g. cef-tazidime) or an extended-spectrum penicillin such as piperacillin or azlocillin is recommended pending sensitivities [572,616,617]. In hospital-acquired Gram-negative pneumonias, these extended-spectrum penicillins and cephalosporins have the advantage of being active against *Ps. aeruginosa* and other common infecting microbes (see section on core organisms, p. 371). Other antibiotics that may prove effective against *Klebsiella* include the monocyclic  $\beta$ -lactam (monobactams aztreonam, carbapenems such as imipenem/cilastin and meropenem, fluoroquinolones such as ciprofloxacin, co-trimoxazole and chloramphenicol).

Local microbiological guidance should be taken as  $\beta$ -lactamase-producing multidrug-resistant strains of *K. pneumoniae* are endemic in some hospitals [618–620].

### Mortality

The mortality from *Klebsiella* pneumonia is high, at least in

part because it tends to cause disease in elderly or otherwise debilitated patients. Fatality rates as high as 68% have been reported in early series [264].

### Complications

*Klebsiella* pneumonia is complicated by bacteraemia in about 25% of cases [621]. Empyema (see Chapter 14), lung abscesses (see Chapter 15), pleural effusions (see Chapter 43) and other complications may occur as described under staphylococcal pneumonia.

### *Pseudomonas pneumonia*

This is almost always caused by *Ps. aeruginosa* (previously known as *Ps. pyocyaneus*), a Gram-negative, aerobic, motile, flagellate rod that characteristically produces pigments, including pyocyanin. This pigment is green, rather like the colour of verdigris (copper rust), hence the Latin root *aeruginosus*. As well as being flagellate, *Ps. aeruginosa* also possesses fine hairs or pili, with which it may attach itself to epithelial surfaces [622]. Its cell wall is covered by a slimy polysaccharide layer that may protect it from phagocytic attack. It produces various toxins and proteases including an endotoxin that may cause 'shock' in bacteraemia, a phospholipase that attacks surfactant and may produce atelectasis and an elastase that can destroy alveolar septa and which may also be responsible for vasculitis in bacteraemic patients [623,624].

Other members of the genus that occasionally cause pneumonia include *Ps. mallei* and *Ps. pseudomallei* (causes, respectively, of glanders and melioidosis, described below) and also *Ps.* (now *Xanthomonas*) *malophilia* and *Ps.* (now *Burkholderia*) *cepacia*, the cause of onion soft rot and an opportunistic pulmonary pathogen in patients with cystic fibrosis.

### Epidemiology

*Ps. aeruginosa* is an opportunistic pathogen for humans, rarely causing disease in otherwise healthy persons. It occurs naturally in water, soil and vegetable material. Its nutritional requirements are simple, in that it can obtain carbon from carbon dioxide and nitrogen from ammonium and is able to survive in distilled water [625]. The carriage rate for *Ps. aeruginosa* in otherwise healthy members of the community is low, being about 5% for the oropharynx [626,627]. It may also be found in the axillae, anogenital area and in faecal flora [628]. The carriage rate in hospital populations is very much higher and may exceed 50%. The organism has a predilection for moist conditions, and reservoirs of infection may build up in mechanical ventilators, nebulizer equipment, sinks and even in disinfectant solutions (particularly those that contain ammonium compounds) [628]. Hospital

epidemics of pseudomonal infection may occasionally arise from such sources. These high rates of colonization predispose to invasive *Pseudomonas* infection in hospital patients [629] and pneumonia is believed to usually follow the microaspiration of the products of such oropharyngeal colonization into the lungs. Patients particularly at risk include those on mechanical ventilators, those in whom the normal flora are suppressed by antibiotics and those who are in any way immunosuppressed. Pseudomonal infection is a considerable problem in burns patients and the organism may be spread about a ward or unit by hand-to-patient contact [628]. Patients with cystic fibrosis are particularly predisposed to *Pseudomonas* respiratory infections (see Chapter 30) and the organism not infrequently colonizes otherwise chronically damaged lungs.

### Incidence

*Ps. aeruginosa* was found by the National Nosocomial Infections Surveillance System of the Centers for Disease Control to be the commonest cause of hospital-acquired pneumonia, accounting for about 17% of all isolates [140]. It is a less common cause of community-acquired pneumonia, mainly (but not always [630]) affecting elderly or otherwise debilitated members of the population.

### Pathology

Consolidation is usually distributed in a patchy manner and affected areas of lung may contain small abscesses and focuses of haemorrhagic necrosis. These areas may be centred around pulmonary vessels, which may show arteritic changes, this leading to thrombosis with lung necrosis and the surrounding areas of haemorrhage typical of this infection [474,631]. The excised lungs may share the characteristic sweet grape-like smell that characterizes laboratory cultures of *Ps. aeruginosa*.

### Clinical features

*Pseudomonas* pneumonia typically occurs in a patient who is compromised by pre-existing lower respiratory disease of a chronic nature (e.g. bronchiectasis, cystic fibrosis), heart failure, blood dyscrasias or immunosuppressive therapy [632,633]. The organism is all too familiar in intensive care units in association with mechanical ventilation and the previous use of broad-spectrum antimicrobials. At other times it may cause an infective bronchitis, characterized by mucopurulent respiratory secretions in the absence of pneumonic consolidation.

Some cases of *Pseudomonas* pneumonia are associated with bacteraemia [634], others not [635], but in either situation the organism probably first reaches the lungs by oropharyngeal microaspiration. Patients who are neu-

tropenic as a result of chemotherapy are more likely to develop *Ps. aeruginosa* bacteraemia. The infection may be fulminating in bacteraemic cases and may result in endotoxin (septic) shock with hypotension and oliguria. The patient may develop ARDS, with pulmonary oedema occurring as a consequence of a pulmonary capillary leak rather than heart failure, as evidenced by normal pulmonary capillary wedge pressure measurements. Such critically ill patients may also develop DIC. Bacteraemic patients sometimes develop a vesicular rash or erythema gangrenosum, the lesions of which comprise a central area of cutaneous necrosis surrounded by a narrow ring of erythema.

The radiographic features, in common with other pneumonias, are non-specific. Shadowing is frequently patchy and bilateral but more confluent lobar consolidation may also occur. Occasionally the shadowing may be nodular and areas of cavitation or lung abscess formation may be detectable. Small pleural effusions may occur but empyemas are unusual. There may be residual fibrotic changes if the patient survives.

The organism can be grown on standard culture media from sputum or respiratory secretions obtained by some invasive means such as BAL (see above) and its isolation in a clinical setting suggestive of pneumonia calls for appropriate antimicrobial treatment. Blood cultures are positive in less than 10% of cases.

### Treatment

Pneumonia in which *Ps. aeruginosa* is thought to be a causal pathogen is usually treated with a combination of an antipseudomonal  $\beta$ -lactam antibiotic and an aminoglycoside (see section on severe hospital-acquired pneumonia) [141]. There is limited evidence to suggest that this approach produces better results than treatment with a single antipseudomonal agent, potential benefits including increased potency and reduced chances of the emergence of resistant strains [636]. Examples include the antipseudomonal penicillin piperacillin, which has been shown to be more active than azlocillin, mezlocillin, ticarcillin and carbenicillin in this regard [637,638]; an antipseudomonal third-generation cephalosporin such as ceftazidime; a carbapenem such as imipenem/cilastin or meropenem. Gentamicin is a suitable partner and treatment may be continued for 2 weeks in the case of bacteraemic pneumonia or for a shorter period according to response when bacteraemia is not present. A fluoroquinolone such as ciprofloxacin may be used with one of the above  $\beta$ -lactams as an alternative to the aminoglycoside or may be combined with an aminoglycoside in patients who are allergic to penicillin. Such treatment may be modified according to the laboratory sensitivities of the organism since strains of *Ps. aeruginosa* may become resistant to any of the aforementioned drugs by differing

mechanisms, the development of resistance to one class of drug sometimes inducing resistance in another [639]. The treatment of *Pseudomonas* infection in cystic fibrosis, including the topics of antibiotic prophylaxis and nebulization, are discussed in Chapter 30.

### **Mortality**

*Pseudomonas* pneumonia is a severe infection, particularly in association with bacteraemia, and is probably the most lethal nosocomial lung infection, with a mortality of over 60% [264,628,639,640]. It is the most common cause of death in intubated patients with pneumonia [641].

### ***Escherichia coli* pneumonia**

Like *Klebsiella* spp., *E. coli* belongs to the family of Gram-negative enteric bacteria, the Enterobacteriaceae. It is also aerobic but is able to grow in anaerobic conditions (i.e. a facultative anaerobe). Unlike *Klebsiella* spp., it is motile.

### **Epidemiology**

*E. coli* causes a wide range of clinical illness in humans, urinary tract infections and enteritis being the most notable in adult practice. The organism is very much part of the normal gut flora, 1 g of stool containing  $10^8$  organisms [617]. The finding of this organism in the sputum of patients who are ill in hospital need not be clinically significant as the oropharynx is commonly colonized by Gram-negative bacilli in this environment laden with broad-spectrum antibiotics. Nevertheless, *E. coli* is a potential pulmonary pathogen in this group as a result of microaspiration. *E. coli* may also cause pneumonia as a result of haematogenous spread from bacteraemic gut and urinary tract infections, to which diabetics are particularly predisposed. *E. coli* as a cause of pneumonia tends to be confined to elderly or debilitated subjects and this is a point of similarity with other Gram-negative enteric pathogens.

### **Incidence**

Although it is the most common urinary tract pathogen in hospital patients and one of the most common bloodstream isolates, *E. coli* is not a frequent cause of Gram-negative opportunistic bacillary nosocomial pneumonia, being a less common isolate than *Ps. aeruginosa*, *Enterobacter* spp. and *Klebsiella pneumoniae*, and accounts for about 6% of cases [140,607]. It is also an uncommon cause of community-acquired pneumonia, *Klebsiella pneumoniae* being the most common Gram-negative bacillary cause in this group.

### **Clinical features**

The clinical features are those of any bacterial pneumonia. However, sputum may be absent and in the presence of bacteraemia the patient may be prostrated and hypotensive. Clinical features of a primary urinary tract or gastrointestinal tract infection may be evident. The chest radiographic appearances may reflect the haematogenous dissemination of the organism, shadowing often being patchy and bilateral [642,643]. The organism is recoverable from the blood in about 25% of cases [642]; otherwise diagnosis depends upon consistent clinical and radiographic features along with the repeated isolation of the organism from sputum or by some other invasive means of obtaining respiratory secretions such as BAL with quantitative culture (see p. 362). This form of pneumonia is sometimes complicated by empyema.

### **Treatment**

*E. coli* may show considerable strain variation in its susceptibility to antibiotics, and as the prevalence of these strains varies from one hospital to another the choice of antibiotic is likely to be influenced by local considerations. A third-generation cephalosporin such as ceftazidime is usually effective, particularly when combined with an aminoglycoside such as gentamicin, with which synergism occurs [616]. Two antibiotics are preferred because of the serious nature of Gram-negative pneumonia but treatment may be modified according to clinical response and full laboratory sensitivities.

### **Mortality**

The mortality is generally reported to be high and this is in part because patients frequently have serious coexisting disease, as is often the case with other Gram-negative pneumonias [43,264]. Fatality rates of about 30% have been reported for *E. coli* pneumonia in the past [264,643], although the impact of this organism on the mortality of ventilator-associated pneumonia is thought by others to be marginal [641].

### **Pneumonia caused by other Gram-negative aerobic opportunistic bacilli: *Enterobacter*, *Serratia*, *Proteus*, *Acinetobacter***

Apart from *Klebsiella* spp. and *E. coli*, a number of other genera in the Gram-negative family Enterobacteriaceae have been causally related to cases of pneumonia either in elderly or otherwise sick and debilitated patients. These include *Enterobacter* spp., *Serratia marcescens* and *Proteus* spp. All are opportunistic lower respiratory tract pathogens, producing disease as a result of the microaspiration of oropharyngeal contents.

*Enterobacter* spp. are more common nosocomial respiratory pathogens than was previously thought, accounting for about 11% of hospital-acquired respiratory infection [140]. These opportunists can be spread between patients on the hands of staff and frequently colonize patients who have been treated with broad-spectrum antibiotics, particularly those on intensive care and burns units. The most common hospital opportunist in this genus is *Enterobacter cloacae*. This group of organisms commonly produce  $\beta$ -lactamases so that it is usual to treat with combined  $\beta$ -lactam/aminoglycoside therapy [644].

*Serratia marcescens* is a less common colonist of the adult gastrointestinal tract than other Enterobacteriaceae and is more likely to be found in the respiratory or urinary tracts of hospital patients. It can be spread on the hands of hospital staff and may be responsible for about 4% of hospital-acquired lower respiratory tract infections [645]. Such infection has been associated with instrumentation of the respiratory tract and the use of contaminated respiratory therapy equipment [646]. About 5% of strains of *Serratia marcescens* produce a reddish pigment called prodigiosin, which may discolour respiratory secretions and be mistaken for haemoptysis. It is usual to treat such cases as for *Klebsiella* or *E. coli* pneumonia, but therapy may have to be modified in the light of multidrug resistance [647].

*Proteus* spp. are highly motile, flagellate bacteria that reside in the gastrointestinal tract but which may cause opportunistic infection in the urinary and, less commonly, respiratory tracts of debilitated patients. Most infections are due to *P. mirabilis* and some to *P. vulgaris*. Antimicrobial treatment is along the lines described for *Klebsiella* spp. but may need modification in the light of sensitivities.

*Acinetobacter* is a genus of free-living, Gram-negative, non-motile coccobacilli belonging to the family Neisseriaceae. It is a common cutaneous colonist, particularly among hospital personnel, and may also colonize the oropharynx of 7% of healthy people [627]. It has a predilection for intensive care units and frequently colonizes tracheostomy sites. It may cause outbreaks of nosocomial pneumonia in this environment, particularly in sick patients who have been treated with broad-spectrum antibiotics [648]. It reportedly causes 3% of cases of hospital-acquired pneumonia in North America [649]. This form of pneumonia has also been acquired in the community and may have a predilection for alcoholics [650]. A small outbreak of *Acinetobacter* pneumonia has been described in iron foundry workers, raising the possibility that dust exposure increased the susceptibility of these subjects to infection by this organism [651,652]. *Acinetobacter* pneumonia has no particular features to distinguish it from pneumonia caused by other Gram-negative opportunistic bacilli except that bacteraemia is said to be unusual. If bacteraemia does occur it may be complicated by hypotension, as is the case with

other Gram-negative organisms [653]. The treatment options are broadly similar to those outlined for *Ps. aeruginosa* above.

### ***Haemophilus influenzae* pneumonia**

*H. influenzae* is a small, non-motile, Gram-negative, aerobic, pleomorphic coccobacillus that may assume filamentous form. It is a strict parasite of humans, with no other natural hosts and occurs in both encapsulated and non-encapsulated forms. The encapsulated group may be serotyped in terms of capsular polysaccharide into types a–e, type b being that which causes invasive infection most frequently, usually in young children in whom it may produce bacteraemia with meningitis, epiglottitis, cellulitis, septic arthritis and sometimes pneumonia. The other five encapsulated types are rarely pathogenic. The non-encapsulated (or non-typable) forms are usually responsible for the more common adult respiratory tract infections with which we are concerned in this section.

### **Incidence**

Pfeiffer in the nineteenth century wrongly believed *H. influenzae* to be the cause of influenza, hence its specific name. Doubt and uncertainty persist about the frequency with which *H. influenzae* causes pneumonia and it is more commonly associated with purulent exacerbations of chronic bronchitis. Such uncertainties are fuelled by the frequency with which the organism occurs in the respiratory tract not only in patients with lower respiratory tract disease other than pneumonia but also in health, so that isolation of the organism in sputum has to be viewed critically. Unencapsulated forms are commonly retrievable from the pharynx but not the lower respiratory tract of fit adults and children and in the mucoid sputum of up to 60% of chronic bronchitics [44]. Encapsulated forms are less commonly carried, being found in up to 6% of healthy subjects [44,643]. The belief has been held that encapsulated strains have usually been responsible for pneumonia, although non-encapsulated forms have also been implicated in both bacteraemic and non-bacteraemic pneumonia [44,654–656]. Spread is by droplet nuclei or other contact with respiratory secretions and lower respiratory tract infection is believed to arise as a result of the microaspiration of the organism from the pharynx.

A study of community-acquired pneumonia carried out in Nottingham ascribed a causative role to *H. influenzae* in 3% of 127 patients [167], and the British Thoracic Society multicentre trial found it to be an aetiological factor in 6% of cases [35]. Series in which the diagnosis is based on sputum isolation overestimate the frequency of *Haemophilus* pneumonia and those purists who accept the

diagnosis only following culture from blood, protected tracheobronchial samples, pleural fluid or direct lung puncture might be expected to underestimate, although a recent Danish study of 254 patients with community-acquired pneumonia isolated *H. influenzae* from transtracheal aspirates in 16 cases and found this organism to be causal in approximately 17% of pneumonias in previously healthy individuals under 50 years of age [657]. Positive cultures from transtracheal aspirates in patients with chronic bronchitis need not be diagnostically valid as *H. influenzae* tends to colonize the trachea in these subjects [658]. *H. influenzae* has been reported in about 6% of cases of nosocomial pneumonia [140].

### *Clinical features*

The onset of *H. influenzae* pneumonia may be more insidious than is usually seen with other acute pneumonias such as that caused by *Strep. pneumoniae*. It usually but not invariably occurs in patients, often elderly, with exacerbations of underlying lung disease, such as chronic bronchitis or asthma, commonly following viral upper respiratory tract infection. It may also occur in association with alcoholism or in patients with impaired immunity, including those with HIV infection [659,660]. There are no specific radiographic findings. Shadowing may be patchy or more confluent and in some cases is lobar [655,661].

Laboratory identification of the organism by Gram staining and culture is not usually difficult. Culture techniques may be applied to specimens of sputum, blood and on occasions pleural fluid or other invasively obtained specimens. The development of techniques to enable more rapid detection of encapsulated forms by the recognition of capsular polysaccharides using counter immunoelectrophoresis (CIE) and other methods have been described [662,663].

### *Treatment*

Although the majority of strains of *H. influenzae* are sensitive to the aminopenicillins amoxicillin and ampicillin, there is concern about the increasing emergence of resistant forms that produce  $\beta$ -lactamases. A survey carried out in the UK in 1981 showed 6.2% of isolates to be resistant to ampicillin [664]. The incidence of strains resistant to ampicillin/amoxicillin in the UK continues increase, rates of 8–15% having been reported across the country, with much higher rates in Spain and the USA so that it is essential to be informed about the sensitivity patterns in ones own locality [121,665,666]. Second- and third-generation cephalosporins such as cefuroxime and cefotaxime are highly active against *H. influenzae* and may be used parenterally in serious infections pending the results of sensitivities, after which treatment may be modified

accordingly [666,667], ampicillin or amoxicillin being the drugs of choice for those susceptible strains that still form the majority. Other effective agents include co-amoxiclav, clarithromycin or azithromycin, fluoroquinolones such as ciprofloxacin, third-generation cephalosporins and extended-spectrum penicillins. Chloramphenicol is usually effective but should rarely be used, particularly when reliable alternatives for severe infection such as cefotaxime are available (see Chapter 9).

By virtue of its polysaccharide capsule, *H. influenzae* type b conjugated vaccines have been developed, their use having been confined to paediatric practice, where this organism is a major cause of morbidity and mortality, largely from meningitis, epiglottitis and pneumonia [668]. Whether or not such vaccines might have an important preventive role in respiratory infection in developing countries, where invasive capsular strains other than type b may be endemic, is not known [18,669].

### *Moraxella catarrhalis pneumonia*

*Moraxella* (previously *Branhamella*, previously *Neisseria*) *catarrhalis* has long been known to live commensally in the oropharynx and was largely ignored as a potential lower respiratory tract pathogen until a spate of reports of significant isolates obtained mostly from patients with coexisting and often chronic lung disease [670–675]. Such isolates are usually found in exacerbations of chronic bronchitis, and *Moraxella* pneumonia is quite unusual, probably accounting for 1–3% of cases of community-acquired pneumonia [121]. It has been described in the immunocompromised and in elderly patients with underlying chronic pulmonary disease, who are particularly susceptible to *M. catarrhalis* infection [676–678]. *M. catarrhalis* is a Gram-negative, aerobic coccobacillus that is a member of the Neisseriaceae family and was known by that name until 1970, when it was given its own genus because of various biochemical and antigenic differences [679]. As an upper respiratory tract pathogen it may cause both sinusitis [680] and acute laryngitis [681] and may extend directly to cause otitis media [682].

The organism is carried in the upper respiratory tracts of about 50% of children, 5% of adults up to the age of 60 years and 25% of people over this age, so that the significance of isolates of *M. catarrhalis* in the sputum has been a subject for debate [683,684]. However, it has become increasingly accepted that a moderate or heavy growth obtained from mucopurulent sputum containing Gram-negative coccobacilli and neutrophils may be clinically important, justifying therapeutic intervention [670,671]. In addition to purulent bronchitis, patchy consolidation may occur.

The reason for the appearance of pathogenic strains is unclear but the frequency with which ampicillin is

prescribed may have encouraged the emergence of  $\beta$ -lactamase-producing forms [671]. Lower respiratory tract infection is believed to arise as a result of the aspiration of the organism from the oropharynx. Bacteraemia is highly unusual [685]. The organism can survive drying and nosocomial infection may occur, cross-infection within a respiratory unit having been confirmed by DNA studies [671,686].

Upwards of 80% of *M. catarrhalis* isolates are  $\beta$ -lactamase producers and are therefore resistant to ampicillin/amoxicillin [671,687,688]. The organism is usually sensitive to macrolides, co-amoxiclav (amoxicillin-clavulanic acid) and ampicillin-sulbactam (USA), second- and third-generation cephalosporins, fluoroquinolones such as ciprofloxacin, as well as tetracycline and cotrimoxazole but is resistant to trimethoprim alone.

### **Pneumonia caused by anaerobes (including aspiration pneumonia)**

The incidence of anaerobic pneumonia is uncertain because it may go undiagnosed unless the suspicions of a physician are raised by the presence of a lung abscess (see Chapter 15), the development of an empyema (see Chapter 14) or a history of either witnessed aspiration or more frequently of presumed aspiration in a predisposed host. It is likely that many cases never come to microbiological diagnosis as most anaerobes are susceptible to a variety of antibiotics, including penicillin, and are dealt with by early antimicrobial treatment.

#### **Pathogenesis**

Anaerobic pneumonia occurs as a result of aspiration. The oropharynx is particularly favoured by anaerobes which multiply there commensally, prodigious quantities of them being found in saliva ( $10^8$ /mL in healthy people, increasing 1000-fold in the presence of dental sepsis), where they outnumber aerobic organisms by 10 to 1 [399]. Radioactive tracer techniques have been used to show that small amounts of saliva are aspirated into the lungs during sleep in 45% of healthy people and in 75% of patients whose level of consciousness is depressed for various reasons [689].

A predisposing factor can be found in the majority of patients in whom anaerobic infection is identified. These factors include conditions in which the cough reflex is lost or depressed, such as alcohol, hypnotic or other sedative drug overdosage, neurological disease including strokes, epilepsy and bulbar palsy, general anaesthesia and other causes of depressed conscious level such as diabetic coma [690]. Any of these situations may cause some of the stomach contents to be aspirated, the low pH of which can cause a chemical pneumonitis that may well predispose to bacterial infection [691]. Conditions that

result in oesophageal obstruction (Fig. 13.15) as well as gingival and chronic sinus infections also predispose.

The organisms found to be responsible for anaerobic lung infections occur in the same relative proportions to those found in the mouth, this tending to corroborate the supposition that aspiration is the source of the infection [689]. The main groups of anaerobes include the following.

- 1 Gram-negative bacilli making up the genus *Bacteroides*, notably *Bacteroides fragilis*. To add to the clinician's difficulties, the taxonomists have consigned some strains of what used to be called *Bacteroides melaninogenicus* to two newer genera, *Prevotella* and *Porphyromonas*.
- 2 Gram-positive cocci, mainly *Peptostreptococcus* and anaerobic or microaerophilic streptococci.
- 3 Long thin Gram-negative rods comprising *Fusobacterium* spp., particularly *F. nucleatum* and *F. necrophorum*.

The likelihood of pneumonia developing following aspiration is probably influenced by the quantity, bacterial content and pH of the material aspirated, and the quality of the patient's lung defences. The latter includes both mechanical clearance and cellular and humoral competence, patients taking corticosteroids or immunosuppressives being more vulnerable. Finally the presence of coexisting lung disease and the speed with which infection is recognized and treated appropriately are clearly relevant.

A pH of less than 2.4 has been shown to produce lung injury in animal models, and in cases of massive aspiration chemical lung injury rather than infection may be the main problem, producing diffuse alveolar infiltrates and sometimes leading to ARDS [692].

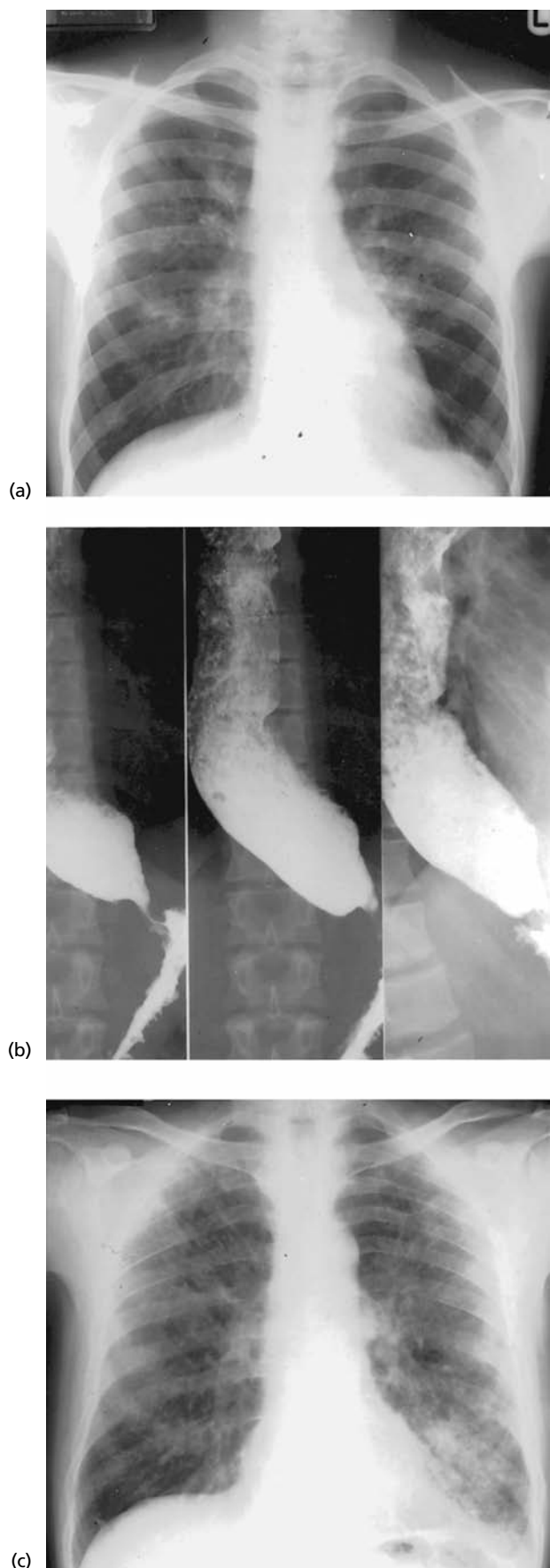
#### **Clinical features**

Cases of aspiration pneumonia acquired in the community are likely to be predominantly anaerobic [693]. Their clinical manifestations may differ from those of other forms of acute pneumonia in that the infection may be rather more insidious and the fever less pronounced, with malaise, weight loss and a cough sometimes productive of foul-smelling sputum.

Nosocomial cases may differ in that the oropharyngeal flora of these patients is likely to have been modified by their hospital stay and by previous broad-spectrum antibiotic treatment, so that in this situation anaerobes are more likely to contribute to a mixed pulmonary infection, which may also contain Gram-negative organisms (e.g. *Ps. aeruginosa*, *Acinetobacter*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus* spp., *E. coli*) and *Staph. aureus*, in which case the pneumonia is likely to be necrotizing and more severe. Any case of aspiration pneumonia may become complicated by lung abscess or empyema (see Chapters 14 & 15).

Cases of witnessed aspiration with chemical lung injury due to low pH may develop respiratory distress due to





pulmonary oedema within minutes and require urgent respiratory support.

### Diagnosis

Radiographic features suggestive of aspiration include unilateral or bilateral pneumonic infiltrates or abscess cavities, typically in the apical segments of either or both lower lobes or in the posterior segment of the right upper lobe, these being the segments most susceptible to aspiration by virtue of their dependent position in subjects who are lying supine (see Fig. 15.2) [694]. Abscess cavities may be large with fluid levels (see Figs 15.4, 15.5 & 15.7) or small with multilocular areas of rarefaction indicating so-called necrotizing pneumonia [695]. A complicating pleural effusion or empyema may be present. Massive aspiration of acid stomach contents may produce pulmonary oedema and ARDS and particles of food may sometimes physically obstruct a bronchus causing persistent distal infection.

Anaerobic infection may be suspected when a variety of Gram-positive cocci and Gram-negative rods are seen under the microscope in a purulent sputum sample that produces no growth on aerobic culture. Precise microbiological diagnosis is difficult in the absence of a readily accessible and uncontaminated pool of infection, such as may be provided by the presence of a complicating empyema. Anaerobic sputum culture is worthless as it is bound to be contaminated by oral commensals. Similarly, any specimen that has been obtained by the passage of a conventional suction catheter or bronchoscope through the mouth is certain to have become contaminated by anaerobic oropharyngeal commensals. When anaerobic infection is thought to be a real possibility, these difficulties may be overcome by transtracheal aspiration, a technique that has been much written about but which is seldom used by practising physicians (see Chapter 8) [69,690]. Oropharyngeal contamination can also be avoided by the passage of a protected specimen brush (PSB) through a specially designed catheter which is in turn introduced through the fiberoptic bronchoscope [70]. Finally when infection is localized, the area of interest may be sampled by percutaneous ultra-thin needle aspiration (see p. 362 and Chapter 8) [79]. Close cooperation with the microbiology laboratory is essential before any such specimens are taken so that they can be received promptly, as anaerobes are particularly fastidious and perish within an hour of exposure to air [696].

**Fig. 13.15** (a) Patchy areas of consolidation in right upper and mid zones and behind left hilum. (b) Barium swallow in same patient showing achalasia of the cardia, responsible for recurrent aspiration. (c) Upper lobe fibrosis and bronchiectasis and left lower lobe consolidation in patient with recurrent aspiration over many years from pharyngeal pouch.

Blood cultures, although carried out routinely in pneumonia, are not usually helpful in isolating anaerobic organisms as bacteraemia occurs in only 2% of cases.

Gas-liquid chromatography has been described as a rapid method for the identification of anaerobes in expectorated sputum, producing a result in less than 1 h and being capable of making a distinction between lower respiratory tract infection and contamination by commensals. This technique detects the presence of the volatile fatty acids that account for the characteristically putrid smell associated with specimens in which anaerobes are contained. The report found no false-positive results but the equipment is expensive and not widely available [697].

### Treatment

An accurate microbiological diagnosis in cases of suspected aspiration pneumonia may prove elusive, as mentioned above, so that the choice of antimicrobial is often based on probability. Community-acquired cases are usually caused by anaerobes. Although penicillin is active against the majority of anaerobes, a significant number of strains, including members of the *Bacteroides fragilis* group, are now resistant as a result of  $\beta$ -lactamase production [698]. These may be dealt with by the addition of metronidazole, which should not be used alone as some anaerobic cocci and most microaerophilic streptococci (e.g. *Strep. milleri/intermedius*) are resistant to it. This may lead to a significant number of treatment failures if the drug is used as monotherapy, whereas these organisms are dealt with if penicillin is used in partnership with it [699]. Two prospective randomized trials have compared benzylpenicillin with clindamycin, which is active against *Bacteroides fragilis* and other penicillin-resistant anaerobes as well as having some activity against *Staph. aureus* [700,701]. Both of these studies showed that clindamycin did better than penicillin in terms of lysis of fever and clearing of sputum, with fewer treatment failures and relapses. Although potentially more toxic, clindamycin may be used singly as a substitute for penicillin and is certainly a rational choice in a patient who is allergic to penicillin. Its most serious limiting side-effect is pseudomembranous colitis.

Many other antimicrobial agents are active against anaerobes *in vitro* but have not been subjected to clinical trials in patients with lung abscess, largely because of the relative infrequency of this type of sepsis and because of the meticulous nature of trial-regulating agencies who require microbiological proof of the responsible organisms. These apparently effective antibiotics include most but not all  $\beta$ -lactams and activity is particularly augmented by combination with a  $\beta$ -lactamase inhibitor, as in the case of amoxicillin and clavulanic acid (co-amoxiclav). Similarly, in the USA, ampicillin is available in combination with the  $\beta$ -lactam inhibitor sulbactam.

When aspiration pneumonia is hospital-acquired, Gram-negative aerobic bacilli should also be covered and the possibility of staphylococcal infection, which may also be present following aspiration, should be considered [572]. Antimicrobials with activity against both anaerobes and Gram-negative aerobic organisms include the extended-spectrum (antipseudomonal) penicillins such as the ureidopenicillins piperacillin, azlocillin and mezlocillin (not available in the UK) and the carboxypenicillins ticarcillin and carbenicillin (not available in the UK) and may be appropriate for hospital-acquired cases. Ticarcillin is also available in combination with the  $\beta$ -lactamase inhibitor clavulanic acid.

Imipenem, which is a carbapenem  $\beta$ -lactam, has excellent *in vitro* activity against anaerobes as well as being active against a wide spectrum of Gram-positive and Gram-negative bacteria including *Ps. aeruginosa*.

Of the cephalosporins, cefoxitin (considered second generation but in fact a cephamycin) is the most potent *in vitro* against the *Bacteroides fragilis* group, tending to be relatively resistant to  $\beta$ -lactamases produced by Gram-negative bacilli. Third-generation cephalosporins, for example ceftazidime, and related drugs are less active against anaerobes.

The management of anaerobic lung infections should include measures directed to the removal of the cause wherever this is possible.

Tachypnoea and hypoxia resulting from low pH lung injury due to massive witnessed aspiration require appropriate airway management and respiratory support. This may include endotracheal intubation and mechanical ventilation when complicated by ARDS. Corticosteroids have no role to play in this situation, which may become complicated by bacterial infection. Atelectasis may raise the suspicion of particulate airway obstruction, in which case bronchoscopy is indicated.

## Viral pneumonias

### Influenza virus pneumonia

Although this infection is usually benign it may be complicated by primary viral or more commonly secondary bacterial pneumonia, which may either follow in the wake of influenzal infection or which may occur simultaneously. A minority of cases with clinical evidence of pneumonia show no evidence of bacterial superinfection and a pure viral aetiology is assumed [702]. The frequency with which this occurs is uncertain but it is likely that influenzal pneumonia is the most common of the viral pneumonias. There is evidence to suggest that it occurs more often in patients with underlying heart disease [703]. It was noted that half the women of child-bearing age who died in the 1957 influenza epidemic were pregnant [704], suggesting that this condition increased their susceptibility to compli-

cating pneumonic infection [705]. It is usual for postinfluenzal pneumonia to occur during seasonal epidemics between October and April.

The syndrome of primary influenzal pneumonia, in common with other viral pneumonias, may vary greatly in severity. At one end of the scale the patient may have relatively few pneumonic symptoms and signs and little radiographic shadowing. More severe cases progress from the typical influenzal syndrome, so that in addition to fever and cough the patient becomes increasingly breathless and cyanosed with widespread crackles, usually in the absence of the classical signs of consolidation. The chest radiograph may show diffuse patchy pulmonary infiltrates. The sputum does not yield pathogenic bacteria and antibiotics are ineffectual.

In addition to inflammation and necrosis of the tracheobronchial epithelium, the pathological changes may also show an intra-alveolar haemorrhagic exudate containing many mononuclear cells.

Bacterial pneumonia as a secondary complication of primary influenzal infection may produce an apparent relapse, following a typical influenzal type of illness, in which fever recurs and mucopurulent sputum may be expectorated. The general principles of supportive treatment of any pneumonia apply and as the organisms involved are usually *Strep. pneumoniae*, *Staph. aureus* or *H. influenzae* [706,707] initial antibiotic treatment during influenza epidemics should be tailored to cover infection by these three bacterial pathogens.

Other aspects of influenzal infection are discussed in Chapters 9 and 12.

### Measles virus pneumonia

Measles is caused by a paramyxovirus belonging to the genus *Morbillivirus*. The measles virus produces a very highly contagious infection that in unvaccinated populations typically afflicts young children. Countries with active vaccination programmes have virtually eradicated the disease but outbreaks increasingly occur in older adolescents or adults who were not vaccinated in childhood and who escaped contact until later life [708]. The disease is spread worldwide and may occur at any time of the year, although most episodes are diagnosed in the winter or spring.

The virus is spread by respiratory droplets. The incubation period is about 10 days, after which a febrile illness occurs with conjunctivitis, rhinitis and cough. Koplik's spots may appear as small white punctate lesions on the buccal mucosa opposite the molars and precede the widespread maculopapular rash by a day or two. Immunocompromised patients sometimes show no rash.

The virus can invade the whole of the respiratory mucosa and may be complicated by pneumonia. This may be primary viral pneumonia or secondary to bacterial

infection, the most common organisms being *Strep. pneumoniae*, *Staph. aureus*, *H. influenzae* and *Neisseria meningitidis* [709–711]. It is difficult to determine the true prevalence of primary measles pneumonia as respiratory symptoms are universal in measles. The reported rate of measles pneumonia in military recruits has varied widely, falling between 3 and 50% depending on the diagnostic criteria used [711]. The severity of measles pneumonia may range from a mild infection to a severe illness, fatalities occurring particularly in young malnourished children or in those who are immunocompromised. Fatality is rare in immunocompetent adults [712]. The clinical findings do not differ significantly from other viral pneumonias including those due to influenza. There may be rhinitis, a dry cough, tachypnoea and hypoxaemia. The chest radiograph usually shows diffuse infiltrates. Coalescence of these lesions into nodules has been described [713].

The syndrome of atypical measles has been described, mainly in patients who had been previously immunized with killed measles vaccine prior to the advent of live measles preparations. The illness is assumed to result from a hypersensitivity reaction to wild measles virus in subjects who possess only partial immunity. It has occurred mainly in young adults or adolescents. The rash is modified and may include petechiae. It starts peripherally and then moves to the trunk, which is the opposite of what occurs in classical measles. Furthermore, rhinitis, conjunctivitis and Koplik's spots may not be seen. Pneumonia is common and pulmonary radiographic infiltrates, which may be persistent, are described in the majority of cases [713]. There may also be hilar lymphadenopathy [714].

The diagnosis of measles is based on the clinical findings and may be confirmed by a fourfold rise in the titre of measles antibody between acute and convalescent serum samples. Measles antigen can be detected by indirect immunofluorescence and an appropriately equipped laboratory can grow the virus in human kidney or monkey cells.

No specific treatment exists for primary measles pneumonia and management is supportive. Secondary bacterial infection is treated with antibiotics to cover the three most likely causative organisms and may be modified in the light of culture results. Prevention is by live attenuated vaccine but this form of immunization should not be used in pregnancy or given to immunocompromised patients, who may be protected by immunoglobulin if given within 72 h of exposure [714].

### Adenovirus pneumonia

Adenoviruses, so named because of their original isolation from human adenoid tissue, are most noted for their capacity to cause respiratory infection and conjunctivitis.

They are transmitted by droplet spread, the faecal–oral route and fomites. They are responsible for about 10% of all respiratory disease in children [715] and although these infections are usually minor, fatal pneumonia may occur and has been described in epidemic form [716]. The incubation period is between 2 days and 2 weeks. Adenoviruses may cause acute tracheobronchitis in adults and epidemics have been described in military bases [717,718], a few cases having been pneumonic and fatal [719,720]. Such episodes occur more frequently in adults than in the paediatric age group and immunocompromised patients are more susceptible [721]. There over 40 serotypes and several may cause lower respiratory tract disease, types 3, 4, 7b, 14 and 21 being among the most important in this regard, although other serotypes may be responsible in immunocompromised patients [714,722].

There are no particular clinical features to reliably distinguish adenovirus pneumonia from other viral pneumonias. The patient feels unwell with a fever, sore throat and cough and may also have conjunctivitis. Lymphopenia may be present but this finding cannot be relied upon. The chest radiograph may show focal infiltrates or more widespread shadowing and is not diagnostic. The presence of a pleural effusion has been described. The organism may be recovered from pharyngeal swabs and has been found in the lungs at postmortem when tissue culture techniques have been applied [719]. Diagnosis is often based on clinical and epidemiological considerations or is retrospective, usually relying upon CFT to detect a fourfold increase in antibody titres between acute and convalescent serum samples [723].

Live attenuated adenovirus vaccines that may be taken orally have been used with good effect in military personnel but are not generally available [718,724]. Treatment is supportive and serious sequelae are unusual in immunocompetent patients. The apparently successful use of intravenous tribavirin (ribavirin) and pooled normal human immunoglobulin has been reported in a case of severe adenoviral pneumonia affecting an immunosuppressed patient [725].

### Chickenpox pneumonia

Chickenpox or varicella is an almost universal and usually mild infection of early childhood. Pneumonia is rarely seen as a childhood complication but may occur in up to one-third of adult cases [726]. A prospective study of military recruits found radiographic abnormalities in 16% of those who developed varicella but only 2% of these subjects became short of breath [727]. Relatively few adults are susceptible to chickenpox, the majority having acquired immunity as a result of childhood infection. Those who have not may contract the disease, usually from children. It has been suggested that tobacco smokers may be more likely than non-smokers to develop chicken-

pox pneumonia and an association with pregnancy has been noted [728,729].

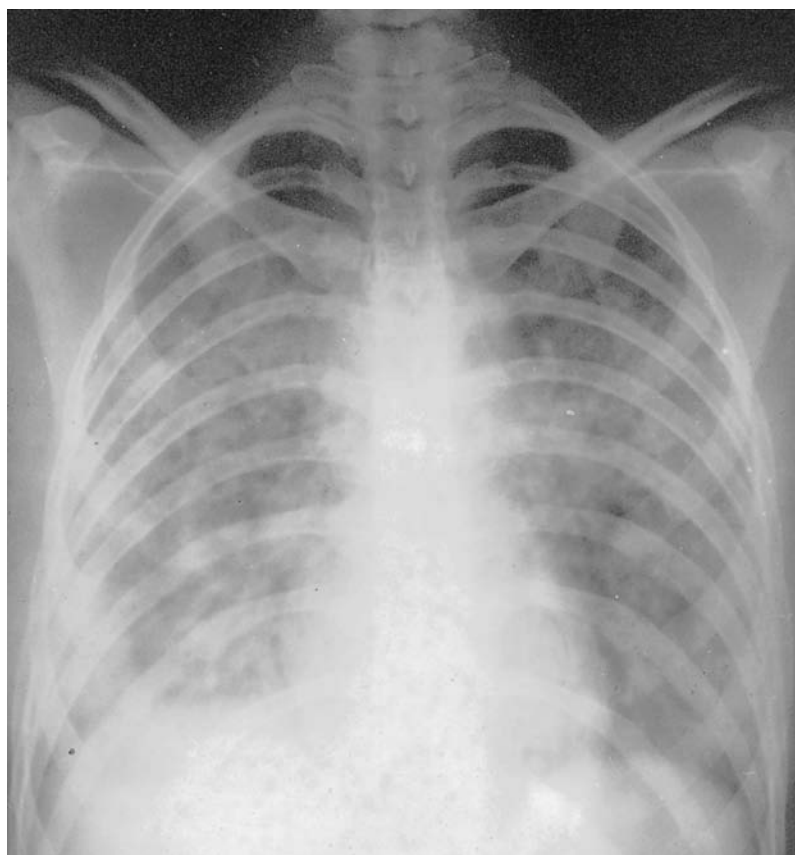
Both herpes zoster and varicella are caused by the same herpes virus known as varicella-zoster virus (VZV), herpes zoster being caused by a reactivation of latent infection. The incubation period for varicella infections is about 2 weeks and patients are infectious for a few days after the appearance of the rash.

Varicella is a febrile illness and is accompanied by an erythematous centrifugal rash with superficial vesicles that crust. Pneumonia may be accompanied by a cough, shortness of breath and sometimes by pleuritic pain. Haemoptysis may occasionally occur. Adults who develop symptomatic chickenpox pneumonia may become severely ill, with tachypnoea and hypoxaemia [730]. Despite the presence of respiratory symptoms, there may be no notable auscultatory findings. Immunocompromised patients are more likely to develop severe disease, with secondary bacterial infection and ARDS [731,732]. Dissemination of the virus to the lungs in patients with herpes zoster (shingles) caused by reactivation of VZV infection is rare.

The diagnosis is based on the finding of a typical rash in a patient with a history of varicella contact. The chest radiograph may show patchy or diffuse bilateral alveolar-type shadowing that may progress rapidly. Hilar lymphadenopathy and pleural effusions occasionally occur. The disease is usually self-limiting, radiographic improvement occurring over the space of a few weeks. It may later result in nodular calcific shadowing scattered throughout both lung fields (Fig. 13.16), this being an occasional incidental finding on a routine chest film that results in a retrospective diagnosis of earlier chickenpox pneumonia [733].

Herpes-like virus particles may be identified in vesicle fluid and respiratory secretions under electron microscopy. A rapid direct immunofluorescent antigen test can be carried out on cell scrapings [714]. The organism can be cultured on cell lines by a virus laboratory but the diagnosis is more usually made clinically, with retrospective confirmation, if required, by the demonstration of a fourfold or greater rise in varicella antibody titre from serum samples or by indirect immunofluorescence, ELISA and neutralizing antibody testing.

Treatment of chickenpox with aciclovir (acyclovir; see Chapter 9) has been shown to shorten the illness in children [734]. There have been no such controlled trials of this agent in varicella pneumonia but case reports imply it is effective [735]. This form of treatment is justifiable because of the significant mortality rates (20–40%) reported from cases ill enough to require hospital admission [730,736]. This drug has also been used in pregnant women with VZV pneumonia [735]. It is conventional to use a higher dose in immunocompromised patients [714,730]. Broad-spectrum prophylactic antimicrobial



(a)



(b)

**Fig. 13.16** (a) Extensive bilateral consolidation in previously well 30-year-old woman with severe varicella pneumonia. The patient recovered with oxygen and supportive therapy. (b) Bilateral small rounded calcified lesions of healed varicella pneumonia.

treatment may be used in this group of patients to cover both Gram-positive and Gram-negative organisms because of the higher risk of superadded bacterial pneumonia. Chickenpox is highly contagious and primary herpes zoster infection may also be acquired from patients with shingles by direct contact, a risk that largely applies to susceptible staff [737]. The patient should be isolated to protect immunocompromised subjects from exposure where possible. VZV immunoglobulin has been used as passive prophylactic immunization and may be effective if given to susceptible patients within 4 days of exposure, but is thought to be ineffective once the disease is established [714]. Trials of varicella vaccine are being carried out but its efficacy in immunosuppressed adults has not yet been demonstrated [738].

### Cytomegalovirus pneumonia

Cytomegalovirus (CMV) belongs to the herpes virus group as do herpes simplex, VZV and Epstein–Barr virus. Latent infection and reactivation may occur, as is the case with other members of the herpes virus group. Serological evidence of previous CMV infection is very common in communities as a whole, ranging between 40 and 100%, the higher prevalence figures tending to be found in developing countries [739]. Transmission appears to be by contact with body fluids and may occur in the perinatal period as well as by sexual contact, blood transfusion and organ transplantation.

Infection by this virus is usually inapparent and associated disease in immunocompetent subjects is rare. It may cause a syndrome of heterophile negative mononucleosis (Paul–Bunnell negative glandular fever) [740], in which the patient may become febrile with malaise and palpable lymphadenopathy. Atypical lymphocytes may also be found in the blood film and there may be mild abnormalities of liver function. Reports of CMV pneumonia in otherwise healthy adults are rare [741]. Such infection is usually mild and self-limiting and is characterized by the finding of diffuse pulmonary infiltrates on the chest radiograph.

In contrast to this, CMV is important as a respiratory pathogen in adult practice mainly as the commonest viral cause of pneumonia in immunocompromised patients and as such is discussed in Chapter 52. It is of particular importance in the recipients of organ transplants and in those with AIDS [742,743]. The likelihood of CMV pneumonia in organ transplantation is related to the degree of immunosuppression, with a higher incidence having been reported in older regimens that relied on bigger doses of corticosteroids [744]. Seronegative recipients receiving organs from seropositive donors are at greater risk, so that transplant units may take steps to avoid this situation arising [745]. The role of CMV in cases of pneumonia in immunosuppressed patients is not always clear as it has been recovered from the lungs of patients with no overt

evidence of pulmonary disease and at other times may be one of a number of other mixed bacterial and fungal pathogens, including mycobacteria and *Pneumocystis carinii*. At other times it may itself be responsible for a fulminating pneumonia [714].

Serology is unhelpful in diagnosing CMV pneumonia, which relies upon the histological demonstration of typical intranuclear inclusion bodies in BAL fluid and transbronchial biopsy specimens in a patient with a consistent clinical picture [474].

The risk of CMV pneumonia can be reduced if the use of CMV-positive blood products is avoided in seronegative immunosuppressed patients. Treatment is with either intravenous ganciclovir or foscarnet (see Chapter 9). The former may cause myelosuppression, especially if given with aciclovir, and the latter renal toxicity. Valacyclovir, an oral prodrug of acyclovir, has been shown to provide effective prophylaxis against CMV infection in groups of immuno-suppressed patients [745].

### Miscellaneous viral pneumonias

There are occasional reports of adult pneumonia occurring in association with other respiratory viral infection, including those caused by coronaviruses [746], Coxsackieviruses [747], parainfluenza viruses [748], rhinoviruses [749] and RSV [750]. RSV is a common cause of lower respiratory infection in infants and is the commonest cause of pneumonia in children under 3 years of age [751]. It may cause a benign upper respiratory tract infection in young adults, occurring in the winter months, and in old age may cause an influenza-like illness or bronchitis that has been associated with pneumonia [752]. RSV can be treated with ribavirin in children but there are no data showing that this is effective in adults. There have also been reports of pneumonia caused by Epstein–Barr virus in patients with infectious mononucleosis [753]. Herpes simplex virus rarely causes pneumonia in previously healthy subjects but may do so in immunocompromised hosts [754,755].

### Hantavirus pulmonary syndrome

In 1993, a previously unidentified North American hantavirus was identified as the infective agent responsible for an initially small outbreak of severe and often fatal respiratory illness, mainly affecting previously healthy young adults many of whom were ethnic Navajos living in a remote rural area of the south-western USA known as the Four Corners [756,757]. The illness was characterized by a short prodromal phase of headache, malaise, myalgia, nausea and abdominal discomfort, during which thrombocytopenia was sometimes found. This was followed by the rapid onset of ARDS and circulatory collapse. The virus, which was later named hantavirus Sin Nombre (SN), belongs to a genus distributed globally, each

species being carried by a different rodent, the reservoir for SN being the North American deer mouse and the virus transmitted to humans by the inhalation of dried deer mouse excreta. Elsewhere in the world, such as Europe and the Far East, other hantavirus species may cause forms of 'haemorrhagic fever and renal syndrome' with varying degrees of thrombocytopenia and renal insufficiency but without any pronounced respiratory symptoms. Over 100 cases of hantavirus pulmonary syndrome have been recorded mainly in the southern USA and the mortality rate has been about 50%. The organism was identified by specific antibody reactivities in the serum and by using a reverse transcriptase PCR. Pathological changes include pleural effusions, gross intra-alveolar oedema with scarce neutrophils and scanty hyaline membrane formation, it having been suggested that the virus damages the integrity of the capillary vascular endothelium rather than causing pneumonia in the more usual sense [758]. The disease should be considered in patients with unexplained respiratory failure following a febrile prodrome in the context of possible rodent contact [759]. Some hantavirus infections may respond to treatment with ribavirin [760].

### Rare and unusual bacterial pneumonias

#### *Pasteurella multocida* pneumonia

*Pasteurella multocida* is a small, aerobic, Gram-negative rod that is mainly pathogenic for animals but is an occasional cause of pneumonia in humans. The organism is distributed worldwide, being found in both wild and domestic animals including fowl. It is of economic importance as the cause of epidemic fowl cholera, haemorrhagic septicaemia of cattle and swine plague. Most recorded human infection is thought to have been acquired from domestic pets, *P. multocida* occurring as an oropharyngeal commensal in up to 55% of dogs and 70% of cats [761]. A local infection with regional adenitis may result if these animals bite or scratch humans. This may be complicated by bacteraemia with resultant metastatic sepsis in lung, bone or elsewhere. Pulmonary infection may also arise as the result of droplet spread, leading first to oropharyngeal infection and subsequently to invasion of the lungs [762,763]. *P. multocida* may colonize the lungs of patients with pre-existing lower respiratory tract infection and may cause pneumonia in such patients [764,765]. Suppuration may occur and empyema may arise as a complication (see Chapter 14).

*P. multocida* has no special growth requirements and is readily cultured from blood or sputum. It may be morphologically confused with *Acinetobacter* or other Gram-negative bacilli [766]. The treatment of choice is penicillin, which should be given parenterally as benzylpenicillin at a dose of 600 mg (0.5 megaunits) upwards, according to the severity of the infection, 6-hourly for up to 2 weeks in

bacteraemic cases or for a shorter time if the illness is less serious. The organism is usually also responsive to amoxicillin, cefuroxime and doxycycline. Erythromycin has poor activity against it.

Recovery is the rule but patients with pre-existing lung disease may be pushed into respiratory failure.

#### Group A streptococcal pneumonia

Group A streptococci, of which *Strep. pyogenes* is the most important pathogen, was one of the principal causes of death from pneumonia in the great 1918–19 influenza pandemic. *Strep. pyogenes* now rarely causes pneumonia, but when it does preceding viral upper respiratory tract infections, such as measles or varicella in children and influenza in adults, remain a common but not invariable feature. As with *Staph. aureus*, *Ps. aeruginosa* and *Klebsiella pneumoniae*, *Strep. pyogenes* is a cause of necrotizing pneumonia. The infection is spread by respiratory droplets from the nasopharynx and epidemics have previously been reported in crowded situations [767]. In contrast to this, cases of *Strep. pyogenes* pneumonia nowadays tend to occur sporadically.

The patient may be severely ill, with fever, rigors, prostration, a cough that may be productive of blood-streaked sputum, and pleuritic pain. Although patchy bronchopneumonic changes in the dependent zones of the lung are typical, the infiltrate may be more confluent and involvement of the upper lobes can occur [768]. The process is typically suppurative and may be complicated by pneumatocele formation and pneumothorax. Early pleural involvement is usual and empyemas may develop in about half of all adult cases. An associated rash similar to that seen in scarlet fever has rarely been reported [769].

Group A  $\beta$ -haemolytic streptococci may be isolated from sputum or pleural fluid and from blood in up to 15% of cases. The treatment of choice is high-dose parenteral benzylpenicillin initially. Penicillin-allergic patients may be treated with a first-generation cephalosporin (e.g. cefazolin), provided the reaction was not anaphylactic, or alternatively with vancomycin. A prolonged course of antimicrobial treatment may prove necessary, with adequate drainage of any pleural collection.

#### Meningococcal pneumonia

*Neisseria meningitidis* is a Gram-negative diplococcus much feared as a cause of fulminant bacteraemic illness and meningitis. It may occur sporadically or in epidemic form, tending to prefer younger members of the population and to cause occasional alarming outbreaks in more crowded situations, such as may be found in educational institutions and military barracks. Although not commonly appreciated, it is also a rare cause of respiratory illness, the true incidence of which is not known as the



organism is carried intermittently in the nasopharynx of up to 20% of the healthy population. Its isolation in secretions that have passed through the nasopharynx may not therefore necessarily indicate that it is the pathogen responsible for the episode of respiratory infection under investigation; furthermore it is fastidious in its growth requirements so that selective media and carbon dioxide enrichment need to be used in order to achieve optimum conditions for culture. So far over 12 different serogroups have been identified on the basis of capsular polysaccharide antigens and the majority of infections are caused by four of them.

A prospective population study, centred on Atlanta over a 5-year period, based the diagnosis of sporadic cases of meningococcal infection on positive cultures from normally sterile sites (blood or CSF). It was found that one-third of these cases occurred in patients aged 18 years or over and that just over a half of these adults had bacteraemia without any evidence of rash or meningitis. Sinusitis, purulent bronchitis or pneumonia were thought to be the cause of the bacteraemia in one-third of this group, most of whom were either over 50 years of age or in some way immunocompromised. The incidence of sporadic respiratory meningococcal infection in the presence of bacteraemia was 0.17/100 000 per year [770].

An earlier study of military recruits in which transtracheal aspiration was used to establish the diagnosis of meningococcal pneumonia found that antecedent upper respiratory tract infection was common, as were cough, sore throat, chest pain and rigors [771].

This infection has no particular clinical distinguishing features and the diagnosis of meningococcal pneumonia may be difficult to make unless infection occurs during an epidemic and unless the organism is recovered from the blood of a patient with consistent respiratory findings [772]. Recently PCR has become available for diagnosing meningococcal infection on specimens including blood and can be useful when prior antibiotic administration has suppressed culture.

The organism is likely to respond to intravenous benzylpenicillin, a third-generation cephalosporin such as cefotaxime, or chloramphenicol. It is usual to treat close contacts of patients with serious meningococcal infection with prophylactic rifampicin 600 mg 12-hourly for 2 days, although ciprofloxacin is probably as effective at eradicating carrier status [773]. A case of meningococcal bacteraemia must be notified to the public health authorities.

### **Brucellosis: *Brucella* spp. pneumonia**

Brucellosis is a chronic disease primarily affecting wild and domestic animals, being transmitted to humans by direct contact with infected live animals or their carcasses or by the ingestion of their milk. This zoonosis is caused by small Gram-negative coccobacilli belonging to the genus *Brucella*, which are found in large numbers in the milk and

urine of infected animals as well as in their products of parturition. Six species are recognized of which four are pathogenic to humans, the most common being *Brucella melitensis*, the primary reservoirs of infection for this organism being goats and sheep; the other species are *B. suis* (hares, pigs, reindeer and caribou), *B. abortus* (cattle and bison) and *B. canis* (domestic dogs). Brucellosis is a common infection in Mediterranean countries, also occurring commonly in the Arabian peninsula, Asia and Central and South America. It is uncommon in the USA, with an incidence of 1 per 200 000, most cases being reported in the southern states. It is rare in the UK where it usually occurs either as an import or as a result of laboratory or experimental mishaps, about 20 cases per year being reported [774]. Most human cases result from the ingestion of unpasteurized dairy products, such as fresh goat's milk cheese; however, the disease may also occur in occupations that entail close contact with the animal hosts in question (e.g. in abattoirs), the organism entering through cutaneous abrasions, by contact with the conjunctivae or by the inhalation of infectious aerosols.

Serological evidence of previous infection may be found in asymptomatic subjects. Those who become ill may develop non-specific symptoms, with fever (which may be undulant), sweats, malaise, fatigue and myalgia that come on either acutely or insidiously after an incubation period of between 2 weeks and 2 months. Any organ system may be involved so that the symptoms are protean. There is sometimes palpable lymphadenopathy and occasionally the liver or spleen may be felt.

Although brucellosis does not usually cause significant respiratory disease, the lungs may become involved either by the inhalation of infected aerosols, such as might arise in slaughter-houses, or perhaps more commonly by bacteraemic spread to the lungs as part of a systemic infection [775]. The patient may develop a cough that is dry [776,777]. The chest radiograph may show non-specific patchy pneumonic infiltrates, hilar and paratracheal lymphadenopathy, and miliary shadowing has also been described, so that tuberculosis is considered in the differential diagnosis [777,778]. Pleural effusions and empyemas are both rare but have been well documented [779,780].

The diagnosis depends upon a good travel and occupational history and can only be made with certainty by isolation of the organism. The organism is rarely identified in sputum but may be recovered from pleural fluid, blood or bone marrow aspirates. However, it may take up to 1 month to culture [776,779,781]. *Brucella* antibodies are most commonly detected by using a serum agglutination test, patients with active infection usually showing titres of at least 1/160. ELISAs are available, although cross-reactivity between species occurs. PCR has been applied in brucellosis but is not generally available [782].

Although tetracycline alone may be used to treat uncomplicated brucellosis, relapse rates of 5–40% have

been reported, so that it is usual to treat serious respiratory infection with two drugs. One such combination is doxycycline 100 mg orally twice daily for 6 weeks with streptomycin 1 g i.m. once daily for the first 2 weeks, which results in a relatively low relapse rate of about 6%. An alternative regimen uses doxycycline as above with oral rifampicin 600 mg once daily, both for 6 weeks, giving a relapse rate of about 14% [783,784]. Children may be treated with co-trimoxazole (5 mg/kg trimethoprim) 12-hourly orally for 6 weeks with gentamicin 2.0 mg/kg for the first 2 weeks. The majority of patients become afebrile within 10 days of starting such treatment [777].

#### **Tularaemia: *Francisella tularensis* pneumonia**

*Francisella tularensis* is a small, Gram-negative, aerobic coccobacillus that is responsible for causing tularaemia in humans. Tularaemia is a zoonosis and the main reservoir for human infection is contained among a variety of wild mammals, including rabbits, hares, squirrels, voles and other rodents, and the parasitic ticks and biting flies such as mosquitoes that parasitize them. Domestic cats may become infected and pass the organism to humans [785,786]. The organism is distributed widely in North America, particularly in the south-eastern and north central USA, approximately 200 cases per year being reported. It was first described in 1911 in Tulare County, California, hence the name. It is not endemic in South America, Africa or Australia but occurs in Asia and parts of Europe excluding the UK, although cases may be imported from endemic areas [787,788].

Infection in humans may be by contact with the carcasses of infected animals; by bites or scratches from either the animals themselves or more usually from parasitic arthropods that have fed upon their blood; by ingestion of undercooked infected meat or contaminated water; and by inhalation of infected aerosols such as may sometimes occur in laboratory workers.

The incubation period may vary from 1 day to 3 weeks. Symptomatology is protean, depending upon the route of inoculation, but malaise, fever and varying degrees of prostration are common. Cutaneous entry is commonest and may result in a skin ulcer with local lymphadenopathy (ulceroglandular form) or lymphadenopathy alone. Ocular contact may produce conjunctivitis and lymph gland enlargement, sometimes mistaken for mumps (oculoglandular form). Ingestion may produce pharyngitis, vomiting, diarrhoea and abdominal pains (oropharyngeal or typhoidal forms) [789,790]. A wide variety of rashes may also occur at some stage in one-third of cases. Pneumonia is said to occur in 7–25% of all tularaemic cases, being more common in older patients and those presenting with typhoidal symptoms and with no history of a bite [791,792]. Any of the foregoing modes of infection can produce bacteraemia and pneumonia may occur secondarily to this, primary pneumonic tularaemia being

uncommon and generally occurring following the inhalation of the organisms by microbiology laboratory workers. Patients with pneumonia usually have a dryish cough. Pleuritic pain sometimes occurs.

The pneumonic changes tend to be patchy and widespread rather than lobar and they may contain necrotizing granulomas. These granulomas may also be found on diagnostic closed-needle pleural biopsy specimens and can cause confusion with tuberculosis. Signs of consolidation are often absent and the chest radiographic appearances are as always highly variable, irregular segmental infiltrates being common [793,794]. There may be hilar lymphadenopathy and pleural effusions are sometimes evident [795].

Tularaemia will be missed unless it is considered, as the organism is fastidious and is unlikely to reveal itself when routine culture methods are used. Deliberate attempts to isolate *F. tularensis* may be rewarded by infection among the laboratory staff, and diagnosis therefore relies upon clinical acumen and either a fourfold or greater rise in serological agglutinating or ELISA titres against the organism or a single titre of 1/160 or more with a consistent clinical picture. Titres usually reach a maximum within 4–8 weeks.

The preferred treatment is a 1–2 week course of intramuscular streptomycin 0.5–1.0 g 12-hourly according to the severity of the case. Gentamicin 2–5 mg/kg daily in divided doses for 1–2 weeks is an alternative in a patient with mild to moderate disease [796–798]. Relapses may occur, although recovery is usual given appropriate treatment and it confers a high level of immunity from further episodes. Without such treatment about 15% of patients may die. A partially effective live vaccine has been used in the USA to prevent infection in occupationally exposed people.

#### **Rickettsial pneumonias**

*Rickettsia* are small, obligate, intracellular coccobacilli. *Coxiella burnetii* (the cause of Q fever) was originally known as *Rickettsia burnetii* but now has its own genus and is described earlier in this chapter. The remaining rickettsial organisms are touched on briefly here as the lungs are occasionally involved. They tend to infect small mammals (commonly rodents) and are transmitted by ticks, mites, lice or fleas according to the species. Apart from human louse-borne typhus, humans are an incidental host and not an important reservoir of infection. The infections that these rickettsiae cause are grouped clinically into the spotted fevers and typhus. The principal pathological feature in both of these groups is a vasculitic lesion caused by proliferation of the organisms in the endothelium of small vessels. The spotted fever most frequently seen in North America is Rocky Mountain spotted fever (*R. rickettsii*) and in southern Europe, Mediterranean spotted fever or boutonneuse (*R. conorii*).

The rickettsioses are characterized by fever, headache and a rash that may be petechial. The site of the insect bite is sometimes marked by an eschar or *tache noir* (black spot). A cough is common in Rocky Mountain spotted fever and pneumonic infiltrates have been described in 10–15% of cases [799]. Pleural effusions and pulmonary oedema may occur in severe cases. Pulmonary involvement has also been described in Mediterranean spotted fever, in which ARDS may also occur [800]. Similarly, pulmonary infiltrates may occur in louse-borne (epidemic) typhus (*R. prowazeki*) and in scrub typhus (*R. tsutsugamushi*) [801,802]. It is likely in all these situations that the pulmonary pathology is a consequence of lung vascular injury rather than pneumonic consolidation in the more usual sense.

Spotted fever or typhus should be considered when the illness occurs in an endemic area and in other situations when a travel or recreational history is obtained. Thus Mediterranean holiday traffic may result in imported boutonneuse fever and travel to Thailand and elsewhere in the Far East has resulted in several reports of scrub typhus pneumonia [802]. Isolation of rickettsiae can only be attempted in specialized laboratories, so that confirmation usually relies on serological testing. This is unlikely to be diagnostic before the second week of the illness so that treatment is started on the basis of clinical probability.

Most of the rickettsiae respond to treatment with tetracycline or doxycycline. Chloramphenicol may be used as an alternative in pregnancy. There have been reports of chloramphenicol- and doxycycline-resistant strains of *R. tsutsugamushi* emerging in Thailand [803].

### ***Salmonella* pneumonia**

A bronchitic cough is not uncommon in patients with enteric fever due to infection with *Salmonella typhi* or *S. paratyphi*, which are Gram-negative bacilli belonging to the family Enterobacteriaceae. *Salmonella* pneumonia is rare in adults, although more common in children in the tropics [804,805]. Patients who are ill with *Salmonella* may develop pneumonia as a result of secondary infection with another organism, although occasionally pneumonia occurs as a result of *Salmonella* bacteraemia originating from the gut or possibly the reticuloendothelial system, so that blood cultures in such cases may be positive. *Salmonella* pneumonia in adults may be more likely to occur in patients who have some degree of immunosuppression and pre-existing respiratory disease [806].

Treatment, which is initially intravenous, should be guided by sensitivities and continued for 2 weeks to reduce the chance of relapse. A fluoroquinolone such as ciprofloxacin is likely to be effective (but is better avoided in children and in pregnancy). A third-generation cephalosporin such as ceftriaxone is a suitable alternative. Strains resistant to chloramphenicol have emerged and

ampicillin is probably now about as effective as this agent. *Salmonella* pneumonia may be complicated by suppuration with lung abscess or empyema formation, in which case more prolonged therapy with drainage of any pleural collection is necessary (see Chapters 14 & 15).

### **Leptospiral pneumonia**

Leptospirosis is a zoonosis caused by motile spirochaetes belonging to the genus *Leptospira*, of which there are at least eight species. These may be subdivided into over 200 serotypes (or serovars). *Leptospira icterohaemorrhagiae* is one of the species that can cause leptospirosis in humans. The most important animal reservoir worldwide is rats but many other mammals can pass infection including cats and dogs. Leptospirosis is transmitted when water contaminated by the urine of an infected animal comes into contact with broken skin or a mucosal surface.

Infection may range from subclinical to an anicteric acute febrile illness with aseptic meningitis to a more severe illness with jaundice and a haemorrhagic tendency (Weil's disease), sometimes with renal failure and cardiovascular collapse. Most infections fall into the first category, 5–10% falling into the second. The classical illness is biphasic, with the initial bacteraemic influenza-like phase lasting up to 1 week, followed after a brief respite by the immune-mediated symptoms and signs associated with circulating antibodies that characterize Weil's disease. Pulmonary involvement in leptospiral infection is reportedly common, occurring in 20–70% of cases, but is often mild and overlooked [807]. More severe respiratory problems tend to occur in the icterohaemorrhagic form of disease. Pulmonary symptoms include cough, haemoptysis, dyspnoea and chest pain. In addition to pneumonia, leptospirosis may be complicated by massive pulmonary haemorrhage and ARDS [808,809].

The earliest radiographic abnormality appears to be bilateral small nodular opacities that may progress to produce more confluent infiltrates not confined to a single lobe. Ground-glass opacification may also occur [810]. Some of these appearances may be due to haemorrhage rather than consolidation [811].

An experienced microscopist may detect leptospirae under dark-ground illumination. Although it is possible to isolate leptospirae from blood, urine and CSF, special expertise is required and the organism is slow-growing so that laboratory confirmation of the clinical diagnosis ordinarily relies upon serology. An indirect haemagglutination test may be used for screening. A fourfold rise in the microscopic agglutination titre or a titre of 1/100 or greater is sufficient to confirm the diagnosis. Failure of a patient to seroconvert may occur if the serotype responsible for the infection is not represented in the test solution. Newer ELISAs are available and PCR has also been applied in certain centres.

Although controlled trials are lacking, there is a general view that both penicillin and tetracyclines have a beneficial effect in shortening the duration of illness and reducing the complication rate. It is currently recommended that a mild case should be treated with doxycycline 100 mg 12-hourly or amoxicillin 500 mg 8-hourly for 1 week. More severe illness may be treated initially with intravenous benzylpenicillin 1.2 g or amoxicillin 1 g 6-hourly in divided doses, continuing after clinical response with an oral agent. Third-generation cephalosporins, such as cefotaxime are probably also effective although clinical data are limited [812,813].

### Listerial pneumonia

*Listeria monocytogenes* is a Gram-positive aerobic bacillus that can infect many different types of animal and is a cause of abortions and meningoencephalitis in cattle and sheep. Human infection is mainly a food-borne infection, the organism having been transmitted from animals to humans in a variety of contaminated foodstuffs, including soft cheese, milk and meat paté.

It can cause bacteraemia and meningitis; pregnant women, their fetuses and neonates of such cases are particularly susceptible, as are other groups of immunosuppressed patients, including transplant recipients and patients with haematological malignancies; indeed *L. monocytogenes* should always be considered as one of the leading causes of meningitis in immunocompromised patients. Listeriosis occurs more frequently in patients with AIDS than in the rest of the population but remains uncommon in this group.

Pneumonia is a rare complication of infection by *L. monocytogenes* but occasional cases have been described in apparently immunocompetent patients [814,815]. Pleural effusions may also occur. The diagnosis in respiratory cases is made by culture of the organism from blood or pleural fluid.

*L. monocytogenes* appears to be equally susceptible to benzylpenicillin and ampicillin. Co-trimoxazole has been used successfully in penicillin-allergic cases.

### Melioidosis: *Pseudomonas pseudomallei* pneumonia

Melioidosis is a suppurative disease acquired in humid tropical climates. It may have many clinical manifestations, of which pneumonia is the most common. It sometimes mimics tuberculosis, so that in Western practice it needs to be borne in mind particularly in patients of Asian origin who look to have acid-fast infection of the lungs but in whom mycobacteria cannot be isolated.

*Ps. pseudomallei* is a small Gram-negative, flagellate, aerobic bacillus that grows well on standard culture media. It occurs as a natural saprophyte in soil, stagnant water and on vegetable produce in endemic areas, princi-

pally South-East Asian countries such as Vietnam, Thailand, Burma, Indonesia and Malaysia [816]. It may also occur in the tropical Northern Territory of Australia and sporadic cases have been reported in West Africa, the Near East and rarely in South America. The disease may occur in Europe and North America in subjects who have travelled from or lived in endemic areas.

Both humans and animals may become infected but rarely infect each other. It is thought that the organism gains entry when broken skin comes into contact with contaminated soil or when the organism is inhaled or ingested. Clinically apparent human melioidosis is rare, whereas evidence of subclinical infection is relatively common [817]. Serological studies in asymptomatic exposed populations have found evidence of subclinical infection in up to 9% of US military personnel serving in Vietnam [818] and in 2% of British and Australian troops engaged in the Malayan campaign [819]. Such serological evidence of infection was more common in cases of trauma, presumably as a result of wound contamination [820] and is also more common in the indigenous populations of endemic areas [821], presumably as a consequence of prolonged exposure. The impression that clinically apparent infection is rare is supported by the observation that of approximately 2.5 million US personnel serving at different times throughout the period of the Vietnam conflict only 343 cases with 36 deaths from melioidosis were recorded [820]. Intercurrent illness such as diabetes mellitus and alcoholism may predispose to clinical melioidosis [822].

### Clinical features

Clinical disease may develop within days of exposure or infection or may remain latent for many years before becoming active, a feature that may produce diagnostic difficulty for physicians living in countries in which the disease is not endemic [823,824]. The symptoms and signs are variable, being governed by the extent of the pathological process, which is essentially one of abscess formation in which suppuration produces a central area of caseation surrounded by a granulomatous margin. This process may be relatively localized to the site of cutaneous inoculation, which may be revealed by localized lymphangitis and lymphadenitis, or it may become widely disseminated in bacteraemic cases so that any organ may be involved by abscess formation and sometimes extrapulmonary suppuration may become very chronic. The lung is the organ most commonly involved.

Pneumonia may be primary, occurring as a result of inhalation, or less commonly may be secondary to bacteraemia [825]. The clinical spectrum of infection in the first case may vary from symptoms suggestive of bronchitis to suppurating pneumonia. Fever, cough, haemoptysis, pleuritic pain and weight loss may all occur. Signs of

consolidation are an inconstant finding. The chest radiograph may show a nodular or patchy upper lobe infiltrate, the areas of shadowing tending to coalesce and cavitate so that the appearances may be indistinguishable from tuberculosis; in more chronic cases the clinical picture may be entirely consistent with this disease [826].

Patients in whom pneumonia has occurred as a result of bacteraemia are much more acutely ill, often becoming prostrated and confused and frequently showing evidence of widespread disease, such as cutaneous pustules, diarrhoea, arthritis, meningitis, etc. Pneumonia that has occurred secondarily to bacteraemia may differ radiographically, with either more diffuse mottling or with larger multiple rounded opacities [826]. Pleural effusions and empyemas may occur in chronic melioidosis but are more common in the acute bacteraemic form.

### Diagnosis

A high level of clinical awareness is necessary. The diagnosis of melioidosis should be considered in any febrile illness that occurs in an endemic area and displays the foregoing clinical features, or if the patient gives a history of travel to South-East Asia or other endemic areas. Such travel need not have been recent and may have taken place many years previously. Affected patients may have an illness clinically consistent with tuberculosis but in which *Mycobacterium tuberculosis* cannot be isolated.

*Ps. pseudomallei* may be readily cultured on most media from the sputum of pneumonic cases, from pus where this is available and from blood in bacteraemic cases, although the laboratory may need to be forewarned of the possibility of melioidosis in order to avoid the misidentification and dismissal of an unfamiliar organism as a contaminant [827]. The persistent culture of a gentamicin-resistant *Pseudomonas* species may also arouse suspicion. Serological evidence of present or past infection may be provided by an antibody titre of 1/8 or greater on CFT or 1/40 on indirect haemagglutinin testing. A fourfold rise in titre provides confirmatory evidence but single high titres may persist for a long time and cannot therefore be used to distinguish between tuberculosis and chronic melioidosis [828].

### Treatment

The choice of treatment is governed by the nature and severity of infection. Asymptomatic subjects with positive serology require no treatment. Those with clinical illness require prolonged treatment with antibiotics, the choice of which should be guided by laboratory sensitivities. *Ps. pseudomallei* is usually sensitive to co-trimoxazole (trimethoprim-sulfamethoxazole), third-generation cephalosporins (e.g. ceftazidime), tetracycline and chloramphenicol. Although a Gram-negative rod, *Ps. pseudomallei*

is resistant to most aminoglycosides. Resistance to macrolides, fluoroquinolones and penicillins is also common, although the organism is usually sensitive to penicillin-clavulanate combinations such as co-amoxiclav (amoxicillin-clavulanate) and ticarcillin-clavulanate. Susceptibility may vary from country to country, so that 20% of strains from Thailand are resistant to co-trimoxazole [829]. Where a choice exists, bactericidal antibiotics should be used preferentially and in severe illness a combination of two antibiotics for the first 4 weeks of treatment is conventional. Such a combination might initially include ceftazidime (120 mg/kg daily) and co-trimoxazole (8 mg/kg daily trimethoprim), continuing with co-trimoxazole or co-amoxiclav alone as maintenance therapy for a further 3–4 months in order to prevent relapse [830,831]. In the case of persisting extrapulmonary suppuration, maintenance treatment may need to be continued for up to a year.

Without antibiotic treatment, nearly all cases who develop clinical illness die and mortality remains high at 30–50% in septicaemic cases despite treatment with appropriate antibiotics [822,832].

### Glanders: *Pseudomonas mallei* pneumonia

Pneumonia due to *Ps. mallei* occurs as a generalized infection known as glanders. This illness, now rare and largely of historical interest, is primarily an equine infection occasionally transmitted to humans. It has been eradicated in the West by a policy of slaughtering affected animals but may still occur sporadically in developing countries. Glanders is caused by a non-motile, aerobic, Gram-negative organism and is acquired either by close contact with horses, mules or donkeys or in the laboratory [833]. Infection may occur via a cutaneous abrasion, conjunctival contact, inhalation or ingestion.

After an incubation period of a few days, the patient may develop either an acute and prostrating febrile illness or a more indolent and chronic infection. Where there has been a cutaneous entry point, local lymphangitis and lymphadenitis may occur and the latter may ulcerate. Inhalation may result in nasal discharge and ulceration and suppurative pneumonia with the formation of lung abscesses. Empyema may follow. Pneumonia may also occur as a result of bacteraemia, which in turn may be associated with widespread metastatic abscesses in muscle, subcutaneous tissues and elsewhere. This suppurative process may become chronic.

The diagnosis is made by culture of sputum, blood or pus and the organism grows readily on ordinary media. A fourfold rise in complement-fixing antibody may occur over the space of 2–4 weeks. Sulfadiazine (sulphadiazine) has been used successfully in laboratory-acquired infections [833], an appropriate dose being 100 mg/kg daily for at least 3 weeks. Because of the paucity of cases, experi-

ence with modern antibiotics is lacking but treatment as for melioidosis would be a reasonable approach whilst awaiting laboratory sensitivities.

### **Bubonic and pneumonic plague: *Yersinia pestis* pneumonia**

*Yersinia pestis* is a Gram-negative bacillus that primarily produces disease in many wild rodent species (sylvatic plague), these animals constituting the natural reservoir of infection. Humans may become involved incidentally, as may dogs and cats, if bitten by a flea that has fed on a bacteraemic animal host. The incubation period is 1–7 days so that cases may travel to areas where the disease is not expected. Sporadic human cases and small epidemics are recorded in the Northern Hemisphere in the desert states of the south-western USA and on the Pacific seaboard [834]. Infection has also been recorded in parts of Africa, South America and the Far East. Great epidemics have occurred historically, such as the Black Death in Europe from the fourteenth century onwards.

#### **Clinical features**

Bubonic plague comprises fever, malaise, myalgia, prostration and painful lymphadenitis in the regional nodes drained by the flea bite. These nodes may suppurate and become painfully enlarged, forming a bubo that may be aspirated to reveal the organisms. About 10–15% of cases develop a more severe prostrating bacteraemic illness in which secondary pneumonia may be a feature [835,836]. This septicaemic plague may cause fulminant Gram-negative shock in the absence of other localizing signs. Meningitis may occur.

Primary *Y. pestis* pneumonia or pneumonic plague is caused by inhalation of the pathogen and is exceptionally rare in the Western world, most recorded cases having occurred in laboratory personnel who have handled either culture material or experimentally infected animals [837]. Veterinarians may contract the disease from cats, as did a 31-year-old man who died of pneumonic plague in Arizona in 1992 in a part of the state where chipmunks were suffering from plague [838]. Such sporadic occurrences are still occasionally put into perspective by major outbreaks of bubonic and pneumonic plague such as happened in the Indian states of Maharashtra and Gujarat in 1994 where there were over 4000 suspected or confirmed cases of plague, many of the pneumonic cases occurring in young men living in two deprived areas of Surat [839,840]. Infection in such cases may be transmitted from person to person. The signs of consolidation may at first seem slight in relation to the severity of the illness but the chest radiograph shows changes consistent with a rapidly progressive pneumonia, which may lead to overwhelming sepsis and death.

#### **Diagnosis**

Diagnosis requires an awareness of the possibility of the illness in endemic areas and should be suspected when rod-shaped, Gram-negative organisms are found in lymph node aspirates or sputum under appropriate clinical circumstances. *Y. pestis* may be demonstrated rapidly by fluorescent antibody staining. The organism grows within 48 h on simple blood media and may be cultured from aspirates of buboes, from blood or from sputum. Laboratory culture is not without risk to personnel because specimens are infectious and it should only be carried out if appropriate facilities are available to protect staff.

#### **Treatment**

Treatment is with intramuscular streptomycin 30 mg/kg daily in two divided doses for 5 days, followed by tetracycline 2–4 g daily in four divided doses to complete a 10-day course [841–843]. Gentamicin may also be used and the organism is also sensitive to chloramphenicol, which can be given intravenously in seriously ill patients, including those with meningitis. Patients should be isolated, vectors eradicated where possible and contacts advised to take prophylactic tetracycline 500 mg 6-hourly for 1 week, children aged 8 years and younger receiving streptomycin [841].

Without treatment about half of those patients with bubonic plague die and virtually all of those with pneumonic plague succumb within a few days. However, most of those who receive appropriate and prompt antibiotic treatment recover [844].

### **Anthrax: *Bacillus anthracis* pneumonia**

Anthrax is a disease mainly of herbivorous animals caused by a large, Gram-positive, spore-forming rod. The main reservoir of infection is in the soil of endemic areas such as Turkey, Iran, Sudan and Pakistan. The spores are highly resistant and may survive in such conditions for 20 years or more. When *B. anthracis* spores are ingested by a grazing animal, they cause a fatal illness so that further spores are released into the soil from the carcass, thereby allowing completion of the life cycle.

Humans are infected incidentally. This may occur in endemic areas in an agricultural setting as a result of the handling of infected animals or their carcasses. In non-endemic areas, infection may result from industrial exposure to spores that contaminate imported goat hair, wool, hides, skins or even bones used in the manufacture of bonemeal, fertilizer or glue. Suspicion surrounds a large outbreak in the former USSR, allegations having been made (and denied) that these cases resulted from an accident at a germ warfare facility that resulted in the

liberation of spores into the air in the region of Sverdlovsk in 1979, causing 42 documented cases of the inhalational form of the disease [845,846].

### **Pathology**

The underlying pathological process is not a true primary pneumonia, for once the inhaled spores reach the alveoli they are ingested by macrophages and carried to the hilar and mediastinal lymph nodes where, following a variable incubation period, they release toxins to cause a haemorrhagic mediastinitis with septic shock. Secondary dissemination and infection from this site to the lungs then results in a severe haemorrhagic pneumonia. Meningitis may also occur.

### **Clinical features**

The two principal forms of anthrax are cutaneous (95%) and inhalational (5%). Intestinal forms (due to ingestion) may occur but are not seen in developed countries. Whereas the cutaneous form produces a systemic illness associated with a painless anthrax sore (the so-called malignant pustule), inhalational anthrax or woolsorter's disease [847] results in a biphasic illness in which a seemingly mild initial fever, malaise and dry cough abruptly give way a few days later to severe dyspnoea with cyanosis.

The chest radiograph usually shows widening of the mediastinum that, in the presence of hypotension, may be mistaken for a ruptured or dissecting aortic aneurysm. In addition to this, pneumonic infiltrates and pleural effusions may also occur [848].

### **Diagnosis**

An accurate clinical diagnosis is unlikely to be reached unless the physician considers the illness in relation to occupational or other exposure to potentially infective materials. *B. anthracis* may be isolated from sputum, blood or pleural fluid, growing well on blood agar plates.

### **Treatment**

Treatment is with large doses of parenteral benzylpenicillin, up to 12 g (20 megaunits) daily, although pneumonic cases usually die within a day or two despite this. This treatment has been shown to prevent disease in exposed Rhesus monkeys, whereas cefuroxime axetil was inactive on *in vitro* testing [849].

## **Other forms of pneumonitis**

This chapter has mostly considered inflammatory lung disease caused by microbial infection. However, inflam-

mation of the lungs may also be caused physically and chemically as a result of the inhalation of a variety of irritant gases and fumes or by the effects of ionizing radiation. The inhalation of irritant gases and fumes usually occurs in an occupational setting and the clinical consequences of such exposures are described in Chapter 54. Individuals may be irradiated as a result of accidents or more often as a result of deliberate interventions by radiotherapists, in which case lung tissue may be selectively involved producing radiation pneumonitis and fibrosis. Chemical pneumonitis sometimes occurs insidiously in a non-occupational setting as a consequence of the aspiration of fatty materials, so-called lipoid pneumonia. These conditions and pulmonary reactions to bronchographic contrast media are described in the sections that follow.

### **Radiation pneumonitis and fibrosis**

Radiation-induced lung damage is most commonly seen after radiotherapy for carcinoma of the breast and also occurs when radiotherapy is directed at lung tumours, the mediastinum and the spine. There are two well-described clinical syndromes, namely radiation pneumonitis and radiation fibrosis [850,851]. Radiation pneumonitis occurs approximately 6–12 weeks and radiation fibrosis about 6–12 months after radiotherapy.

The extent to which both these syndromes develop depends upon a number of factors. These include the volume of lung irradiated and the total dose of irradiation given, including any previous courses. Radiation, formerly measured in rads, is now measured in grays (Gy). A fractionated dose of less than 30 Gy (3000 cGy or 3000 rad) is unlikely to cause clinical damage, whereas doses exceeding 40 Gy produce sequelae that are radiographically apparent [852]. Courses of radical radiotherapy may deliver a total dose of 40–60 Gy, whereas palliative treatment may rely on a single fraction of 6–8 Gy or in certain circumstances several fractions delivering a total of 20–30 Gy. The method of fractionation in radical radiotherapy is evidently important, fewer fractions for the same total dose (i.e. a higher dose rate) tending to cause more damage. The previous or simultaneous use of various cytotoxic drugs, including bleomycin and busulfan (busulphan), may also sensitize the lung to the adverse effects of radiotherapy, making radiation pneumonitis more likely [852,853]. Sometimes the subsequent administration of a cytotoxic drug may produce pneumonitis that may be strikingly limited to the anatomical field encompassed by an earlier course of radiotherapy [854]. This phenomenon may be termed 'recall radiation pneumonitis'.

### **Radiation pneumonitis**

Radiotherapy has a tendency to produce genetic damage



in any normal lung tissue that lies in its path. The sequence of events is incompletely understood but the process probably involves the production of free radicals with subsequent genetic and inflammatory cellular damage [855]. BAL samples obtained following radiotherapy have shown increased lymphocyte counts, especially in those with pneumonitis [856,857]. Radiation pneumonitis involves all components of the lung; in cases where lung subsequently becomes available for pathological study, an inflammatory infiltrate is found in the alveolar walls and interstitium, with the formation of hyaline membranes and an alveolar exudate, along with destruction of type 1 and 2 pneumocytes, endothelial injury and small vessel thrombosis [851]. The reasons that such changes are subacute, usually taking 6–12 weeks before symptoms become manifest, is unclear but has led to speculation that capillary endothelial cells are able to maintain their integrity until chromosomal aberrations prevent further replication, at which point the leakage of proteinaceous fluid across their walls occurs [858]. The development of symptoms at a stage earlier than 6 weeks implies that a more severe episode of pneumonitis will develop. The risk of radiation pneumonitis increases with the dose and the proportion of lung irradiated, so that the radiotherapist is always concerned to limit the field of irradiation.

### *Clinical features*

Symptoms of radiation pneumonitis are estimated to occur in approximately 5–15% of patients who receive radiotherapy to the chest [851]. The clinical features of radiation pneumonitis include the onset of dyspnoea, usually accompanied by a cough that may be dry or productive of pinkish sputum. A fever and associated constitutional symptoms may develop. Chest pain is sometimes present as a result of associated pleurisy or as a consequence of rib fractures that may themselves be caused by radiation necrosis of bone. Auscultatory signs tend to be sparse, a few crackles being sometimes heard over the affected area of lung. A pleural effusion may develop but this is an unusual accompaniment. Rarely, severe dyspnoea of sudden onset may develop, being accompanied by cyanosis and respiratory failure, the clinical picture resembling ARDS [859,860].

The chest radiograph shows poorly defined, hazy, reticulonodular opacification characteristically confined to the field of irradiation, so that the abnormal area of shadowing often has a sharp, straight edge, the pneumonitis being abruptly limited in its extent by the margin of the radiotherapy port. This has been referred to as the 'straight edge effect' and may produce a quite striking appearance on the film. Unsurprisingly, high-resolution CT is more sensitive than plain radiography at detecting changes in radiation pneumonitis [861]. This form of imaging may also be helpful in separating radiation

damage from other differential diagnoses, such as lymphangitis carcinomatosa.

Occasionally a phenomenon known as 'recall pneumonitis' may be observed, in which pneumonitis may occur in association with cytotoxic therapy within the distribution of a previous radiotherapy field as indicated by a straight edge effect; it has been hypothesized that the radiotherapy sensitizes or primes the lung tissue to the toxic effect of the chemotherapeutic agent [862].

### *Treatment*

Mild radiation pneumonitis requires only reassurance and supportive therapy. When symptoms are more severe, 60 mg of prednisolone daily may be given until the pneumonitis begins to remit, after which the dose is reduced, according to response, to approximately 20 mg daily, from which point medication may be tapered off over the space of several weeks. Such treatment is empirical as there have been no controlled trials to assess its efficacy in humans. However, animal studies suggest that benefit may be expected [863]. Furthermore, it has been noticed that the withdrawal of therapy from patients already taking corticosteroids at the time of radiotherapy may coincide with the onset of radiation pneumonitis, which clears once the drug is restarted [851,864]. However, routine prophylactic corticosteroid administration is not justifiable.

Anticoagulants have been used in the past in an attempt to prevent radiation-induced lung damage, the rationale being the limitation of vascular occlusion in affected lung tissue, although no convincing benefit has been shown [865].

The outcome in radiation pneumonitis is usually one of spontaneous improvement within a week in mild cases, others recovering more slowly following treatment with corticosteroids as above. The most severe cases deteriorate progressively and die [865].

### **Radiation fibrosis**

Radiation fibrosis develops 6–12 months or more after attempts at radical radiotherapy as a result of the genetic damage sustained by lung tissue, which ultimately results in scarring with disruption of normal lung architecture. To some extent this may be a continuum of the subacute process described but need not have been preceded by the more acute symptomatic radiation pneumonitis described above.

### *Clinical features*

When radiation fibrosis is extensive enough to cause symptoms, patients usually exhibit varying degrees of dyspnoea. Occasionally this may be disabling, being accompanied by a severe restrictive impairment of lung

function and by respiratory failure that may lead to cor pulmonale [866]. The chest radiograph shows localized fibrotic shadowing in the field of irradiation. Patients in whom serial radiographs have been taken from the stage of radiation pneumonitis sometimes show a gradual evolution of change [867] that may culminate in the usual features of fibrotic loss of lung volume, with distortion of surrounding structures. These features are reflected by the pathological findings of dense fibrosis with collagen formation in those cases that come to postmortem examination [851].

In practical terms it may be difficult to distinguish between radiation-induced lung disease and recurrent neoplastic disease or infection. The presence of changes that extend beyond the radiotherapy field implies another cause and the availability of serial chest radiography or CT sometimes makes the distinction clearer. Unsurprisingly, there is no evidence of any benefit accruing from the use of corticosteroids to treat late radiation fibrosis.

### **Lipoid pneumonia**

Lipoid pneumonia develops as a result of the aspiration of fatty or oily material into the lungs. It is an infrequent cause of morbidity that is likely to evade diagnosis unless considered in cases of apparently unresolving pneumonia.

#### **Causes**

The aspiration of any oil, whether animal (e.g. cod-liver oil), vegetable (e.g. olive oil) or mineral (e.g. paraffin), may result in lipoid pneumonia. Liquid paraffin has been responsible for most cases as a consequence of its relatively common usage for aperient purposes over prolonged periods of time [868]. Other causes have included the habitual use of mineral oil-based nasal drops [869]; the application of liquid paraffin eye drops for xerophthalmia, this topical preparation presumably finding its way to the lungs via the nasolacrimal ducts and nasopharynx [870]; the aspiration of milk feeds or cod-liver oil in children with feeding difficulties [871]; the aspiration of *ghee* (rendered animal fat) following the cultural practice of force-feeding infants with this substance in south-western Saudi Arabia [872]; the aspiration of oil-containing folk remedies [873]; the aspiration of diesel oil by ship-wrecked sailors [874]; the inhalation, in Guyana, of the smoke of 'blackfat' tobacco, to which oil has been added in the production process [875]; the inhalation of fine mists of mineral oil used in industry for coolant or lubricating purposes or of hot oils inhaled by those working in close proximity to burning fat [876,877].

Sometimes the possible cause is overlooked until histology suggests the diagnosis, as in the case of a woman who

habitually applied Vaseline petroleum jelly to her nostrils before retiring to bed [878], or the patient who ingested oil-based cutaneous emollients for laxative purposes [879], or the woman who misused a pressurized spray lubricant (WD-40) to relieve her rheumatism [880]. Even more bizarre cases of lipoid pneumonia sometimes arise, for example due to the inhalation of paraffin-based ignition fluid by a clown in the course of her fire-eating act [881], or the case of a psychologically disturbed patient who accidentally self-administered olive oil intravenously while attempting to inject this substance into his scrotum [882].

#### **Age of the patient**

Lipoid pneumonia is usually encountered in elderly patients as they are the most likely group to have made habitual use of liquid paraffin. However, it may occur at any age and was first described in children with feeding difficulties that resulted in the aspiration of milk or cod-liver oil [871]. A disturbed swallowing mechanism in any patient may act as a predisposing factor but is not a prerequisite, as it has been shown that iodinated oil placed in the nostrils of healthy sleeping subjects can be detected radiographically in their lungs the next morning [883].

#### **Pathology**

Vegetable oil is emulsified and mainly removed by expectoration, causing little damage to the lung. Animal fat is hydrolysed by lung lipases, resulting in the formation of fatty acids that may produce a severe inflammatory reaction, with haemorrhagic bronchopneumonia [474,884]. Mineral oils such as paraffin are not hydrolysed but are emulsified and in part removed by coughing. Some of the residuum is transported to regional lymph nodes, whilst that fraction remaining in the lungs acts as a foreign body, being ingested by macrophages which eventually disintegrate, releasing the oil once again. Examination of lung tissue may show large amounts of foamy vacuolated material in the alveoli, both lying free and as oil droplets within alveolar macrophages [885,886]. This results in alveolitic changes and the persistence of oil in the lungs for a sufficient length of time produces fibrosis, which may at length be complicated by secondary infection. Sometimes a chronic localized granulomatous and fibrotic process may become set up, so-called paraffin granulomas or paraffinomas, which clinicians may mistake for neoplasms [887].

#### **Clinical features**

There may be few symptoms and signs; thus when a liquid paraffin aperient or nose drops are responsible, the patient is unaware of a causal relationship, as mineral oil is so

bland that it may pass the glottis and enter the lungs without even evoking a cough. Symptoms may remain minimal despite the development of radiographic signs, although cough, sputum production, haemoptysis and dyspnoea may occur and crackles may be present over affected areas of lung.

There are no specific radiographic findings but the lower zones are more commonly affected, presumably as a result of the gravitation of oil to these most dependent parts. The right lower lobe is affected more often than the left but opacification is frequently bilateral. The infiltrates may mimic patchy pneumonic consolidation, which sometimes cavitates; at other times reticulonodular appearances are produced [888–890]. More localized irregular mass-like lesions may be paraffinomas, their true nature becoming evident only after resective surgery for supposed lung cancer. CT may demonstrate areas of low attenuation consistent with fat [891].

### Diagnosis and treatment

The diagnosis should be reached by obtaining a history of mineral or other oil usage in patients with chest radiographic appearances consistent with chronic or unresolving pneumonia. Once the diagnosis is considered, the cytological examination of sputum or BAL material may show large macrophages with strongly positive intracytoplasmic staining for lipid, if special stains such as Oil-red O are used [886,892,893]. However, caution should be exercised as less strong lipid-staining reactions may be produced by the endogenous release of lipids when lung tissue breaks down distal to an obstructed airway [893,894]. Characteristic histological and lipid-staining

changes have been demonstrated on transbronchial lung biopsy material [878,890] but sometimes the diagnosis is only made after more invasive surgical procedures, as alluded to above.

Treatment is by removal of the cause. Prednisolone has been used but there are no controlled trials, experience being limited to case reports with variable results [895,896]. There have been occasional reports of the successful use of whole lung lavage [897]. Prevention may be partly achieved by the avoidance of laxatives and nose drops containing mineral oil.

### Pulmonary reactions to bronchographic contrast media

Abnormal pulmonary reactions have been described following the use of radiographic contrast media employed in bronchography. These have occurred up to 5 days after examination when oily propyl iodone (Dionosil) has been used. Clinical features have included fever, productive cough and breathlessness. Crepitations may be heard over both lung fields and the chest radiograph may show bilateral patchy shadowing. An apparent response was obtained in three cases following treatment with 20–60 mg of prednisolone daily [898].

Other oily contrast media such as Lipiodol (40% iodine in poppy seed oil) may cause the formation of granulomatous lesions if normal clearance from the lung is not achieved [888]. These reactions are probably of largely historical interest as the commercial production of bronchographic contrast media has ceased following the adoption of CT as the investigation of choice in cases of suspected bronchiectasis.

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# EMPHYEMA

DOUGLAS SEATON

The word 'empyema' is used to denote the presence of pus in a natural body cavity. In respiratory medicine that space is the pleural cavity and the term is often also used to cover pus in a postpneumectomy space. Some texts still use the Latin term for thoracic empyema, *empyema thoracis*, but are seldom consistent enough to embrace the classical plural form.

The diagnosis can only be confirmed by examination of pleural fluid. If this is frankly purulent, then no doubt remains; if it is not obviously turbid, then diagnostic confirmation requires the microscopic finding of a cell count showing a predominance of neutrophil leucocytes. The finding of organisms on Gram stain or culture is also confirmatory, although these may have been suppressed by antibiotics and are not always detectable. Empyemas are sometimes described as acute or chronic but the division between the two is indistinct and arbitrary, the latter term usually being reserved for those cases that have passed through the early exudative stage to reach a stage of organization in which a pleural rind has formed (see below).

Early descriptions of empyema and its treatment by surgical drainage have been attributed to Hippocrates [1]. By the nineteenth century, pleural aspiration, underwater seal drainage and rib resection were all practised, but despite these best available forms of treatment the condition was frequently fatal [2]. So it was with Sir William Osler in 1919 [3]. Others fortunate enough to recover, including notables such as King George V, often had to endure a protracted illness [4]. Nowadays with the availability of antibiotics, the more affluent parts of the world enjoy relative freedom from suppurative lung disease so that the finding of an empyema may come as something of a surprise. This is not the case in most parts of the globe where thoracic empyema continues to present a considerable problem.

## Pathology

Once infected by pathogenic organisms, the connective

tissue layers within the pleural membranes become oedematous and produce an exudation of proteinaceous fluid that starts to fill the pleural cavity. The deepest layers of the pleural membrane are relatively impervious so that infection tends to be contained within the pleural cavity itself and spread beyond it is unusual. At this early *exudative* stage the pleural fluid is thin with a relatively low white cell count and the visceral pleura and underlying lung remain mobile [5]. If the infection proceeds unchecked by antimicrobial agents, the inflammatory process continues so that newly formed layers of fibrin become laid down on the epithelial surface within the pleural cavity, particularly on the parietal pleura. The empyema fluid now becomes thicker and more turbid, containing a higher white cell count. With the deposition of fibrin on both pleural surfaces, lung movement in this later *fibrinopurulent* stage may become increasingly restricted [5]. Depending upon the nature of the infecting organism and whether or not antibiotics and drainage procedures have been employed, these thickened fibrinous layers organize as collagen and become vascularized by an ingrowth of capillaries. This *organizational* stage may begin within 2 weeks [6] but usually takes 4–6 weeks to develop to a point at which the empyema cavity becomes surrounded by a cortex, 'peel' or 'rind' that may be more than 2cm thick [7]. By this time the empyema contains frank pus, which may be viscid. The inner layers of the thickened empyema cortex continue to show a considerable inflammatory cell infiltrate and the fibrous outermost layers exert an increasingly restrictive effect, both compressing the underlying lung (the so-called 'trapped lung' effect) and also tending to draw the overlying ribs together, ultimately producing a chest deformity with a dorsal scoliosis that is concave towards the affected side.

An empyema may become localized to one part of the pleural cavity or it may involve the whole of it. Such large empyemas may become loculated into smaller collections by the development of septate fibrinous bands, making the work of percutaneous aspiration difficult or impossi-

ble. Ultimately an inadequately treated empyema cavity may become obliterated and its rind may calcify, producing a so-called fibrothorax, particularly in the case of old tuberculous pleural infection (Fig. 14.1).

## Pathogenesis

### Introduction of infection

Empyemas may be of traumatic or non-traumatic origin (Fig. 14.2). Non-traumatic cases are more commonly encountered in peaceful society and usually arise as the result of direct extension from an adjacent site, lung infection being the most common cause, accounting for over half the cases [8,9]. Aspiration pneumonia forms an important subgroup and a significant number of these patients are alcoholics [10]. Obstruction of a bronchus as a result of lung cancer or an inhaled foreign body occasionally underlies the pneumonic process. Suppurative lung disease, such as bronchiectasis (see Chapter 28) or lung abscess (see Chapter 15), are less commonly associated than pneumonia. Patients with rheumatoid disease are peculiarly susceptible [11]. Surgical trauma ranks as the second most frequent cause after pulmonary infection, this group including instrumentation and rupture of the oesophagus, leakage of an oesophageal anastomosis after resection and the development of a bronchopleural fistula following pneumonectomy. Organisms may also be introduced by pleural aspiration of any effusion or by tube drainage of a malignant effusion. Infection is the commonest present-day complication of that dwindling group of

patients who were treated for pulmonary tuberculosis by surgical plombage in the era before antibiotics [12]. Less common sources of infection include abdominal sepsis, which may first localize to form a subphrenic abscess before extending to the pleural cavity by lymphatic drainage [10]. Liver abscesses, including those caused by *Entamoeba histolytica*, may also be implicated (see Chapter 22) and sepsis in the pharynx, thoracic spine or chest wall may extend to the pleura, either directly or via the tissue planes of the mediastinum [13].

Non-surgical penetrating trauma to the chest may occur as a result of gunshot wounds, blast injuries and stab wounds. From the time of the First World War to the Korean War, such injuries were associated with empyema in about 25% of cases [14]. By the time of the Vietnam conflict the figure had fallen to around 6%, presumably as a result of prompt surgical drainage of haemothorax and the use of antibiotics [15,16]. The chance of such injuries resulting in empyema has been found to be doubled if a haemopneumothorax as opposed to a haemothorax is present [17].

### Microbiology

The pathogenic organisms isolated in cases of empyema vary according to whether (i) antibiotics have been used, (ii) the infection has arisen as a complication of community-acquired or aspiration pneumonia or as a result of some other predisposing factor such as oesophageal surgery, and (iii) the patient is an adult or a child. In general, anaerobes and Enterobacteriaceae are often present in mixed cultures, whereas other organisms



**Fig. 14.1** Right-sided empyema with air–fluid level due to bronchopleural fistula that developed during an aeroplane flight. Note calcified wall medially, raising suspicions of a tuberculous aetiology.

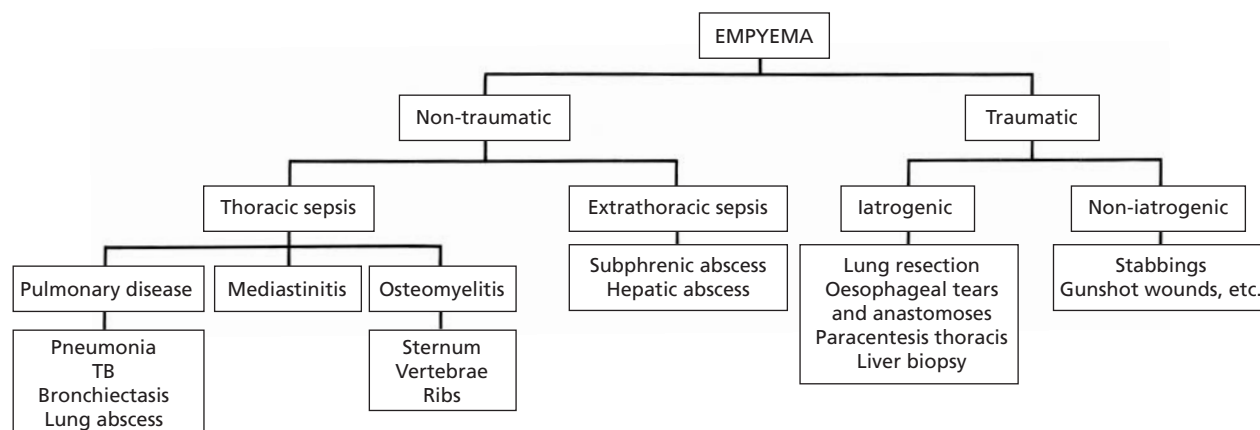


Fig. 14.2 Pathogenesis of thoracic empyema.

such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and organisms of the *Strep. milleri* group (syn. *Strep. intermedius* group) may be recovered as pure isolates [11].

#### Influence of antibiotics

Before antibiotics were available, pneumococci (*Strep. pneumoniae*) and  $\beta$ -haemolytic streptococci (e.g. *Strep. pyogenes*) caused empyemas with much greater frequency than is now the case [18]. Thus in a study of 3000 cases of non-tuberculous empyema, published from data collected before the Second World War, pneumococci were responsible for 64%,  $\beta$ -haemolytic streptococci for 9% and *Staph. aureus* for 7% of the remainder [19]. The decline of empyema as a complication of pneumococcal pneumonia has resulted in an alteration in the frequency with which the major pathogenic bacteria are found in empyema fluid, so that when all aetiologies are considered Gram-negative bacilli such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus* species and *Klebsiella pneumoniae* made up the largest group and accounted for almost 30% of positive isolates in one series [8]. *Staph. aureus* accounted for slightly fewer isolates (25%), whereas the proportions of pneumococci and anaerobic organisms were 15% and 11% respectively. However, the pneumococcus remains a very important pathogen in groups of young previously healthy adults, as evidenced by a report of 197 cases of empyema from two large military hospitals in which *Strep. pneumoniae* accounted for 70 isolates [9]. The author has seen several cases of pneumococcal empyema developing in patients who had been inappropriately treated with the quinolone antimicrobial ciprofloxacin as an oral first-line agent for community-acquired pneumonia. Viridans organisms of the *Strep. milleri* group (now referred to as *Strep. intermedius* group) have also been identified as an

important pathogen in empyema and lung abscess [20–23]. Anaerobic infections (usually bacteroides, peptostreptococci and fusobacteria) are probably more common than is often reported, the frequency with which they are found to some extent reflecting the care, or lack of it, that is taken in looking for them [24,25]. Mixed bacterial infections commonly occur, one detailed microbiological study recording both anaerobic and aerobic organisms in 54% of cases and aerobes in only 38%, whereas anaerobic organisms were the sole isolate in only 8% of cases [20]. It is clear that anaerobic cultures should be carried out routinely whenever pus is obtained from the thoracic cavity, but care should be taken with the specimens and liaison with the microbiologist or infectious disease specialist should be close [25,26]. Despite the fact that the majority of patients have already received an antibiotic by the time empyemas are diagnosed, it is nevertheless usual for organisms to be isolated, the pus being found to be sterile in only one-third of cases [8]. A recent British multicentre study of empyema found that anaerobes and Enterobacteriaceae were often present in mixed culture, whereas pneumococci, staphylococci and *Strep. milleri* organisms were usually pure isolates [11]. In this series, *Strep. milleri* organisms and anaerobes were each identified in about one-third of patients, the pneumococcus in about one-quarter and *Staph. aureus* and Gram-negative aerobes each in about one-sixth [11].

#### Influence of predisposing factors

Empyemas arising in adults as a complication of community-acquired pneumonia are often pneumococcal, whereas those occurring as a consequence of frank aspiration are more likely to contain anaerobes and, as with lung abscess (see Table 15.1), often occur in association with alcoholism, epilepsy or other cause of a depressed conscious level, in which situations there may be palatal weakness or incoordination, particularly if there is coexisting dental or other oropharyngeal sepsis. Aerobic



Gram-negative enteric bacilli are likely to be implicated in the spread of infection to the pleura from below the diaphragm or as a result of oesophageal instrumentation [8]. In addition to aerobic Gram-negative bacilli, there is also a high frequency of *Staph. aureus* infection in empyemas following external trauma and in those that complicate haemothorax [27,28]. This organism may also be found more commonly in pleural fluid cultures of patients with human immunodeficiency virus (HIV) infection compared with immunocompetent patients [29]. Uncommon microbial causes (see below) such as mycobacteria or fungi may be causal in immunosuppressed patients, such as those with organ transplants or AIDS, although an empyema is rarely found in isolation in these patients who often have disseminated infection. Acid-fast bacilli are demonstrated on pleural fluid microscopy in about 15% of AIDS patients with tuberculous pleural effusions compared with about 1% of tuberculous pleural effusions in the non-AIDS population, a finding in keeping with the supposition that such effusions in the immunocompetent population are usually caused by delayed hypersensitivity reactions to the mycobacterium rather than by direct infection of the pleural space by the organism [29].

### Influence of age

*Staph. aureus* is a common infecting organism in childhood empyema, particularly in infancy, accounting for 92% of empyemas in children under the age of 2 years in one early series [30,31]. Gram-negative organisms other than *Haemophilus influenzae* are relatively unusual causes of empyema in childhood, although *Ps. aeruginosa* was second in frequency to *Staph. aureus*, being isolated in 10 of 57 Nigerian children in one series [32]. *H. influenzae* is an important pathogen in children, accounting for 24% of isolates in one retrospective study compared with 30% for *Strep. pneumoniae* and 38% for *Staph. aureus* [31]. Anaerobic and mixed infections are also important in children, aerobes accounting for 67% of infections, anaerobes for 24% and mixed infections for 10% in the report by Brook [33]. Of the aerobes, *Staph. aureus* accounted for 17% of isolates, whereas the proportions for the pneumococcus and *H. influenzae* were 22 and 25% respectively [33].

### Uncommon microbial causes

Empyema may be caused by many groups of organisms other than the more common ones referred to above. Tuberculous empyema, now uncommon in 'developed' countries, should never be forgotten and may be particularly indolent [34,35]; this and other complications of tuberculosis are discussed in Chapter 17. Empyema may be rarely caused by fungi, particularly in immunocompromised hosts. *Aspergillus* species may infect the pleural space and result in empyema formation; before the antibi-

otic era, this sometimes occurred as a late complication of cases of pulmonary tuberculosis where artificial pneumothorax or thoracoplasty had been employed [36]. *Cryptococcus neoformans* has little virulence other than for immunocompromised hosts in whom infection may cause serious pulmonary and more rarely pleural disease [37,38]. *Blastomyces dermatitidis* may cause chest wall as well as pulmonary disease, and infection may arise without predisposing factors [39]. Blastomycosis is not endemic in Europe, but in the USA is found particularly in the river basins of the Ohio, Missouri and Mississippi and to the west of Lake Michigan. Another fungus *Coccidioides immitis* causes coccidioidomycosis. This may produce an acute self-limiting febrile illness known as San Joaquin Valley fever, a chronic cavitary and suppurative pulmonary disease of which empyema is an occasional and well-described complication [40,41]. The disease is endemic in the south-western states of the USA and in parts of Central and South America but is occasionally seen in Europe as a result of modern forms of travel. Empyema is a rare complication of histoplasmosis [42].

*Actinomyces* is a genus of common anaerobic Gram-positive filamentous bacteria that live commensally in the mouth and rarely cause chronic, granulomatous, suppurative infection of the lung and pleural space, classically resulting in extensive sinus formation with so-called 'sulphur granule' discharge. Such manifestations of actinomycosis are now rare, as infection is usually contained by treatment with antibiotics [43–46]. *Nocardia* is a related genus of weakly Gram-positive but aerobic filamentous bacteria that was erroneously thought to be mycotic. Resultant pulmonary nocardiosis may produce similar suppurative pleural and chest wall involvement to that seen in actinomycosis but such infection is rare in immunocompetent hosts [47,48].

Clostridia are anaerobic organisms found as normal faecal flora and may colonize the skin by contamination. They rarely cause pleuropulmonary infection in the absence of some form of penetrating chest wall trauma, which is often iatrogenic, but can sometimes also reach the pleura as a result of aspiration of oropharyngeal contents or secondary to bacteraemia [49]. These Gram-positive bacilli (usually *Clostridium perfringens*) have been well described as causative agents of both necrotizing pneumonia and empyema [49–52].

Organisms belonging to the aerobic Gram-positive genus *Bacillus* are infrequent pathogens but may rarely cause necrotizing pneumonia and empyema in patients who are immunosuppressed, in which situation *Bacillus cereus* is most frequently implicated [53–55]. Group A streptococci, of which *Strep. pyogenes* is the most important pathogen, was an important cause of suppurating pneumonia and empyema in the pre-antibiotic era (see Chapter 13) but is now a rare cause of sporadic cases. *Brucella*

*melitensis* may rarely cause empyema, and brucellosis should be considered in patients who have stayed in endemic areas such as the Middle East, the Mediterranean, Latin America and Asia [56]. *Pasteurella multocida*, an aerobic Gram-negative coccobacillus found commonly in the oropharynx of domestic and wild animals, may cause pneumonia and empyema in patients with chronic pulmonary disease [57–59]. *Salmonella enteritidis*, of which there are over 1700 serotypes, may unusually cause pneumonia and rarely results in empyema, sometimes in the absence of gastrointestinal tract symptoms [60–63].

Hydatid disease, caused by cestodes of *Echinococcus* spp., may involve the pleural space, as may paragonimiasis, a disease caused by the lung fluke, *Paragonimus westermani*, a trematode endemic in the Far East and parts of Africa [64–66]. An empyema associated with systemic and pleural fluid eosinophilia is highly suggestive of such infection [67].

Protozoa belonging to the genus *Trichomonas* have been recorded in empyemas but are an exceptionally rare cause of this condition [68,69]. Amoebiasis is the third leading parasitic cause of death in the world. Pleural complications include right-sided sympathetic effusions, although *Entamoeba histolytica* infection may also cause empyema, usually when an amoebic abscess within the right lobe of the liver ruptures and erodes through the diaphragm to involve the pleural cavity directly [70,71].

Lung colonization in cystic fibrosis by the relatively drug-resistant *Burkholderi cepacia* (previously known as *Pseudomonas cepacia*) is well described and this organism may cause pleural infection in such patients when they are immunocompromised following lung transplantation [72–74]. *Listeria monocytogenes* has been described as a rare cause of empyema in an HIV-infected patient [75].

## Clinical manifestations

The clinical manifestations of an empyema vary widely depending on both the nature of the infecting organism and the competence of the patient's immune system. The spectrum ranges from an almost complete absence of symptoms to a severe illness with all the usual manifestations of systemic toxicity. The presenting features may vary according to the way in which the empyema has arisen: following pneumonia (see Chapter 13), surgery or other forms of trauma or as a consequence of mediastinitis (see Chapter 49) or subdiaphragmatic sepsis.

The onset of symptoms may be more indolent in cases of anaerobic infection. The presenting features are often non-specific and may not suggest respiratory disease to the primary care physician, so that the diagnosis may be delayed if a chest radiograph is not requested [11]. Fever is common, although if the empyema cavity is well walled off or the patient elderly this need not be present. General malaise and loss of weight are common features as is pleu-

ritic pain, which may take the form of dull chest wall discomfort. Dyspnoea may result from the compression of underlying lung by the empyema or from primary disease involving the lung itself. A cough is frequent and in the presence of a bronchopleural fistula variable quantities of purulent sputum, which is sometimes foul-smelling, may be expectorated. The volume of sputum may depend on the position that the patient adopts or, in the case of air travel, the pressure of the aeroplane cabin [34].

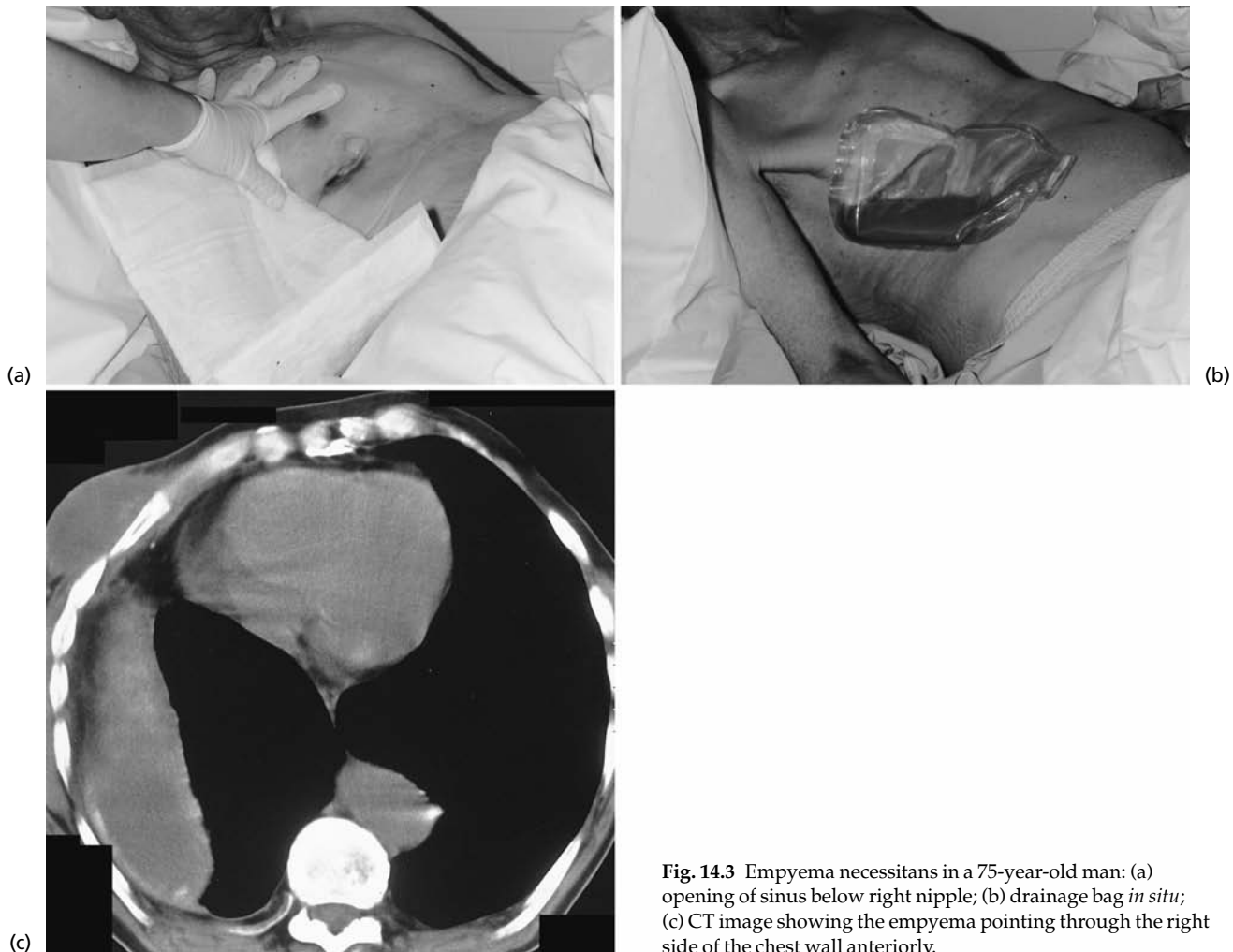
In addition to the signs of any associated disease, the physical signs of an empyema are those of a pleural effusion (see Chapters 6 & 43). Finger clubbing may be an accompaniment of more chronic empyemas. The suppurative process, if undrained and uncontrolled by antibiotics, may extend beyond the pleural cavity, with pointing occurring in an intercostal space often close to the sternum where the chest wall is thinnest. The term 'empyema necessitatis/necessitans' may be used to denote any such lesion that has ruptured through the chest wall to the subcutaneous tissues, ultimately reaching the surface through the skin to form a discharging sinus (Fig. 14.3). Occasionally suppuration may track caudally behind the diaphragm, tending to point and discharge in either the lumbar region or the groin. Such behaviour is unusual in modern practice but may occasionally be seen with tuberculous, actinomycotic and other empyemas [46,73]. The finding of a mouth full of decaying teeth may increase the chance of the responsible organisms being anaerobic.

## Diagnosis

The possibility of a complicating empyema should always be borne in mind in a patient with a lower respiratory tract infection. Although the history and physical findings may be suggestive, the diagnosis can only be made with confidence when suspicious chest radiographic findings lead to thoracentesis. Other findings, such as a mild normochromic normocytic anaemia, neutrophil leucocytosis and hypoalbuminaemia, are commonplace and non-specific but should alert the clinician to the possibility of empyema in a patient with an abnormal chest radiograph.

## Diagnostic imaging

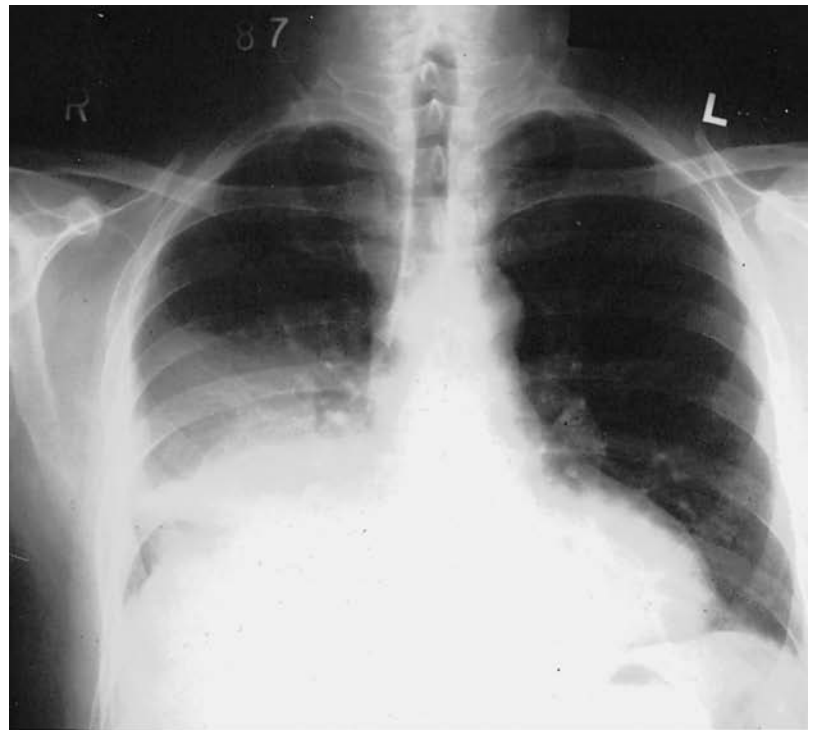
The chest radiographic appearances of empyema may, in the early stages, be identical to those of an uncomplicated pleural effusion. As time passes, fibrosis develops around the empyema cavity so that the fluid is contained in one location, irrespective of the patient's posture. This homogeneous shadowing usually extends upwards from either hemidiaphragm and a useful clue is the common finding of posterolateral loculation, producing a typical appearance on the lateral chest film, with an opacity that is convex anteriorly, sometimes tapering at its upper and lower ends and extending into the thorax from the direc-



**Fig. 14.3** Empyema necessitans in a 75-year-old man: (a) opening of sinus below right nipple; (b) drainage bag *in situ*; (c) CT image showing the empyema pointing through the right side of the chest wall anteriorly.

tion of the spine (Fig. 14.4). This so-called 'D-shaped shadow' may be associated with obliteration of the ipsilateral costophrenic angle on the posteroanterior (PA) view. The appearances on the PA view not uncommonly mislead and the lateral projection helps to reduce doubt. An air–fluid level may be present, indicating an associated pneumothorax, bronchopleural fistula, the presence of gas-forming organisms such as clostridia, or a previous imperfect thoracentesis that has allowed air into the chest (see Fig. 14.1). Interpretation of the radiograph may be complicated by underlying pulmonary shadowing and the differential diagnosis may include delayed resolution of pneumonia, lung abscess, tumours of the lung, mediastinum and pleura, hydatid cyst and partial lung collapse. When unequivocal radiographic evidence of fluid is not present, thoracentesis may be carried out with some uncertainty as to the likely result. This uncertainty may be reduced by the use of diagnostic ultrasound which, provided the empyema abuts the chest wall, is capable of detecting a localized pocket of fluid that shows as an echo-

transmitting (anechoic or echo-free) space bounded by the wall of the cavity [76]. Ultrasonography may also show septa when there is loculation, and a more echogenic image is obtained as organization takes place. Ultrasound is also very useful in targeting an empyema for needle or tube drainage, particularly when access proves difficult, and it is probable that its use reduces delay in diagnosis. CT of the thorax may be similarly helpful, often showing a rind of pleural thickening, frequently with a typical encapsulated biconvex configuration, and sometimes also unexpected collections [77,78] (Figs 14.5 & 14.6). Associated intrathoracic inflammatory lymphadenopathy on CT is a common finding [79]. Radionuclide scanning, in which leucocytes or non-specific IgG are tagged with radioactive indium [ $^{111}\text{In}$ ], has also been used to localize collections of pus in various body cavities, although the utility of this investigation is limited by both the spatial resolution of the gamma camera and the fact that false-positive results may be produced by other unrelated intrapulmonary pathology; thus it appears to have no advantage over



(a)



(b)

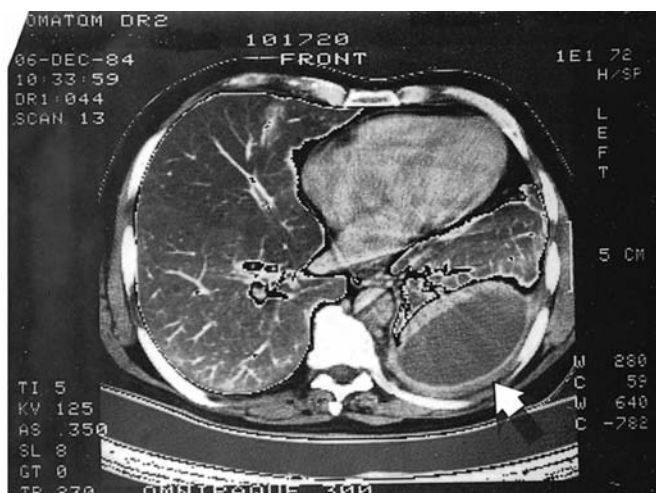
**Fig. 14.4** Posteroanterior (a) and lateral (b) views of large right loculated empyema.

conventional radiography supplemented by ultrasound and/or CT examination [80,81].

### Microbiology

Provided that grossly purulent fluid is obtained at thoracentesis the diagnosis is confirmed. The specimen should

be taken to the laboratory with minimum delay and anaerobic as well as aerobic cultures should be set up as a matter of course. In addition to routine Gram staining, liaison with the laboratory is important so that a specific search for acid-fast bacilli and fungi is made in appropriate cases. Organisms are obtained from empyema fluid in the majority of cases despite prior use of antibiotics; even if they are



**Fig. 14.5** CT image of a left-sided empyema showing the thickened pleural 'rind' (arrow) that surrounds the collection of pus.



**Fig. 14.6** The chest radiograph (a) in this 39-year-old man with an empyema suggested a single laterally placed collection, but the CT image (b), while confirming the main collection, also showed two smaller separate loculations situated anteriorly and posteromedially.

not, the diagnosis of empyema is accepted provided the turbidity is accounted for by cells that are predominantly neutrophil leucocytes [8,11,20,31]. Empyema fluid can be distinguished from pleural fluid that is turbid due to the presence of chyle by the use of centrifugation, in which case a whitish layer of chylomicrons is found on the surface of the pleural fluid [82]. The diagnosis of empyema is also accepted if organisms are obtained from pleural fluid irrespective of its gross appearance.

The visual appearance of the fluid provides clues as to the responsible organism only infrequently, although the

unusual case of *E. histolytica* is well known for its association with 'anchovy sauce' and *Actinomyces* spp. for 'sulphur granules' [83]. The olfactory senses do not have to be highly developed to detect the stench of putrefaction that is peculiarly characteristic of anaerobic infection, which once smelt is never forgotten. In one recent series, empyema fluid was described as malodorous in 62% of cases, anaerobes being recovered from half of these, whereas pneumococcal empyemas rarely smelt bad [11].

Blood cultures were positive in about 7% of one recently reported series [11]. Sputum culture is unhelpful in most cases as the organisms recovered often differ from those isolated directly from the empyema fluid itself [11].

### Biochemistry

Pleural effusions occurring in association with pneumonia

are exudates (see Chapter 43) and may be described as 'parapneumonic'. Work has been carried out to determine whether it is possible to predict from biochemical criteria which minority of these parapneumonic effusions are 'complicated', i.e. will develop into empyemas. Such complicated parapneumonic effusions have been found to have a low pH and glucose and a raised lactate dehydrogenase (LDH) [84]. The results of such measurements may be more pertinent in the opposite sense: effusions that do not meet given criteria are unlikely to become empyemas [85]. Thus if the pH of the pleural fluid is greater than 7.2, the LDH content less than 1000 iu/L and the glucose content either greater than 3.3 mmol/L (60 mg/dL) or in a ratio to blood glucose greater than 0.5, then it is improbable that the effusion will develop into an empyema. The opposite cannot always be relied upon to indicate that a parapneumonic effusion will require management as an empyema, as the pH is less than 7.2 in most 'rheumatoid' effusions and in some neoplastic and tuberculous effusions [86,87]. Pleural fluid glucose may also be significantly lowered in the same situations [88,89]. The reduced pH and glucose levels associated with empyemas may occur as a result of leucocyte and bacterial anaerobic metabolism of glucose, a process that produces lactic acid [86]. The accurate measurement of pleural fluid pH requires anaerobic collection in a heparinized syringe and removal to the laboratory on ice [82], although immediate transfer of an aliquot of the main aspirate to a heparinized syringe appears to be a practical option [90]. It has also been argued that when the pH criteria for the development of an empyema are met, the diagnosis is usually obvious by virtue of pleural fluid turbidity or the demonstration of an organism; furthermore, no prospective randomized trials have been carried out to assess whether drainage based on the biochemical parameters of a parapneumonic effusion improve outcome when compared with drainage based on clinical assessment [91,92].

## Management

There are two basic principles for the successful management of thoracic empyema: (i) control of infection with appropriate antimicrobial therapy and (ii) adequate drainage of pus. Adherence to these principles should return the pleural cavity to its former sterile state and allow full re-expansion of the underlying lung. Although many empyemas are treated entirely satisfactorily without recourse to operative surgical procedures, consultation with an experienced thoracic surgeon is advantageous, may become essential and is advised earlier rather than later in order that a suitable management plan can be agreed.

A prospective multicentre study of 119 patients with empyema found that the size of the empyema had an important influence on whether operative surgical inter-

vention would be required [11]. Medical treatment, comprising antimicrobial agents, aspiration and/or tube drainage, was successful in about 80% of patients in whom the empyema was judged to fill 20% or less of the hemithorax on the radiograph; the success rate for medical treatment fell to 50% for empyemas of intermediate (20–40%) size, and to only 24% in empyemas judged to be large (>40%) [11].

## Antimicrobial therapy

The choice of antibiotic (see Chapter 9) is usually determined from the results of microbiological culture and sensitivity testing.

### Anaerobes

Anaerobic infection may be treated with benzylpenicillin. Because of the increasing problem of penicillin-resistant strains, it is usual to add metronidazole to cover  $\beta$ -lactamase producing Gram-negative anaerobes. Some authors have found a better response when comparing clindamycin with penicillin as this is active against *Bacteroides fragilis* and other penicillin-resistant anaerobes (see Chapter 15) [93]. Metronidazole should not be used alone because some anaerobic cocci and most microaerophilic streptococci (e.g. *Strep. milleri/intermedius* group) are resistant to it.

Many other antimicrobial agents are active against anaerobes *in vitro* but have not been subjected to controlled clinical trials in patients. These apparently effective antibiotics include most but not all  $\beta$ -lactams, activity being particularly augmented by combination with a  $\beta$ -lactamase inhibitor, as in the case of amoxicillin (amoxycillin) and clavulanic acid to produce co-amoxiclav. Similarly, in the USA, ampicillin is available in combination with the  $\beta$ -lactam inhibitor sulbactam.

Other penicillins with activity against anaerobes include the extended-spectrum (antipseudomonal) penicillins such as the ureidopenicillins piperacillin and azlocillin and the carboxypenicillin ticarcillin. These are not usually required for treating empyemas but may sometimes be appropriate when the infection has been acquired in hospital, in which case a mixed flora with Gram-negative aerobes as well as anaerobes is more likely to be encountered. Ticarcillin is also commercially available combined with the  $\beta$ -lactamase inhibitor clavulanic acid, as is piperacillin with tazobactam.

Similarly, imipenem and meropenem, which are carbapenem  $\beta$ -lactams, have excellent *in vitro* activity against anaerobes as well as being active against a wide spectrum of Gram-positive and Gram-negative bacteria including *Ps. aeruginosa*.

Of the cephalosporins, cefoxitin (considered 'second generation' but in fact a cefamycin) is the most potent *in*

*vitro* against the *B. fragilis* group, tending to be relatively resistant to  $\beta$ -lactamases produced by Gram-negative bacilli. Third-generation cephalosporins, for example ceftazidime, and related drugs are less active against anaerobes and better avoided in this clinical setting.

Chloramphenicol is very effective *in vitro* against virtually all anaerobes but, because of its potential for marrow suppression, tends to be used only in life-threatening situations when other therapy is judged to be failing or is unavailable.

Macrolides (such as erythromycin, clarithromycin and azithromycin) are not ideal as single agents as they have poor activity against anaerobic fusobacteria, although this can be offset by combining them with metronidazole.

Tetracyclines are best avoided as significant numbers of resistant anaerobic strains have emerged. Quinolones as a group are also relatively ineffective against anaerobes. Of the other  $\beta$ -lactam antibiotics, aztreonam is ineffective. So are co-trimoxazole (trimethoprim-sulfamethoxazole) and the aminoglycosides, although the latter may be considered as part of a combination regimen to cover Gram-negative aerobic bacilli.

### Pneumococcus

Pneumococcal empyema usually responds to high-dose benzylpenicillin initially, continuing with oral phenoxymethylpenicillin (penicillin V) or amoxicillin. The problem of penicillin-resistant pneumococci is discussed in Chapter 13. Alternatives for penicillin-allergic individuals include a first-generation cephalosporin such as cefradine (cephradine) or a macrolide such as clarithromycin.

### *Staphylococcus aureus*

In the UK, *Staph. aureus* is ordinarily treated with flucloxacillin. This drug is unavailable in the USA where dicloxacillin is marketed for oral treatment and methicillin, oxacillin or nafcillin are available for parenteral use. A first-generation cephalosporin such as cefradine may be used, orally or parenterally, as an alternative antimicrobial in penicillin-allergic patients. Methicillin-resistant *Staph. aureus* presents special problems and is discussed in Chapter 13. It may be treated with the glycopeptide antibiotics vancomycin or teicoplanin (see Chapter 9). When treatment with these single agents fail, gentamicin or rifampicin or both are sometimes added.

### Gram-negative aerobes

Serious Gram-negative aerobic infection may be treated with the combination of a third-generation cephalosporin such as ceftazidime and an aminoglycoside such as gentamicin. When concern exists about the possibility of a mixed infection including both anaerobes and Gram-

negative aerobes, a ureidopenicillin or carboxypenicillin might be a better choice (see above). *H. influenzae* is still usually responsive to amoxicillin, although  $\beta$ -lactamase-producing organisms may require co-amoxiclav, a macrolide such as clarithromycin, or ciprofloxacin as possible alternatives. Adults with empyema who are admitted from the community and in whom the infecting organisms have not yet been identified may be treated initially with a combination that includes a  $\beta$ -lactamase-resistant penicillin such as co-amoxiclav, metronidazole and flucloxacillin, this regimen being modified in the light of cultures and the patient's clinical response. The duration of chemotherapy in patients treated medically is likely to be several weeks and it is prudent to continue drug treatment for at least 3 weeks after all drainage has ceased.

### Tuberculosis and unusual organisms

Tuberculous empyema requires conventional combination chemotherapy (see Chapter 19), although this may need to be continued for longer than the usual 6 months according to sensitivities and response. Eradication of infection will not be achieved without adequate drainage.

The treatment of other more unusual organisms also requires drainage with appropriate antimicrobial chemotherapy. *Aspergillus* may require amphotericin or itraconazole. Cryptococcosis in the immunocompromised patient is treated with amphotericin and flucytosine, the latter being continued as maintenance therapy. Blastomycosis is also treated with amphotericin in patients who are immunocompromised or severely ill, whereas itraconazole is an alternative in less sick patients. Coccidioidomycosis may be treated with amphotericin or itraconazole.

Actinomycosis is treated with high-dose benzylpenicillin followed by prolonged therapy with oral amoxicillin or phenoxymethylpenicillin, whereas tetracycline has been used most widely in penicillin-allergic patients. *Nocardia* may respond to co-trimoxazole, sulfadiazine (sulphadiazine) or imipenem as single agents.

Clostridial empyemas are treated with high-dose benzylpenicillin initially, metronidazole or imipenem being alternatives. Ill patients infected with *Bacillus cereus* may be treated initially with vancomycin, while a combination of doxycycline and rifampicin may be used to control *Bruceella* infection. Benzylpenicillin, amoxicillin and doxycycline are among the drugs usually effective in *Pasteurella multocida* infection. *Salmonella* may be treated with ciprofloxacin or a third-generation cephalosporin such as ceftazidime.

Hydatid infection is generally treated by surgical excision with albendazole cover. Praziquantel is effective against the lung fluke *Paragonimus westermani*. Rare cases of *Trichomonas* empyema may be treated with metronida-



zole. Empyema complicating amoebiasis is treated with metronidazole and diloxanide furoate.

Drug therapy for *Burkholderi cepacia* is based on sensitivities but strains may be susceptible to ureidopenicillins, third-generation cephalosporins, co-trimoxazole, ciprofloxacin and chloramphenicol.

## Drainage

Drainage of an empyema may be closed or open (Fig. 14.7) and the technique used depends on the stage of the empyema (see above) at the point of intervention.

### Closed drainage

Closed drainage may be either 'intermittent', in which repeated aspiration (thoracentesis) is carried out, or 'continuous', in which an intercostal tube is connected to an underwater seal (closed-tube thoracostomy). Closed drainage is preferred provided that the pus is accessible and not too viscid to permit adequate removal by these methods. These conditions are more likely to appertain in the exudative stage but can be continued into the fibrino-purulent stage in some cases.

### Thoracentesis

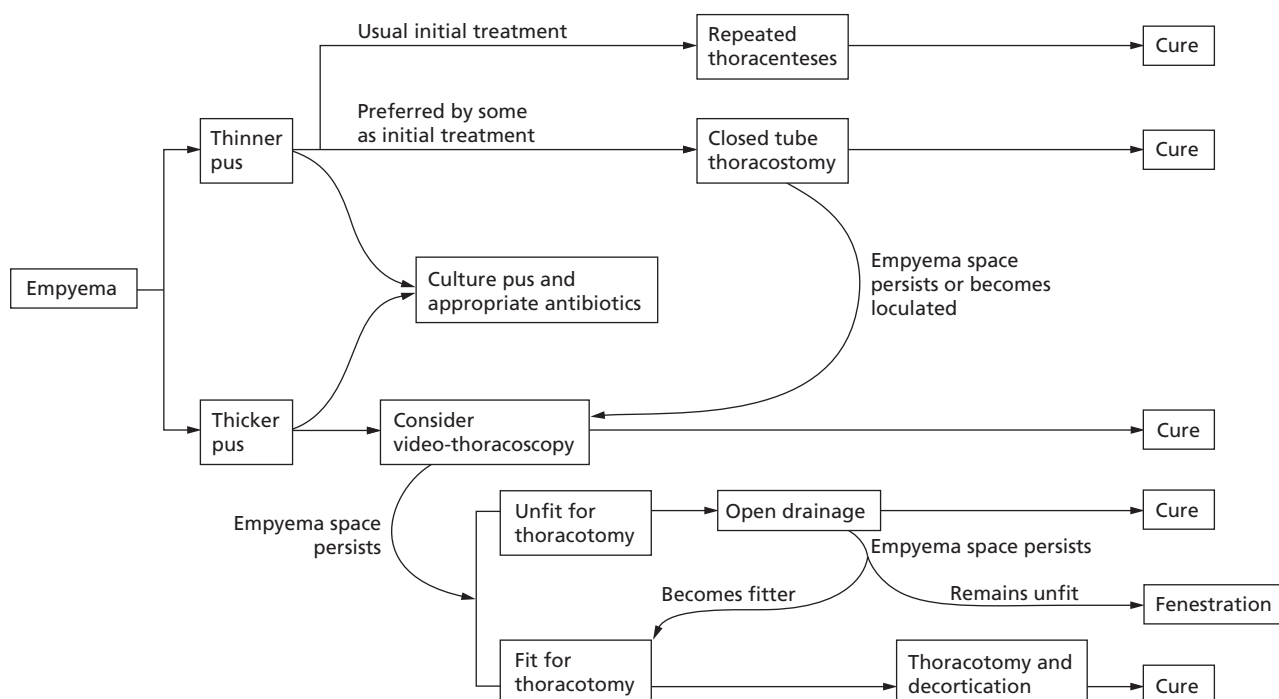
The site of the pus can often be confirmed with the local

anaesthetic needle. Aspiration is thereafter best carried out using a needle or cannula of sufficient bore to allow the pus to flow without too much exertion on the part of the operator. Sharp needles are best avoided for fear of damaging underlying lung. The use of an Abrams punch biopsy needle is useful initially, as it is of sufficiently wide calibre to allow easy aspiration and also permits diagnostic biopsy of the parietal pleura/empyema cortex for histological examination and culture. The frequency with which thoracentesis is repeated depends upon the rate at which pus reaccumulates, which in turn is judged by the clinical and radiographic findings. Aspiration may be required daily or two or three times per week at first, diminishing as infection responds to antibiotics, and may sometimes extend over a prolonged period, during which time the patient is usually ambulant and visits the hospital as an outpatient. Such medical treatment with antibiotics and repeated thoracentesis is appropriate for many individuals with pleural empyema and these patients may have a shorter and less complicated stay than those treated by tube drainage [94].

### Closed-tube thoracostomy

Closed-tube thoracostomy is preferred by some clinicians from the start once the diagnosis of empyema has been confirmed [85,94]. It has the advantages that drainage is continuous and that it is more likely to be successful when the infected material is too viscid to be removed by manual aspiration, but with the disadvantage of greater discomfort and immobility for the patient; furthermore,

Fig. 14.7 Management of empyema.



introduction of new infection at the drainage site is a possibility and the tube itself may become blocked by fibrin [95]. Malécot-type self-retaining soft rubber catheters have advantages over the modern disposable rigid plastic cannulae in widespread use, in that underlying structures are less likely to be impaled during introduction, they can be made to fit the cutaneous incision snugly with less chance of leakage around the tube and they are less likely to fall out [96]. Regrettably, however, they are no longer available in most centres. Under local anaesthesia the tube is placed in the most dependent part of the empyema cavity, a site that may be determined by ultrasound examination, CT or the injection of a little radio-opaque contrast material. Ultrasound may also be used to place a small catheter (such as an 8 French gauge pigtail nephrostomy tube with 10 side-holes) in larger loculations and this may be connected to a plastic drainage bag attached to the chest wall. Patency may be maintained using streptokinase (see below).

When underwater seal drainage through a conventional large-bore intercostal tube becomes slight, the tube may be cut off, transfixed with a safety pin (to prevent it falling into the empyema cavity) and covered with a gauze dressing to allow the patient greater mobility until it is removed. Sinography may be carried out by injecting contrast down the tube in order to assess the adequacy of drainage [97]. When the residual sinus is small and drainage minimal (e.g. <150 mL daily for two consecutive days, including 6-hourly 20-mL saline flushes), the tube is removed.

A technique somewhere between thoracentesis and closed-chest drainage has been described in which a 20–28 French gauge plastic cannula is passed into the empyema cavity under local anaesthesia using ultrasound control, fibrinous septa being broken down and pus rapidly removed by strong negative pressure (–13 kPa), after which the cannula is removed and the skin resutured [98].

### *Fibrinolytic and irrigation therapy*

The instillation of antiseptics, antibiotics and fibrinolytic agents has long been practised in order to attempt to sterilize the contents of the empyema cavity and to break down fibrinous loculations that contain pus [99–101]. ‘Irrigation therapy’ was reported to be effective in 1876 and although it continues in use in different centres and in various forms, it remains controversial [102–104]. The use of streptokinase as an intrapleural fibrinolytic to break down fibrin bands in order to allow loculae to drain more freely was reported in 1949 [105]. The technique was abandoned due to allergic reactions, only to be taken up again with the availability of purer commercial preparations of streptokinase, urokinase also being sometimes used [106–108]. A recent small, randomized, controlled trial examined the effect of once-daily streptokinase on closed-tube thoracos-

tomy [109]; 12 patients with infected parapneumonic effusions or empyemas were assigned to receive 6-hourly 20-mL normal saline flushes via a 14 French gauge intercostal drain that had been placed by a radiologist under ultrasound guidance; 12 further patients received the same 6-hourly flushes, one of which contained 250 000 units of streptokinase that was started at the time of diagnosis and given for three consecutive days, the catheter being clamped for 2 h after the streptokinase before being returned to suction. The fluid was overtly purulent in only 11 of the 24 patients. All patients received antibiotics and the catheter in each patient was connected to an underwater drain and kept on 2 kPa [20 cmH<sub>2</sub>O] suction [109]. The protocol allowed drains to be removed after the fifth day of treatment provided that drainage had fallen to less than 150 mL daily, including flushes, for two consecutive days. The duration of hospital stay was similar for the two groups but a larger volume of drainage and greater chest radiographic improvement at discharge was achieved in the streptokinase group, none of whom required surgical referral, whereas three of the control group did [109]. Although this suggests that the technique may improve the drainage of infected or potentially infected material from the pleural space, further work is required to confirm the safety and efficacy of intrapleural fibrinolytics in improving key outcomes, such as the need for open surgical drainage, length of hospital stay and mortality [110,111]. Total doses of up to 1.5 million units of intrapleural streptokinase given over 3 days do not appear to cause significant activation of systemic fibrinolysis [112], although there are isolated reports in the literature of life-threatening *local* haemorrhage that may lead to thoracotomy [113,114].

Closed drainage, whether by thoracentesis or intercostal tube, is likely to be successful if the empyema is small [11] and if treatment of the empyema is started in the acute exudative or early fibrinopurulent stages of infection, in which case the wall of the empyema cavity gradually becomes reabsorbed allowing re-expansion of underlying lung and obliteration of the pleural space. This process can be expected to take several weeks in adult practice. Bronchoscopy is recommended following the successful conclusion of closed drainage in order to exclude any possible endobronchial causes of obstruction, such as tumour or foreign body. High resolution CT may be used if underlying bronchiectasis is thought likely.

The techniques outlined above may fail to cure an empyema if the pus is too thick to drain by thoracentesis or tube, if a bronchopleural fistula has developed or if pockets of pus become loculated and inaccessible. When closed drainage has failed to enable the lung to re-expand fully, a more invasive surgical procedure has to be employed. Such procedures include thoracoscopy, open drainage with rib resection, thoracotomy and decortication and, rarely, thoracoplasty.

### Video-assisted thoracoscopic surgery

If closed drainage does not result in prompt re-expansion of the lung and especially if loculi have been identified ultrasonically, a decision to intervene relatively early using video-assisted thoracoscopic surgery (VATS) with débridement and drainage is sometimes made. A small prospective randomized controlled trial in patients with fibrinopurulent empyema has compared treatment by VATS with fibrinolytic therapy using chest-tube pleural drainage and streptokinase; this showed that VATS was more effective, with faster resolution and a shorter hospital stay than that achieved with fibrinolytic therapy [115]. Provided that the empyema is in the fibrinopurulent stage, with the thickened rind caused by fibrin rather than the mature scar tissue that forms when an empyema has become chronic, VATS enables the operator to achieve adequate débridement, breaking down loculi, evacuating pus and debris and freeing the lung. This may then result in prompt re-expansion of the lung and obliteration of the pleural cavity, avoiding the need for repeated or prolonged attempts at drainage [116,117].

### Open drainage

Open surgical drainage is used if an empyema persists both clinically and radiographically in a patient in whom closed drainage has proved unsuccessful. It may be avoided if the empyema is suitable for drainage by VATS. When VATS is unavailable, unsuccessful or considered inappropriate, open drainage may be carried out in patients whose general condition is such that they are judged to be too debilitated to undergo the more invasive procedure of thoracotomy and decortication. Open drainage, which has been carried out in a sitting position under local anaesthetic to avoid spread of sepsis to the unaffected lung, often involves resection of the lowest rib above and below which pus can be aspirated [96]. The surgeon makes an incision large enough to allow adequate drainage, cleans the inside of the empyema cavity and places a wide-bore tube surrounded by gauze in the unsutured wound. Daily redressing under surgical supervision with sterilization and replacement of the tube is recommended. Successful open drainage results in gradual obliteration of the empyema space, which allows ultimate removal of the tube and cure. Thoracotomy and decortication (see below) may still be recommended if, during open drainage, the patient's general condition improves sufficiently.

When drainage is protracted and the patient remains too ill or is otherwise unsuitable for thoracotomy, then a more permanent fenestration or open-window thoracotomy (sometimes referred to as an Eloesser flap) may be performed. Such procedures involve the removal of sections of two or more ribs in order to fashion a larger

stoma, which is kept open by suturing the skin to the parietal pleura/cortex thereby creating a pleurocutaneous fistula [96]. The stoma may be closed if the underlying lung re-expands or may occasionally be left permanently open with daily dressing changes. Fenestration procedures are sometimes used in empyemas that complicate pneumonectomy. This form of empyema is often associated with a bronchopleural fistula through the bronchial stump. These fistulae, if small, may close spontaneously but if large do not close without a surgical procedure, such as resuturing with or without the transposition of pediculated intercostal muscle in order to cover the bronchus and also to help obliterate the empyema space [96]. A persistent bronchopleural fistula in this situation prevents successful closure of the fenestration [118,119].

### Decortication

This is an elective surgical procedure, unsuitable for patients who are ill and toxic, in which the fibrous wall of the empyema cavity, variously referred to as the cortex, rind or peel, is exposed at thoracotomy and stripped off the adjacent visceral and parietal pleura, which may be left intact. A bronchoscopy is carried out first in non-traumatic cases to exclude an underlying tumour or foreign body [96]. Decortication is carried out in patients in whom closed drainage and/or thoracoscopic methods have been unsuccessful, provided that they are fit enough to undergo this major procedure. It may also be used in the patient whose condition has stabilized following open drainage but who has entered a chronic phase in which the underlying lung does not expand because of failure of the cortex or rind to become reabsorbed. There is no consensus about the optimal time at which to perform a decortication, some surgeons arguing for early intervention and others adopting a more conservative approach [120–122]. In the early stage of organization the empyema cortex is poorly demarcated and friable, making decortication difficult. In intermediate stages of formation it is rather vascular so that decortication may be best delayed 2 or 3 months in order to reduce morbidity. It should not be forgotten that the cortex surrounding an empyema cavity does have a capacity to resolve spontaneously, albeit over a number of months, so that surgical decortication may be avoided altogether [123].

Heavily calcified chronic empyemas may occur in 'old' inadequately treated tuberculosis. These may be technically impossible to decorticate and if silent are best left alone. Where they point and discharge through the skin (empyema necessitans, see above and Fig. 14.3) surgical dilatation of the fistulous track or tracks may assist drainage, which can be collected in colostomy bags. When more radical surgical intervention is necessary in these cases, such as following the development of a

bronchopleural fistula, pleuropneumectomy may be required [34,96].

## Thoracoplasty

Thoracoplasty was once widely practised as a surgical management for cavitary tuberculosis, but is now used only rarely in order to (i) obliterate an empyema space fol-

lowing pneumonectomy or (ii) manage a persistent empyema cavity in patients where extensive ipsilateral parenchymal lung disease would prevent re-expansion after decortication and in whom extrapleural pneumonectomy would be unacceptably hazardous [124]. Thoracoplasty is a mutilating procedure that produces a grotesque chest wall deformity but is nevertheless still sometimes used as a last resort.

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# LUNG ABSCESS

DOUGLAS SEATON

A lung abscess is a localized area of destruction of lung parenchyma in which infection by pyogenic organisms results in tissue necrosis and suppuration. Lung abscesses may be single or multiple and they frequently contain air–fluid levels. When multiple and small (<2 cm in diameter) they are sometimes referred to as necrotizing or suppurative pneumonia, but they are an expression of the same pathological process and the distinction is an arbitrary one. It should not be forgotten that in addition to the more usual anaerobic and aerobic organisms, lung abscesses may also be found in tuberculosis (Chapter 17) and may be caused by non-bacterial organisms including fungi and protozoa (Chapters 21 & 22). Similar radiographic appearances may also be produced by other pathologies such as necrosis in a lung tumour or infection within a lung cyst.

## Mechanisms of infection

There are several ways in which pyogenic infection may reach the lung (Table 15.1) but by far the most important of these and the commonest cause of lung abscess is the aspiration of oropharyngeal contents [1].

### Aspiration

Saliva is particularly rich in anaerobic bacteria, the concentration of which may reach  $10^8$ /mL in healthy people. These count rates may be increased 1000-fold in subjects with dental or periodontal sepsis and about 350 different bacterial species have been encountered [2,3]. Various aerobic pyogenic organisms may also colonize the mouths of susceptible individuals. Radioactive tracer techniques have been used to show that small amounts of saliva are aspirated into the lungs during sleep in 45% of healthy people and in 75% of patients whose level of consciousness is depressed for various reasons [4]. Patients who are particularly liable to aspirate their oropharyngeal contents include those whose conscious level and cough reflex is impaired as a result of general anaesthesia, excessive

alcohol or other sedative drugs, head injury, cerebrovascular accidents, epileptic seizures, diabetic coma or other prostrating illness, including those resulting in mechanical ventilation on intensive care units. Although this last group of patients have cuffed endotracheal or tracheostomy tubes in place, it is clear that some of the secretions that pool above the cuffs find their way into the lower respiratory tract. When the level of consciousness is depressed in any of these situations, stomach contents may be aspirated and the low pH can cause a chemical pneumonitis that is probably an important predisposition to bacterial infection [5]. Spill-over into the trachea is also favoured by abnormalities of deglutition, whether these are mechanical, as in benign or malignant oesophageal strictures, or due to neuromuscular dysfunction, as in bulbar palsy or oesophageal achalasia.

The presence of dental sepsis or gingivitis increases the likelihood of aspiration pneumonitis and lung abscess as does dental extraction under general anaesthesia, due to the high content of anaerobic bacteria in the saliva of many of these patients [2,6]. Conversely, only 10–15% of patients with anaerobic lung abscesses have no obvious periodontal disease or other predisposition to aspiration [7]. It is of note that lung abscesses are seldom found in edentulous patients and carcinoma of the lung should be suspected when they are.

Further support for the importance of aspiration of oropharyngeal contents in causing the necrotizing pneumonia that may lead to lung abscess formation is provided by the observation that 75% of such abscesses occur in the posterior segment of the right upper lobe or the apical segments of either lower lobe, these being the segments to which aspirated material has been shown to gravitate in the supine subject [6,8].

The likelihood of an abscess developing following aspiration is probably influenced by the quantity, bacterial content and pH of the material aspirated, and the quality of the patient's lung defences. The latter includes both mechanical clearance and cellular and humoral competence, patients taking corticosteroids or other immuno-

**Table 15.1** Factors predisposing to lung abscess.**Aspiration of oropharyngeal flora**

Dental/periodontal sepsis  
 Paranasal sinus infection  
 Depressed conscious level  
 Alcohol/sedative drug abuse  
 Anaesthesia  
 Epilepsy  
 Head injury  
 Cerebrovascular accident  
 Diabetic coma  
 Other prostrating illness  
 Impaired laryngeal closure  
 Cuffed endotracheal tube  
 Tracheostomy tube  
 Recurrent laryngeal nerve palsy  
 Disturbances of swallowing  
 Oesophageal stricture (benign or malignant)  
 Oesophageal motility disorders, e.g. systemic sclerosis  
 Neuromuscular disease, e.g. bulbar/pseudobulbar palsy  
 Achalasia  
 Pharyngeal pouch  
 Neck surgery  
 Delayed gastric emptying/gastro-oesophageal reflux/vomiting

**Necrotizing pneumonia**

*Staphylococcus aureus*  
*Streptococcus milleri/intermedius*  
*Klebsiella pneumoniae*  
*Pseudomonas aeruginosa*

**Haematogenous spread from a distal site**

Urinary tract infection  
 Abdominal sepsis  
 Pelvic sepsis  
 Infective endocarditis (right-sided)  
 Intravenous drug abuse  
 Infected intravenous cannulae  
 Septic thrombophlebitis

**Pre-existing lung disease**

Bronchiectasis  
 Cystic fibrosis  
 Bronchial obstruction  
 Tumour  
 Foreign body  
 Congenital abnormality

**Infected pulmonary infarct****Trauma****Immunodeficiency**

Primary or acquired

claimed that patients receiving this type of medication as prophylaxis against 'stress' peptic ulceration while in the intensive therapy unit are more likely to develop lung sepsis due to aspiration than those receiving sucralfate (which has little antacid activity) for the same purpose [9,10].

**Other mechanisms**

Other mechanisms are less common and include blood spread. This sometimes occurs when there is a focus of Gram-negative sepsis elsewhere, such as in the urinary tract, possibly following catheterization or urethral instrumentation, or in the abdominal or pelvic cavities [11,12]. Anaerobic infection may also spread haematogenously from intra-abdominal, pelvic or even periodontal sepsis and lung abscesses may also complicate staphylococcal bacteraemia [13–15].

Septic emboli may reach the lungs from right-sided bacterial endocarditis, which most commonly complicates intravenous drug abuse (Fig. 15.1), the usual organism being *Staphylococcus aureus* (see below). Septic emboli may also arise from infected intravenous cannulae or from thrombophlebitis arising in the deep veins of the legs or pelvis or in relation to superficial cutaneous cellulitis [16]. The infected thrombi may contain *Staph. aureus*, *Streptococcus pyogenes* or anaerobes. A bizarre case of septic embolism has been described in a patient with Münchhausen's syndrome following intravenous self-injection of faeces [17].

Colonization of the lower respiratory tract with pyogenic organisms may occur in patients who have chronic lung disease such as bronchiectasis or cystic fibrosis, both of which may be complicated by lung abscess formation [18,19].

The inhalation of aerosolized bacteria is an unusual way for lung abscesses to arise other than as a consequence of tuberculosis. *Legionella* species may cause lung abscess but only rarely. Contaminated respiratory equipment such as nebulizers possess the potential to carry pyogenic organisms to the lungs of susceptible patients, and chemically induced lung abscesses have been described in itinerant paraffin-breathing fire-eaters [20,21].

The development of lung abscesses is also favoured by conditions that prevent normal clearance of pulmonary secretions, such as lung tumours, bronchiectasis and inhaled foreign bodies, the last situation particularly applying to children [22]. Lung cancer itself may cavitate and become infected. Secondary infection may also occur in congenital abnormalities such as bronchopulmonary sequestrations and lung cysts (see Chapter 50), which may be indistinguishable from primary lung abscesses in the absence of previous radiographs. Areas of thromboembolic pulmonary infarction may similarly cavitate and become infected, with resultant abscess formation [16].

suppressing agents being more vulnerable. Finally the presence of coexisting lung disease and the speed with which infection is recognized and treated appropriately are clearly relevant.

Oropharyngeal colonization with Gram-negative bacilli has been found to be more common in subjects treated with histamine H<sub>2</sub>-receptor blockers and it has been





**Fig. 15.1** Multiple lung abscesses (arrows) in a 27-year-old intravenous heroin addict with septic embolization arising from *Staphylococcus aureus* tricuspid valve endocarditis caused by self-injection of heroin into the right femoral vein. Complete resolution followed a 4-week course of intravenous flucloxacillin.

## Microbiological characteristics

Lung abscesses may be caused by a wide variety of different organisms and it is common to obtain a mixed bacterial growth from a single abscess when the pus is cultured. When lung abscesses have followed overt tracheo-bronchial aspiration, the frequency with which particular organisms or groups of organisms are found is related to whether the infection was acquired in the community or in hospital (see Chapter 13). Thus anaerobes only were isolated in 69% of community-acquired cases, whereas in hospital-acquired cases anaerobes were obtained in pure culture in only 7% of cases, other organisms such as *Staph. aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* playing a major role [23]. Mixed aerobic and anaerobic infections were found in 92% of all cases.

## Anaerobic organisms

Anaerobes are the group most frequently implicated. One published series of 93 lung abscesses recorded microbiological recovery of anaerobes in 89% of cases by the now seldom used transtracheal aspiration technique (see Chapter 8) [24]. Aerobic organisms were also recovered in 43% of all cases. Another study, in which 50 consecutive cases of 'chronic destructive cavitary pneumonia' were investigated by invasive microbiological methods, recorded a recovery rate for anaerobes of 60% and for aerobes of 80% of the total, 54% of infections being mixed [25]. The diagnostic techniques in this study included percutaneous lung puncture, transtracheal aspiration and open lung biopsy. When anaerobes are recovered from lung abscesses it is common for many different organisms

to be found [26]. This accords with the multiplicity of anaerobes recoverable from the oropharynx [2,3]. One large series of 193 patients collected over 7 years documented the involvement of 461 strains of anaerobic bacteria. In about half of these patients anaerobes were recovered in pure culture, while in the remainder anaerobes combined with aerobes or facultative anaerobes [27]. In a review of six series of patients with lung abscess the author found the incidence of anaerobic bacterial infection to be 85–93% [27].

The main groups of anaerobes are as follows.

- 1 Gram-negative bacilli making up the genus *Bacteroides*, notably *Bacteroides fragilis*. To add to the clinician's difficulties, the taxonomists have consigned some strains of what used to be called *B. melaninogenicus* to two new genera, *Prevotella* and *Porphyromonas*.
- 2 Gram-positive cocci, mainly *Peptostreptococcus* and anaerobic or microaerophilic streptococci.
- 3 Long thin Gram-negative rods comprising *Fusobacterium* species, particularly *F. nucleatum* and *F. necrophorum*.

## Aerobic organisms

Aerobic organisms tend to cause lung abscesses as part of a necrotizing pneumonia that can be seen to be radiographically more diffuse than is the case with classical anaerobic lung abscess, in which the surrounding lung parenchyma may appear relatively normal on the chest film. A possible exception to this is the *Strep. intermedius* group (also known as *Strep. milleri*), comprising *Strep. intermedius*, *Strep. constellatus* and *Strep. anginosus*, all belonging to the viridans group of streptococci. Isolates of

*Strep. intermedius* may be mistaken for anaerobic streptococci as they require carbon dioxide and may grow better under microaerophilic or anaerobic conditions. *Strep. intermedius* is the most common viridans species associated with pyogenic infection [28–30], and was the commonest single isolate (aerobic or anaerobic) in one study of lung abscess and empyema [26]. Notably, the viridans group of streptococci (unspciated) was also the most common isolate in a series of ‘chronic destructive pneumonia’ containing a high proportion of cavitation [25].

### Gram-positive aerobes

*Staph. aureus* is one of the major Gram-positive aerobic organisms to be implicated in lung abscess formation (see also Chapter 13). This may be acquired as a respiratory pathogen in the community, typically causing severe pneumonia following influenza in previously healthy individuals, and may result in the formation of lung abscesses and thin walled cyst-like spaces known as pneumatoceles that are sometimes seen in adults but which occur particularly in infants, *Staph. aureus* being the leading cause of lung abscess in children [31]. *Staph. aureus* also not uncommonly occurs in older adults as a hospital-acquired complication of coexisting illness [32]. Lung abscesses caused by this organism may result from blood-borne spread of infection from septic foci elsewhere, including endocarditis of the tricuspid valve in intravenous heroin abusers [33]. This haematogenous spread typically produces multiple pulmonary infiltrates (see Fig. 15.1) and these may sometimes mimic pulmonary metastases when the infection has arisen from a central line in patients receiving chemotherapy for neoplastic disease [34].

Other Gram-positive aerobes rarely cause lung abscesses. *Strep. pyogenes* (syn. Group A streptococcus,  $\beta$ -haemolytic streptococcus) used to be a very common cause of suppurative pneumonia before penicillin and its derivatives became widely available, particularly affecting children after viral and other upper respiratory tract infections but also adults, notably after influenza [35]. There appears to have been something of a resurgence of reports of invasive *Strep. pyogenes* infections in recent years, once again often with a history of preceding upper respiratory tract infection [36,37]. *Strep. pneumoniae* (see also Chapter 13) does not ordinarily cause lung abscess, although this complication has occasionally been recorded, notably with serotype 3.

### Gram-negative aerobes

The most common Gram-negative aerobe to cause necrotizing pneumonia associated with lung abscess is *K. pneumoniae*, at one time known as Friedländer’s bacillus. *Klebsiella pneumoniae* (see Chapter 13) is associated with

one or more abscesses in over 25% of cases and may also be associated with bacteraemia. It will be overdiagnosed if sputum culture alone is relied upon for, as is often the case with other isolates, this may merely reflect oropharyngeal colonization. It has a high mortality, with an apparent predilection for elderly and infirm patients and those receiving cytotoxic chemotherapy or corticosteroids. It is seemingly also more common in diabetics [38].

*Ps. aeruginosa* attacks a similar population, immunosuppressed patients and those with serious coexisting disease being particularly susceptible. In *Pseudomonas pneumonia* (see Chapter 13), abscesses are usually multiple and small, occurring as part of a patchy necrotizing process.

Lung abscesses resulting from necrotizing pneumonia caused by other Gram-negative aerobes, such as *Haemophilus influenzae*, *Escherichia coli*, *Acinetobacter* species, *Proteus* species and *Legionella* species, may occur but are unusual [39–42].

### Other less usual causes

Tuberculosis and other non-tuberculous mycobacterial infection may result in fluid-filled cavities, particularly in the upper lobes or the apical segments of the lower lobes [43,44].

Fungal infections (Chapter 21) that sometimes produce fluid-filled cavities in the lungs of immunocompetent hosts from endemic areas include chronic pulmonary histoplasmosis (*Histoplasma capsulatum*) [45], blastomycosis (*Blastomyces dermatitidis*) [46] and coccidioidomycosis (*Coccidioides immitis*) [47]. Reactivation of infection by these organisms may occur in patients with immune deficiency, including those with positive human immunodeficiency virus (HIV) serology. However, the most important fungal pneumonias occurring in the immunocompromised host result from infection with *Aspergillus* species and *Cryptococcus neoformans*, both of which may result in cavitation and abscess formation [48,49]. Uncommon fungal opportunists in the immunosuppressed patient include *Candida* species [50], and members of the order Mucorales causing the group of diseases known as mucormycosis (syn. zygomycosis, reflecting the class name of these fungi) [51]. Rarely *Pseudoallescheria boydii* and *Dactylaria constricta* may cause localized lung sepsis [52,53]. The main risk factors for all the opportunist fungal infections are neutropenia, corticosteroid use and HIV infection.

Single large lung abscesses may occasionally occur in pulmonary actinomycosis (Chapter 21), usually caused by the Gram-positive branching bacterium *Actinomyces israeli*, although other species belonging to the same genus may also be implicated. This infection usually causes a lung infiltrate containing a honeycomb of small abscess cavities that may communicate with the chest wall, with bony destruction and sinus formation [54–56]. *Actino-*

*myces* are often microaerophilic but tend to grow best anaerobically. Other genera within the same order Actinomycetales include *Arachnia* and *Nocardia*. These may cause chronic pulmonary disease, and both single and multiple lung abscesses are described in nocardiosis [57].

Pulmonary botryomycosis (bacterial pseudomycosis) is a term applied to a rare condition in which there is an unusual tissue response to infection, with some histological features resembling actinomycosis. It may arise as a response to a variety of infecting organisms, including Gram-positive cocci (*Staph. aureus*, *Streptococcus* species) and Gram-negative bacilli (*Pseudomonas* and *Proteus* species, *E. coli*). Although botryomycosis is more commonly found in the skin and subcutaneous tissues, visceral involvement may occur and single large or multiple small abscesses may be found in the lungs. The diagnosis depends upon histology. It has been described in previously normal hosts as well as in patients with pre-existing disease, including HIV infection and cystic fibrosis [58,59].

Other rare causes of lung abscess documented in immunocompetent patients include pneumonic plague (*Yersinia pestis*) [60,61], *Salmonella* infection [62,63], *Pasteurella multocida* infection [64], *Lactobacillus casei* infection [65], *Strep. mitis* (also of the viridans group) infection [66], brucellosis (*Brucella abortus*) [67] and pulmonary anthrax (*Bacillus anthracis*), although the main thoracic feature of anthrax is haemorrhagic mediastinitis with necrosis and oedema of the hilar lymph nodes [68,69]. Lung abscesses of protozoan origin, typically containing a 'chocolate' exudate, may occur in invasive amoebiasis (*Entamoeba histolytica*) [70]. Melioidosis (*Ps. pseudomallei*) is endemic, particularly in South-East Asia, and may cause pneumonic upper lobe infiltrates that may cavitate and simulate tuberculosis, suppuration sometimes occurring [71].

In the immunosuppressed patient, many organisms that are not usually pathogenic or are usually of low virulence may become implicated in sepsis. *Rhodococcus* (formerly *Corynebacterium*) *equi*, a variably acid-fast Gram-positive bacillus, is one example of such an opportunist that usually causes slowly progressive cavitating pneumonia in immunosuppressed patients, particularly those with AIDS [72]. Another example is *Alcaligenes xylosoxidans*, a Gram-negative rod [73].

## Pathology

Lung abscesses begin as areas of pneumonia in which small zones of necrosis (or microabscesses) develop within the consolidated lung. Some of these areas coalesce to form single or sometimes multiple areas of suppuration that, when they reach an arbitrary size of 1–2 cm in diameter, are customarily referred to as abscesses.

If the natural history of this pathological process is interrupted at an early stage by appropriate antimicrobial

treatment, then healing may be complete with no residual radiographic evidence of damage. However, if treatment is delayed or inadequate, the inflammatory process may progress, entering a more chronic phase. Bronchi adjacent to the area of inflammation may become eroded so that part of the purulent contents of the abscess may be expectorated as foul sputum. Fibrosis may occur in and around the abscess cavity, which may become loculated and walled off by dense scar tissue. With such loculation, drainage of one part of the abscess may occur into a bronchus only for further suppuration to develop in another part. Spillage of pus into the bronchial tree may also serve to disseminate infection either to other parts of the same lung or to the opposite lung.

The extent to which this suppurative process continues can be checked by antibiotics. These may sterilize the abscess cavity so that granulation tissue forms over the fibrous tissue, this then becoming covered by squamous or ciliated columnar epithelium that grows in from adjacent bronchi [74]. It has been shown bronchographically that an epithelialized cavity such as this may have several bronchial communications. The ready availability of antibiotics has made extensive damage of this type exceptional in communities with fully developed health services.

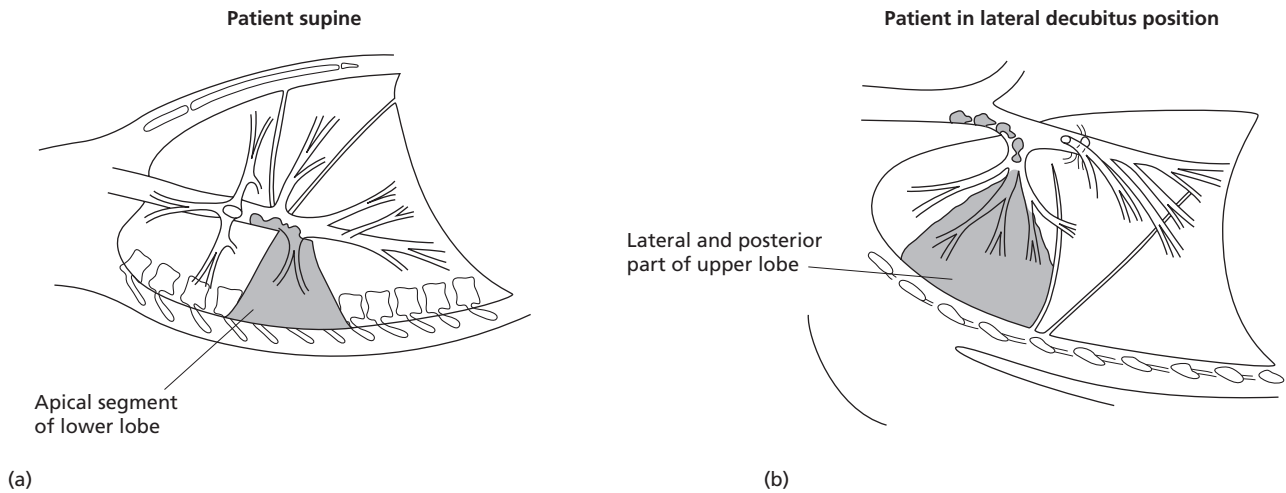
Abscesses arising as a result of aspiration usually occur close to the visceral pleural surface in dependent parts of the lungs. This was demonstrated by Brock over 40 years ago when he introduced small amounts of iodized oil into the tracheas of subjects in various postures. Three-quarters of lung abscesses occur in the posterior segment of the right upper lobe or the apical segments of either lower lobe, the anatomical disposition of these segmental bronchi accepting the passage of aspirated liquid in the supine position most readily [6,8] (Fig. 15.2). Following the same principle, in his classic surgical monograph Brock [6] also engagingly described the case of a coal-heaver with gross periodontal infection who developed a middle lobe abscess supposedly as a result of occult oropharyngeal aspiration occurring in his usual stooped working posture (Figs 15.3 & 15.4).

Despite the close proximity of lung abscesses to the visceral pleura, spread of infection through this membrane with resultant empyema is not the rule, occurring in less than one-third of cases [75]. Lung abscesses that occur as a result of haematogenous spread may be found in any part of the lungs (see Fig. 15.1).

## Clinical features

### Symptoms

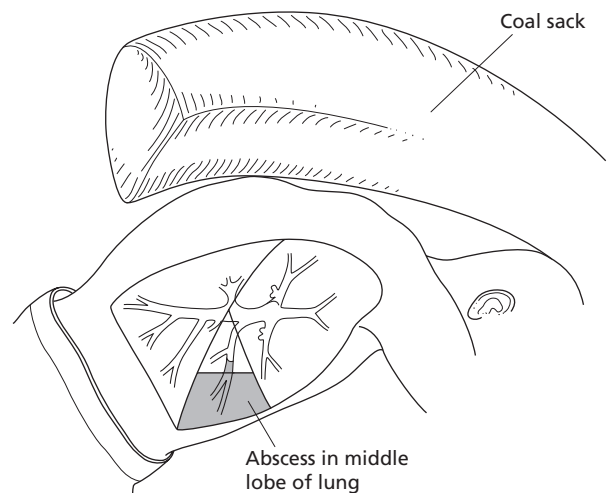
The presenting features of lung abscesses vary considerably. Firstly, there may be symptoms of any associated disease process, such as bronchial obstruction due to lung



**Fig. 15.2** Relationship between posture and focal incidence of lung abscess. When the patient is lying supine (a) the apical segment of the lower lobe is vulnerable; when the patient is in the lateral decubitus position (b) the upper lobe is affected. (From Brock [6].)

cancer, oesophageal obstruction due to achalasia, right-sided endocarditis, and so forth (see Table 15.1). Secondly, the clinical picture is influenced by the manner in which the abscess has arisen. The abscess may arise as a result of presumed aspiration in a predisposed host, in which case a history suggestive of this event may be obtained. Such patients are commonly less acutely ill than might be the case in more typical bacterial pneumonia, presumably because the aspirated material contains organisms of relatively low-grade pathogenicity. There may follow an illness of insidious onset with subacute symptoms that may not be sufficiently severe to warrant hospital admission until 2 weeks or longer has elapsed; indeed the patient may be taken aback and resistant to the offer of hospital admission [6]. A few patients may have particularly indolent presentation extending over weeks or months, with constitutional upset, weight loss and symptoms of anaemia [1,76]. The predominant symptoms are usually cough with purulent sputum, fever (sometimes with chills and rigors), dyspnoea and chest pain [77]. The chest pain may be pleuritic or it may be a more deep-seated aching discomfort. There may be large amounts of purulent sputum once a bronchial communication has been established and a putrid smell is indicative of anaerobic infection. Haemoptysis is not uncommon and can occasionally be life-threatening [78]. A subacute onset may also be found in patients who are intravenous drug abusers presenting with septic pulmonary infarcts (usually *Staph. aureus*), typically arising from endocarditis of the tricuspid valve (see Fig. 15.1).

The subacute presenting symptoms associated with presumed aspiration need to be distinguished from massive, often witnessed, aspiration such as might occur



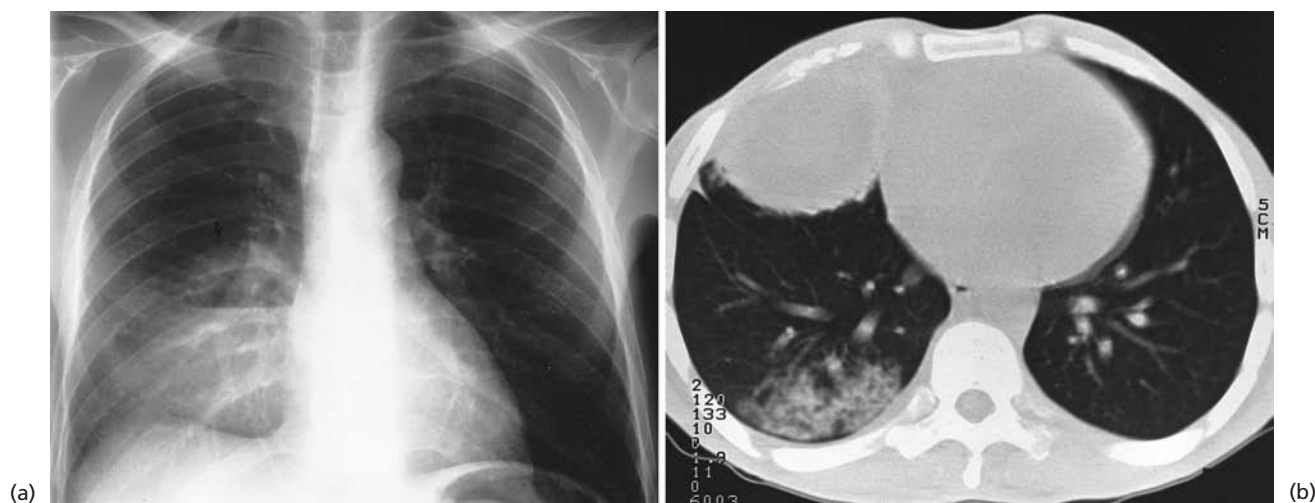
**Fig. 15.3** Occupational posture adopted by a coal-heaver who had gross periodontal disease and who presented with a middle lobe abscess similar to that shown in Fig. 15.4. (After Brock [6].)

during cardiopulmonary resuscitation, in which the immediate pulmonary problem is chemical injury from acid gastric contents, leading to lung infiltrates and possible adult respiratory distress syndrome. This may or may not be followed some days later by pulmonary infection.

The illness also tends to be more abrupt and severe when lung abscesses arise as a consequence of necrotizing pneumonia caused by predominantly aerobic organisms (e.g. *Staph. aureus* or *K. pneumoniae*). Such more acute illness may sometimes be fulminating so that symptoms attributable to abscess formation are usually lost in the more severe symptomatology of the pneumonia itself.

### Signs

There are no signs specific for lung abscess. Digital clubbing may develop within a few weeks if treatment is inadequate. Dullness to percussion and diminished breath



**Fig. 15.4** (a) Chest radiograph of a 34-year-old man with an eating disorder and suspected self-induced vomiting showing *Streptococcus anginosus* abscess in the right middle lobe. (b) CT of the same patient showing the middle lobe abscess but also pneumonic changes in the apical segment of the right lower lobe.

sounds may be present if the abscess is large and situated near the surface of the lung. There may be evidence of associated consolidation and a pleural friction rub is sometimes heard. The 'amphoric' or 'cavernous' breath sounds traditionally associated with lung cavities are rarely elicited in modern practice. There may be signs of an associated pleural effusion, empyema or pyopneumothorax.

## Investigation

The blood count characteristically shows a neutrophil leucocytosis, the white cell count often exceeding  $20 \times 10^9/L$ . A mild normochromic normocytic anaemia may be a feature if the history has been prolonged. The erythrocyte sedimentation rate and plasma viscosity are likely to be raised in non-specific fashion. Sputum may be submitted for cytological examination if a cavitating carcinoma enters into the differential diagnosis.

## Radiography

The radiographic abnormality may start with a pneumonic infiltrate (see Fig. 13.14), followed by the development of one or more spherical areas of more homogeneous density in which air–fluid levels often arise, indicating the formation of a bronchial communication (Figs 15.4 & 15.5). The abscess cavities may be large and are sometimes multilocular with several different fluid levels within one opacity. At other times a pneumonic infiltrate is found to contain numerous small areas of rarefaction, so-called necrotizing pneumonia. Bulging of an interlobar septum

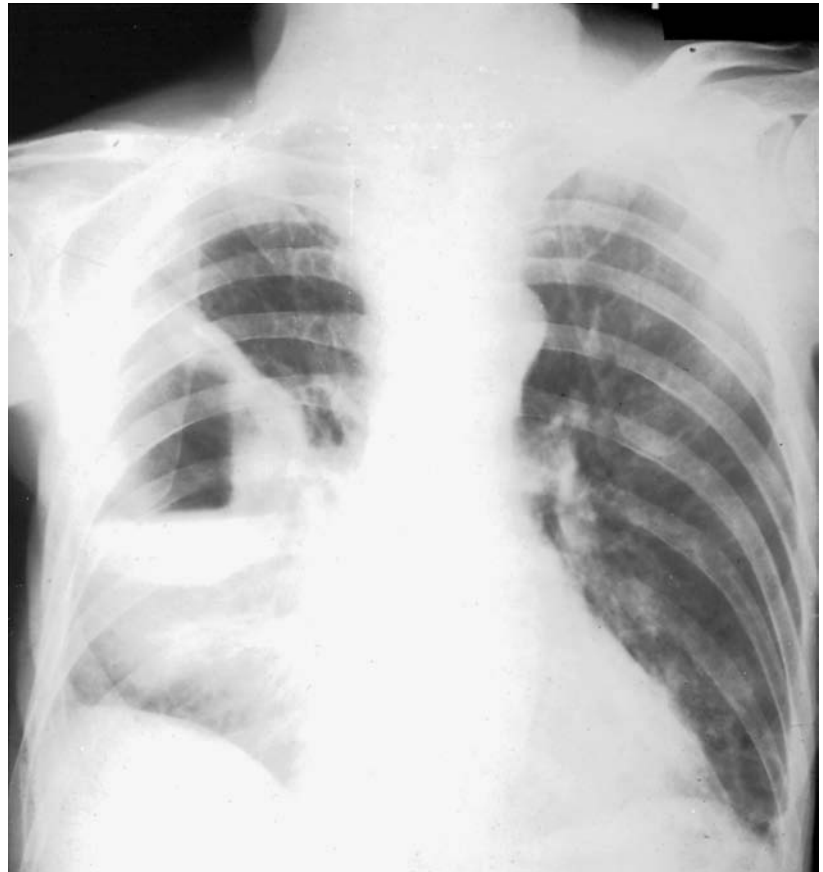
in such cases is said to be a feature of *Klebsiella* infection, which tends to affect the dependent segments, as is the case with other forms of lung abscess arising as a result of the aspiration of oropharyngeal contents [79]. A lateral chest radiograph helps to localize the abnormalities, which are typically subpleural in one of the dependent segments. When aspiration has occurred with the patient lying supine, the apical (superior) segments of the lower lobes tend to receive the aspirate. On the other hand, if the patient is lying on his or her side then the posterolateral parts of the upper lobe tend to receive the aspirate (see Fig. 15.2). The posterior segment of the right upper lobe is affected most commonly, followed by the apical segment of either lower lobe [6]. Occasionally the radiographic features of a complicating effusion, empyema or pneumothorax may be evident (Chapters 14, 43 & 44).

As a lung abscess heals, first the pneumonic infiltrate resolves and during this process the wall of the abscess cavity typically becomes thinner, diminishing in size until it is no longer detectable. A study of 71 patients with lung abscesses found that 13% of cavities had disappeared in 2 weeks, 44% in 4 weeks, 59% in 6 weeks and 70% within 3 months after treatment with appropriate antibiotics [80]. There is residual chest radiographic shadowing when extensive fibrosis has occurred.

Endoscopic or water-soluble, non-ionic contrast (e.g. lopamidol, Gastromiro) examination of the oesophagus should be undertaken if the patient has dysphagia or other symptoms suggestive of gastro-oesophageal reflux, whereas high-osmolality contrast media such as Gastrografin are avoided as spill-over may result in pulmonary oedema.

## Other imaging techniques

When the conventional chest radiographic findings are ambiguous, thoracic CT may be very helpful in accurately defining the extent and disposition of both lung abscesses



**Fig. 15.5** Large lung abscess in right mid zone following staphylococcal pneumonia. Pneumonic changes can be seen below the lesion and also in the left lower zone.

and empyemas [81]. Multiple small air cavities may be clearly demonstrated by CT in necrotizing pneumonia [82]. Fluoroscopy, ultrasound or CT may also be helpful in guiding percutaneous diagnostic thin-needle aspiration of lung abscesses (see below). Although radioactive indium [ $^{111}\text{In}$ ]-labelled leucocytes are taken up in lung abscesses [83], positive results may be produced by other unrelated intrapulmonary pathology so that the investigation has no advantage over conventional radiography.

### Microbiological sampling

#### Blood

Blood cultures should be taken, as pathogens are occasionally isolated in cases of blood-borne (or 'metastatic') lung abscess or when the abscess has complicated pneumonia. Positive blood cultures are unusual in anaerobic infection. Serology may sometimes be helpful, for example when hydatid disease or amoebiasis are considered in the differential diagnosis.

#### Sputum

Sputum examination and culture is also routine as aerobic pathogens may be isolated. There is no point in culturing sputum anaerobically because of inevitable oropharyn-

geal contamination. A clue to anaerobic infection may be the finding in mucopurulent sputum of large numbers of neutrophils with a mixture of many different morphological forms of Gram-positive cocci and Gram-negative rods or fusiform bacilli, the subsequent culture yielding only mixed aerobic respiratory organisms [1,84]. The isolation of aerobes from sputum also has to be treated with some caution because of the same problem of oropharyngeal commensal contamination, although the repeated isolation of a predominant organism suggests that this may be a true pathogen. House staff need to be reminded to specifically request stains and cultures for acid-fast bacilli and fungi in appropriate cases, otherwise these are often not done.

Gas-liquid chromatography has been described as a rapid method for the identification of anaerobes in expectorated sputum, producing a result in under 1 h [85]. It has been claimed that laboratories possessing this facility should be able to use it reliably to distinguish between lower respiratory tract infection and oropharyngeal commensal contamination, the former giving a much stronger response than the latter [86]. The technique detects the presence of the volatile fatty acids that anaerobes produce and that account for the putrid smell associated with this type of infection. No false positives were recorded in one study that made use of this methodology but the equipment is expensive and not widely used [86].



### Other methods

Other methods have been used to obtain specimens uncontaminated by oropharyngeal commensals for the purpose of anaerobic culture. These include percutaneous transtracheal aspiration [87,88], percutaneous needle aspiration of a lung abscess under fluoroscopic or CT control, and bronchoscopic sampling using the fiberoptic instrument and a brush designed to be protected from contamination by oropharyngeal flora [89] (see Chapter 8).

The value of transtracheal aspiration is based on the observation that the trachea is sterile in normal individuals. The procedure requires a cooperative patient and should not be carried out in the presence of hypoxaemia or a bleeding tendency. Although it has been shown to be helpful in diagnosing anaerobic lung infections in research institutions, few practicing physicians in the wider world have mastered the technique, which is now seldom used [27,87,90].

Percutaneous needle aspiration may be used to obtain pus from an abscess of sufficient size to be visible fluoroscopically so that a fine needle can be guided into the lesion under direct vision. The procedure may also be carried out under ultrasound or CT guidance [91,92]. Any air bubbles are expelled from the syringe, which is then sealed and transported directly to the microbiology laboratory. A high diagnostic yield (82%) may be obtained in experienced hands and may lead to changes in antimicrobial therapy [93]. This technique has been compared very favourably with transtracheal aspiration in the diagnosis of anaerobic lung abscess [94]. The prerequisite technical skills are more likely to be provided by an invasive radiologist than by a respiratory physician although, as with transtracheal aspiration, percutaneous needle aspiration of lung abscesses is infrequently carried out in practice, most clinicians basing their choice of antimicrobial therapy on empiricism.

'Protected brushing' via the bronchoscope has been described as a method for obtaining lower respiratory tract secretions that have not been contaminated by oropharyngeal flora [89]. The success of the technique is somewhat limited by the antibacterial properties of lidocaine (lignocaine) so that, ideally, limited quantities of preservative-free local anaesthetic should be used. The temptation to pass a fiberoptic bronchoscopic brush into a large lung abscess should be resisted as this action can precipitate a great flood of pus that may overwhelm a small suction channel and threaten to compromise the patient [95]. Quantitative cultures of bronchoscopic brushings or aspirates have also been proposed, a yield of greater than  $10^3$  colony forming units [cfu]/mL being taken to indicate infection rather than colonization [96,97].

Anaerobes show some degree of susceptibility to the many antimicrobial agents used to treat lower respiratory infection and this adds to the difficulty of isolating them. It

is stressed that close cooperation with the microbiologist is essential when the presence of fastidious organisms such as anaerobes is suspected, in order that specimens are retrieved under optimal conditions and dealt with by the laboratory appropriately and without delay.

### Bronchoscopy

As well as providing a possible method of microbiological sampling (see above), bronchoscopy is diagnostically important when the differential diagnosis includes cavitating lung cancer and when it is necessary to exclude an obstructive proximal lesion such as a bronchial tumour or, less commonly, to identify and remove a foreign body.

## Differential diagnosis

### Cavitating lung cancer

Although lung cancer (usually squamous cell) is a more common cause of a cavitating lung opacity than lung abscess in males over the age of 50 years in the UK, there is usually little difficulty in making a distinction between the two. Patients with a bronchial tumour have no history suggestive of aspiration, and the lesion need not be situated in a typically dependent segment of the lung (see p. 464). A fever, systemic complaints, purulent sputum and leucocyte count greater than  $11.0 \times 10^9/L$  are more likely to be found in the presence of an abscess, as is a response to antibiotic treatment [98]. A chest radiograph showing an eccentric cavity with thick irregular walls may favour the diagnosis of malignant disease but it is unwise to place too much reliance on these features (Fig. 15.6). The cytological examination of sputum or of bronchial aspirates obtained through the fiberoptic bronchoscope may be helpful and any material obtained by percutaneous needle aspiration (see above) should be submitted for cytology as well as microbiological staining and culture.

Lung cancer and lung abscess may occur together, particularly in elderly patients, since necrotic tissue in a tumour may become infected, as well as the tumour itself causing the stagnation of distal secretions with subsequent infection. Where there is persisting doubt about whether the lesion is an abscess or a carcinoma, thoracotomy and removal of the lesion with the surrounding lobe of lung may need to be undertaken, provided that the patient is otherwise fit (see below). Other intrathoracic malignancies, including lung metastases and lymphoma, may also cavitate [99].

### Localized empyema

It may be difficult to distinguish radiographically between a localized empyema with a bronchopleural fistula and a





**Fig. 15.6** Cavitating squamous carcinoma in the right lower zone. Note thick irregular wall and absence of any surrounding pneumonic change.

lung abscess. Classically the empyema is seen on the lateral chest radiograph as a 'D-shaped' opacity, with the convexity projecting anteriorly from the posterior chest wall (see Fig. 14.4). CT may be helpful in doubtful cases, showing an abscess wall of varying thickness with an irregular intraluminal margin and exterior surfaces, whereas the walls of empyema cavities tend to be smooth, separating the thickened pleural layers with compressed lung beneath the visceral layer.

#### **Infected bulla containing a fluid level**

The patient is less ill than might be suggested by the chest radiograph. There may be little evidence of consolidation in surrounding lung when compared with an abscess. The margin of the bulla can often be seen to have a thin, smooth wall on plain films or CT [100] (Fig. 15.7). An earlier chest radiograph may assist in making this diagnosis. Infection within a bulla may cause its obliteration but this is rare [101].

#### **Infected congenital pulmonary lesions**

Bronchogenic and other congenital foregut cysts may be impossible to differentiate from a lung abscess unless previous films are available for comparison. Similar difficulties may be posed by infection in a congenital sequestered segment. The diagnosis is made by the posi-

tion of the lesion (usually lower lobe) and by retrograde aortography. The diagnosis and management of congenital lesions is discussed in Chapter 50.

#### **Pulmonary haematoma**

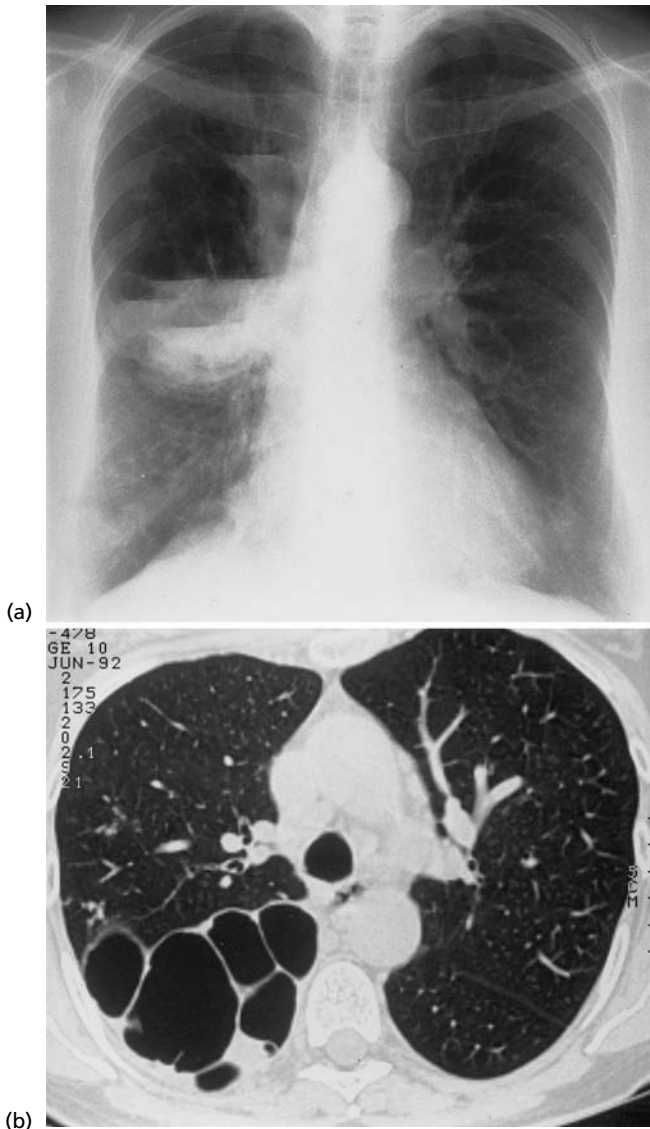
A history of recent trauma to the chest suggests the diagnosis. Sputum, if present, is not purulent and spontaneous dissolution of the haematoma usually occurs within a few weeks.

#### **Cavitated pneumoconiotic lesions**

Large, well-defined, rounded lesions that may cavitate sometimes develop in coal-workers whose serum is positive for rheumatoid factor, whether or not arthritis is present. The patient gives a history of occupational exposure and need not be ill. Progressive massive fibrosis in coal-miners and silicotic patients may also cavitate (see Chapter 54).

#### **Hiatus hernia**

The diagnosis is suggested by a 'double cardiac shadow' on the posteroanterior chest radiograph and confirmed on the lateral view by the typical appearance of a gastric air bubble behind the heart, often with a fluid level (Fig. 15.8). Further diagnostic confirmation may be provided by a



**Fig. 15.7** (a) Multiple fluid levels on the chest radiograph of a 67-year-old woman with infected cysts or bullae who presented as an outpatient with recurrent cough productive of purulent sputum. She remained symptom-free between infrequent exacerbations. (b) CT of the same patient demonstrating the cysts or bullae after expectoration of their contents.

barium meal or upper gastrointestinal endoscopy if there is doubt.

### **Tuberculous, fungal and actinomycotic infection**

As indicated above, lung abscesses are not all caused by the usual anaerobic and aerobic bacteria and acid-fast bacilli, fungi and *Actinomyces* may also cause pulmonary suppuration (Chapters 17 & 21). Chronic cavitary histoplasmosis may simulate tuberculosis radiographically, as may rhodococcal infection in immunosuppressed patients

and melioidosis (caused by *Ps. pseudomallei*) in patients from endemic areas [71].

### **Hydatid cysts and other lung parasites**

Hydatid cysts may rupture and develop bacterial superinfection [102]. The diagnosis should be suspected in people who have lived in sheep-farming areas. In such cases aspiration should not be attempted as this is likely to disseminate the disease. Latex agglutination, complement fixation and enzyme-linked immunosorbent assay are available for detecting antibodies in the serum (Chapter 22). Paragonimiasis (*Paragonimus westermani*, the lung fluke) may also simulate lung abscess and is endemic in parts of West Africa, the Indian subcontinent, the Far East and Central and South America [103].

### **Other conditions**

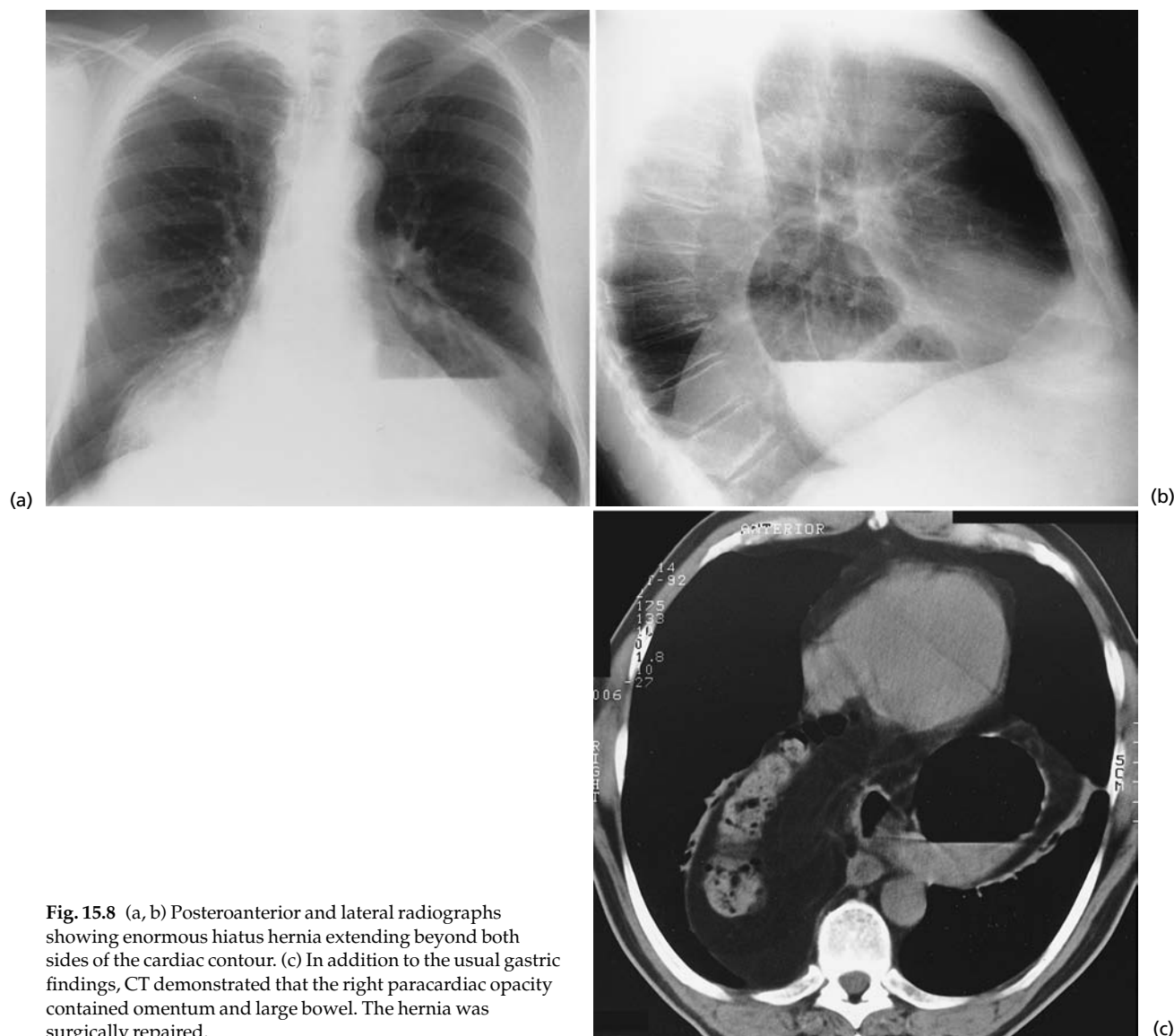
Other conditions that can be confused with lung abscess include cavitating pulmonary infarcts and Wegener's granulomatosis [16,104,105]. Sarcoidosis may rarely cavitate [106]. Massive pulmonary gangrene is a rare complication of pneumonia and can result in cavitation [107].

## **Treatment**

### **Antibiotics**

Antibiotic therapy has been the mainstay of treatment in lung abscess for over 40 years. Penicillin has retained its prominence throughout this period and has only recently fallen back slightly from the vanguard, largely as a result of the emergence of strains of  $\beta$ -lactamase-producing Gram-negative anaerobic bacilli. Nearly all lung abscesses form early communications with the tracheobronchial tree, hence the appearance of fluid levels. Their contents can therefore be coughed up and with the ready availability of antibiotics it is now unusual for operative surgical treatment to be required, about 90% of patients with anaerobic (putrid) lung abscess responding to medical treatment [108].

As mentioned above, there are inherent difficulties and inevitable delays in obtaining reliable microbiological information in cases of lung abscess so that, as with pneumonia, the clinician is usually obliged to adopt an empirical approach to therapy, basing the choice of antibiotic on probability. The majority of lung abscesses are related to aspiration and are caused by anaerobes; thus a history and clinical findings consistent with community-acquired lower respiratory tract infection followed by a localized area of abscess formation suggests that these organisms are very likely to be the culprits and treatment may be tailored accordingly. When, as is less usual, a lung abscess is thought to have been acquired during a period in hospital,



**Fig. 15.8** (a, b) Posteroanterior and lateral radiographs showing enormous hiatus hernia extending beyond both sides of the cardiac contour. (c) In addition to the usual gastric findings, CT demonstrated that the right paracardiac opacity contained omentum and large bowel. The hernia was surgically repaired.

the range of antibiotics may need to be broadened in order to cover not only anaerobes but also the wider spectrum of organisms that tend to colonize the pharynx in sick hospitalized patients and lend themselves to aspiration. These include genera within the family Enterobacteriaceae, such as *Klebsiella*, *Proteus*, *Serratia*, *Enterobacter* and *E. coli*, as well as other pathogens such as *Ps. aeruginosa*, *Acetivobacter* species and *Staph. aureus* (see Chapter 13).

#### **Benzylpenicillin, clindamycin and metronidazole**

Although most anaerobes remain sensitive to benzylpenicillin (penicillin G), increasing numbers of strains are becoming resistant. These include the  $\beta$ -lactamase-producing Gram-negative organisms previously known as *B. melaninogenicus* (now assigned to the genera

*Prevotella* and *Porphyromonas*), members of the *B. fragilis* group and some strains of *Fusobacterium*.

Although benzylpenicillin as a single agent may still be effective, particularly in less severe infections, concerns about resistance led to two prospective randomized trials in the 1980s in which penicillin was compared with clindamycin. This drug is active against *B. fragilis* and other penicillin-resistant anaerobes, as well as having some activity against *Staph. aureus* [109,110]. Both of these studies showed that clindamycin had the edge over penicillin in terms of lysis of fever and clearing of sputum, with fewer treatment failures and relapses. Although potentially more toxic, clindamycin may therefore be used as a substitute for penicillin and is certainly a rational choice in a patient who is allergic to penicillin. Its most serious limiting side-effect is pseudomembranous colitis. Another

approach has been to add metronidazole to penicillin as a second supporting antibiotic in all but the mildest infections [26,111]. Metronidazole is a suitable choice as it is active against all Gram-negative anaerobes, including *B. fragilis* (which is resistant to penicillin but sensitive to clindamycin) as well as *Clostridium* species. It is *not* standard practice to use metronidazole alone, as some anaerobic cocci and most microaerophilic streptococci (e.g. *Strep. milleri/intermedius*) are resistant to it, which may lead to a significant number of treatment failures if the drug is used singly, whereas these organisms will be dealt with by the addition of penicillin [112].

Dosage depends on the severity of the infection. In the case of benzylpenicillin, high doses are recommended [113]. A daily regimen using 6–12 g (5–10 megaunits) intravenously is usually appropriate, although doses of up to 24 g (20 megaunits) can be used. It is appropriate to supplement this with metronidazole 500 mg intravenously every 8 h by infusion. Modifications to treatment may be made according to response or in the light of culture and sensitivity results. As infection comes under control it is possible to reduce the dose of penicillin, switching to an oral form such as phenoxymethylpenicillin (penicillin V) 0.5–1 g every 6 h and to give the metronidazole, which is very well absorbed, in standard oral dose (400 mg every 8 h). The dose of clindamycin is 600 mg intravenously every 6–8 h, switching to oral therapy at a dose of 300 mg every 6–8 h.

### Other antibiotics

Many other antimicrobial agents are active against anaerobes *in vitro* but have not been subjected to clinical trials in patients with lung abscess, largely because of the relative infrequency of this type of sepsis and because of the fastidious nature of trial-regulating agencies who require microbiological proof of the responsible organisms. These apparently effective antibiotics include most but not all  $\beta$ -lactams, activity being particularly augmented by combination with a  $\beta$ -lactamase inhibitor, as in the case of amoxicillin and clavulanic acid (co-amoxiclav). Similarly, in the USA, ampicillin is available in combination with the  $\beta$ -lactam inhibitor sulbactam.

Other penicillins with activity against anaerobes include the extended-spectrum (antipseudomonal) penicillins, such as the ureidopenicillins piperacillin and azlocillin and the carboxypenicillin ticarcillin, which may be appropriate when the infection has been acquired in hospital, in which case a mixed flora with Gram-negative aerobes as well as anaerobes is more likely to be encountered. Ticarcillin is also commercially available combined with the  $\beta$ -lactamase inhibitor clavulanic acid as ticarcillin–clavulanate, and piperacillin has been combined with the  $\beta$ -lactamase inhibitor tazobactam as piperacillin–tazobactam.

Imipenem, which is a carbapenem  $\beta$ -lactam, has excellent *in vitro* activity against anaerobes, as well as activity against a wide spectrum of Gram-positive and Gram-negative bacteria, including *Ps. aeruginosa*.

Of the cephalosporins, cefoxitin (considered 'second generation' but in fact a cephamycin) is the most potent *in vitro* against the *B. fragilis* group, tending to be relatively resistant to  $\beta$ -lactamases produced by Gram-negative bacilli. Third-generation cephalosporins, for example ceftazidime, and related drugs are less active against anaerobes and better avoided in this clinical setting.

Chloramphenicol is very effective *in vitro* against virtually all anaerobes but, because of its potential for marrow suppression, tends only to be used in life-threatening situations when other therapy is judged to be failing or is unavailable.

The macrolides (e.g. erythromycin, clarithromycin and azithromycin) are not ideal as single agents as they have poor activity against anaerobic fusobacteria, although this can be offset by combining them with metronidazole.

Tetracyclines are best avoided as significant numbers of resistant anaerobic strains have emerged. Quinolones as a group are also relatively ineffective against anaerobes. Of the other  $\beta$ -lactam antibiotics, aztreonam is ineffective. So are co-trimoxazole (trimethoprim–sulfamethoxazole) and the aminoglycosides, although the latter may be considered as part of a combination regimen to cover Gram-negative aerobic bacilli.

Multiple lung abscesses or septic infarcts occurring in association with staphylococcal bacteraemia ordinarily respond to flucloxacillin or other antistaphylococcal penicillins, whereas vancomycin or teicoplanin (see Chapter 9) tend to be effective in pulmonary sepsis due to methicillin-resistant *Staph. aureus* [114].

The optimum route and duration of treatment in lung abscess have not been determined but it is common practice to give antibiotics intravenously initially as above, converting to oral therapy when a favourable response has become plainly evident. The pyrexia usually settles more gradually than is the case in non-suppurative pneumonia and may take 7 days or more to return to normal. A reappraisal of the treatment regimen is reasonable if the pyrexia has not begun to settle after 1 week [1]. Radiographic improvement also tends to be slow, commonly extending over weeks and there may be some residual fibrosis. It is usual to treat for 4–6 weeks and this may sometimes need to be extended for up to 3 months in order to achieve cure and prevent relapse. The point of discontinuance is impossible to define precisely, being determined empirically by the patient's clinical state and by a satisfactory radiographic improvement with the chest radiograph showing either complete clearing or a stable residual area of fibrosis.

## Physiotherapy

Physiotherapy may be useful in helping the patient to clear purulent material, the site of the abscess having been determined radiographically, so that postural drainage can be applied with the affected pulmonary segments uppermost.

## Bronchoscopy

Bronchoscopic drainage of lung abscesses using cardiac catheters has been described [115,116]. However, this technique is seldom used and it should be remembered that on rare occasions pus from a large abscess may flood into the tracheobronchial tree, so that rigid bronchoscopy is probably safer as it allows adequate suctioning [95]. As previously mentioned, the main role of bronchoscopy in lung abscess is diagnostic.

## Surgery

Surgical management is rarely required in countries where early and effective antibiotic treatment is available [108,117]. Such treatment was reviewed by Le Roux [118] whose South African practice afforded him considerable exposure to cases of pleuropulmonary sepsis.

These approaches include intercostal catheter or tube drainage to an underwater seal bottle [119,120]. Such intervention carries the risk of haemorrhage, pneumothorax, bronchopleural fistula and empyema, although a number of reports in the literature indicate that these complications are infrequent and that these procedures are usually effective where medical treatment has failed [7]. Modern interventional radiography has made it possible for experienced hands to place small catheters with considerable accuracy [121].

Open drainage via pneumonostomy is even less frequently carried out, the drain being removed within 48 h

of insertion as the cavity tends to close more rapidly than in empyema, in which longer periods of drainage are required.

Surgeons may resort to resective surgery if antimicrobial treatment fails and if external drainage has also been ineffective but this too is rarely required. In modern practice any form of surgical intervention, other than bronchoscopy, is required in less than 10% of patients with lung abscess, although in occasional cases medical treatment with antimicrobial agents may serve only to convert a subacute abscess into a more chronic one, so that serious and protracted symptoms result from the presence of an area of grumbling sepsis surrounded by extensively damaged and functionless lung. In this situation thoracotomy and lung resection (usually lobectomy) may have to be carried out. However, the most frequent indication for thoracotomy and resection is the suspicion that the abscess is a cavitating tumour or that it has occurred in close association with a carcinoma that cannot be convincingly excluded by other means. Lung resection is also occasionally necessary for massive and life-threatening haemoptysis. This alarming event may require emergency rigid bronchoscopy. Suction is applied to rid the contralateral lung of blood so that the patient is prevented from drowning. The situation may be improved by bronchoscopic tamponade with gauze swabs, by the placement of a balloon catheter in the bleeding bronchus or preferably by the use of a double-lumen endotracheal tube. Such large bleeds may be preceded by smaller haemoptyses. Bronchoscopy may be usefully carried out at this stage in order to identify the bleeding bronchus for future reference should a large bleed occur. Fortunately such massive haemoptyses are rare [117].

In a surgical series of 89 patients collected between 1968 and 1982 only 9% came to resective surgery and in all but two of these surgery was performed because carcinoma was suspected [77]. Hagan and Hardy [117] recorded resections in 10% of 184 cases between 1980 and 1982.

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# TUBERCULOSIS: PATHOGENESIS, EPIDEMIOLOGY AND PREVENTION

A. GORDON LEITCH

Tuberculosis is a disease of great antiquity. What were almost certainly tuberculous lesions have been found in the vertebrae of neolithic man in Europe and on Egyptian mummies dating possibly from as early as 3700 BC [1]. Today, tuberculosis has become the most important communicable disease in the world, with over 8 million cases of pulmonary tuberculosis occurring each year, 95% of which are in developing countries [2–4]. The World Health Organization (WHO) estimates that the annual number of new cases of tuberculosis will increase to 10 million by 2000 and that deaths attributable to tuberculosis will rise from 2.5 million to 3.5 million by the end of the millennium [5]. The advent of human immunodeficiency virus (HIV) infection has had a substantial impact on the incidence of tuberculosis, particularly in developing countries [6], and is compounded by the inadequate provision of, and access to, services in these countries [5]. Nor is tuberculosis unknown in the economically developed world: in 1991 in New York City, 3673 cases were reported, representing an increase of 143% over the incidence in 1980 [7]. This increase in tuberculosis cases in New York was largely attributed to the decline of tuberculosis control programmes [8] and their reinstitution led to a fall in annual notified cases to 3235 in 1993 [9], but not before the rates in central Haarlem (>150 cases per 10000 population) had equalled those in some parts of sub-Saharan Africa [10]. The New York experience is an extreme example of the consequences of assuming that a previously established annual decline in notifications of tuberculosis will continue. As tuberculosis has declined in the developed world there has been an associated decrease in experience and awareness of the disease, as reflected by increasing numbers of diagnoses of tuberculosis made after, rather than before, death [11–15]. Even in teaching hospitals delays in diagnosis due to failure to suspect the disease are not uncommon [15]. As tuberculosis has been a curable disease since the principles of chemotherapy were established almost 40 years ago [16,17], such a situation is to be deplored and the author makes no apologies for considering the subject in some detail. This chapter is concerned

with the pathogenesis of the disease, its epidemiology and methods of control and prevention.

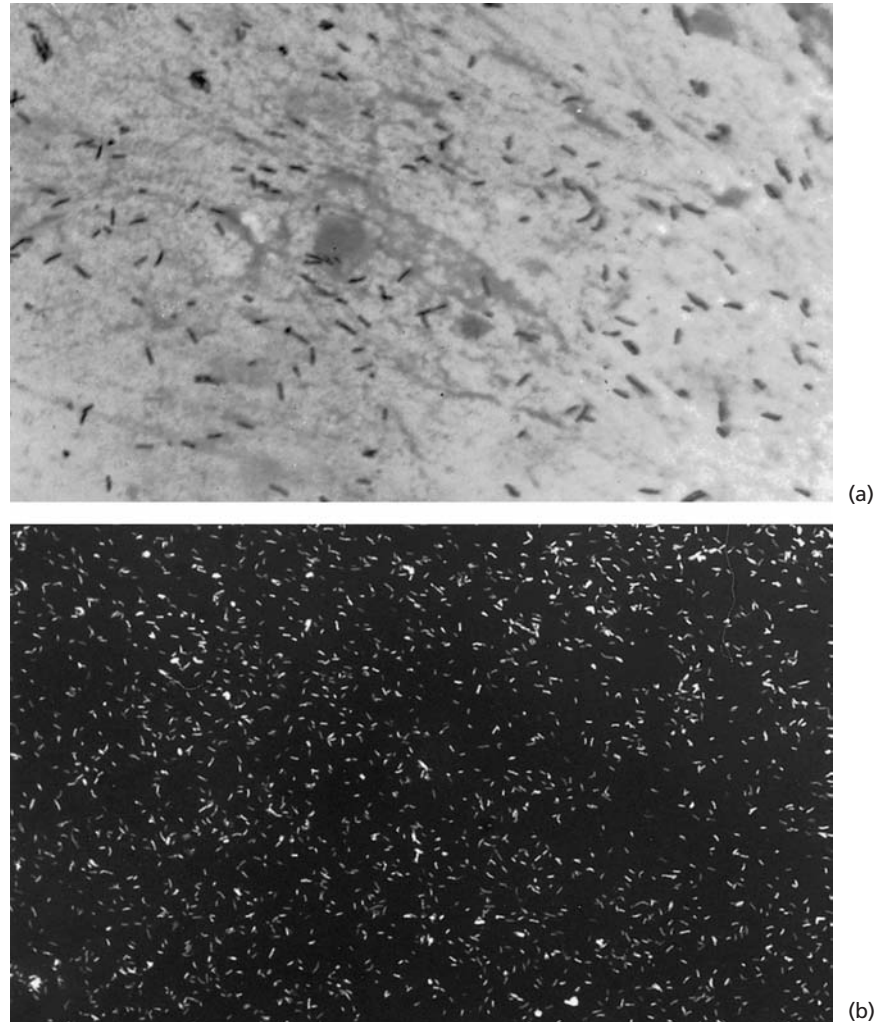
## Pathogenesis

### Tubercle bacillus

Koch first described the tubercle bacillus now known as *Mycobacterium tuberculosis* in 1882 [18]. Mycobacteria are now known to comprise a large group of acid-fast, alcohol-fast, aerobic or microaerophilic, non-spore-forming, non-motile bacilli [19]. Of the many different mycobacteria, only *M. tuberculosis*, *M. bovis* and *M. africanum* are recognized as tubercle bacilli, these all being subspecies of a single species. *M. tuberculosis* is an obligate parasite that is infectious to humans, other primates and to many other mammals. It produces progressive tuberculous disease in guinea-pigs.

Tubercle bacilli are difficult to stain but once stained they strongly retain the dye, which is not removed by acid-alcohol solution. This acid and alcohol fastness can be demonstrated by the Ziehl–Nielsen staining procedure, of which there are various modifications (Fig. 16.1a). Tubercle bacilli can also be stained by fluorescent dyes, such as auramine and rhodamine, and acid-fast staining procedures have been developed with these fluorescent dyes in which the bacilli fluoresce strongly (Fig. 16.1b).

In culture tubercle bacilli grow slowly, taking 2–6 weeks to form colonies on egg (e.g. Lowenstein–Jensen medium) and oleic acid–albumin agar media. Growth is optimal at temperatures of 33–39°C at pH 6.5–6.8 in an atmosphere of 5–10% CO<sub>2</sub>. Identification tests include production of niacin, of which *M. tuberculosis* produces the most. Supportive tests for *M. tuberculosis* include strongly positive nitrate reduction and loss of catalase activity at 68°C. *M. bovis* is weak on nitrate reduction and is a low niacin producer; in general *M. africanum* appears to be intermediate in characteristics between *M. tuberculosis* and *M. bovis*, although some have questioned the validity of this subspecies [20].



**Fig. 16.1** (a) Ziehl–Nielsen stain of sputum: acid-fast bacilli stain purplish pink ( $\times 1000$ ). (b) Fluorescent (auramine–phenol) stain of same specimen showing massive numbers of tubercle bacilli ( $\times 400$ ).

In stained smears of pathological material, *M. tuberculosis* is seen as slightly bent rods, 2–4  $\mu\text{m}$  long and 0.2–0.5  $\mu\text{m}$  wide, which may be evenly stained or beaded and granular. On solid or liquid media the bacteria tend to be parallel and form long threads or cords.

It is important to recognize that all three mycobacteria cause disease in humans that is histopathologically and clinically indistinguishable.

### Transmission

For many years tuberculosis was thought to be transmitted genetically. Even today, patients who have little or no idea of the theory of infection may express surprise when informed of the diagnosis of tuberculosis because 'it's not in my family, doctor'. Even before the tubercle bacillus was described, there were those who had their suspicions about the mode of transmission. In 1856, the English epidemiologist William Budd wrote: 'Everywhere along the African seaboard, where the blacks have come into contact and intimate relations with the whites, phthisis causes a

large mortality among them. In the interior, where intercourse with Europeans has been limited to casual contact . . . there is reason to believe that phthisis does not exist' [21]. It is now known that infection is transmitted by the airborne route and that the unit of infection is a small particle called a droplet nucleus.

The importance of the size of the infecting particle was first shown by Wells *et al.* [22]. Rabbits inhaling two or three bovine tubercle bacilli dispersed as single units contracted more pulmonary tuberculosis than those inhaling 10000 bacilli dispersed in large aggregates. The smaller particles were deposited on the alveolar surface, whereas the larger particles impacted in large airways and were cleared by mucociliary transport mechanisms. In small mammals it has been shown that almost all tubercle bacilli inhaled as single organisms reach an alveolus and produce a tubercle and that it is unusual for more than a single organism to be deposited at any one site [23,24]. It was postulated that airborne tuberculosis develops in humans by inhalation of a single bacillus contained in a droplet nucleus.

Coughing, spitting, sneezing, singing and other respiratory manoeuvres generate droplet nuclei due to evaporation of small respiratory droplets. These droplet nuclei are dispersed throughout space without settling and the organisms that they contain can remain viable for extended periods of time [25]. They are not filtered by simple gauze masks nor prevented from entering room air by covering the mouth and nose during coughing. Outdoors, organisms in droplet nuclei are eliminated by infinite dilution and by radiation from the sun.

In an elegant experiment reported by Riley *et al.* [26], the contribution of droplet nuclei to transmission of infection from smear-positive patients was investigated. A six-bedded research ward occupied by a succession of smear-positive patients had its air vented through exhaust ducts past guinea-pig colonies housed in exposure chambers in a penthouse on the roof of the hospital. All guinea-pigs were tuberculin tested at monthly intervals and positive reactors sacrificed and replaced by uninfected animals. In the first year of the study, of the 135 guinea-pigs that were exposed an average of approximately three per month became infected. The characteristic lesion was the single pulmonary tubercle with hilar node and spleen involvement. Control animals exposed to ward air disinfected with ultraviolet light did not become infected. In most instances the drug-susceptibility patterns of bacilli from infected guinea-pigs could be matched against similar organisms in the sputum of a patient in the ward at the time the animal was infected.

From this experiment, knowing the number of infectious particles (number of infected guinea-pigs) and the volume of air in the exhaust, it was possible to estimate the concentration of infectious particles in the air. Hence, ward air was calculated to contain one infectious particle per 340 m<sup>3</sup>. It would take a nurse in such a ward about 1 year on average to inhale one infectious particle, an observation consistent with epidemiological data on the time of tuberculin conversion in nurses working on such wards in the era before chemotherapy [27].

Another example that emphasizes the importance of droplet transmission compares with spread by direct contact is seen in the outbreak of tuberculosis aboard the naval vessel *Richard E. Byrd* [28], which carried a single smear-positive tuberculous crewman. The air in the interior of the ship was recirculated and the ventilation systems serving two large bunking compartments were interconnected. Occupants of the two compartments had very little contact with each other at any time. Nevertheless, the rate of infection with tuberculosis in crewmen who had no contact with the smear-positive index case was the same as in those who had direct contact because they shared the same compartment.

These reports emphasize the importance of droplet nuclei in the transmission of tuberculosis. Riley's study confirms that, in general, prolonged contact with a highly

infectious case is necessary before infection is acquired. At the other extreme, infection may be acquired by a single exposure, for example in laboratories or postmortem rooms [29]. Hospital staff exposed to patients with tuberculosis (even smear-negative tuberculosis) undergoing intubation, assisted ventilation and fiberoptic bronchoscopy have shown a high rate of tuberculin conversion [30]. Transmission to and from the HIV-infected patient is more likely [31], particularly where cough-inducing procedures such as sputum induction or pentamidine nebulization are being employed, and recommended precautions should be taken [32,33].

A number of factors, apart from smear positivity, may influence the infectivity of a particular patient. A bout of coughing produces up to 3500 droplet nuclei, a number that equates with speaking for 5 min in a normal tone. Loudon and Roberts [34,35] compared patients' nocturnal cough frequency recorded on tape with the percentage of their household contacts infected. Patients who coughed more than 48 times per night infected 48% of their contacts, while patients who coughed less than 12 times per night infected only 28% of their contacts. Duration of coughing prior to diagnosis is also clearly important. In one study 84% of patients had been coughing for 3–6 months [36]. The physical and chemical characteristics of the sputum may also influence infectivity. Guinea-pigs exposed to artificially atomized standard doses of different infected sputum samples show a marked variation in degree of infection [37]. Tenacious sputum may be more infectious than watery sputum. Finally, sputum from patients on effective chemotherapy is much less infectious, as shown by the low rate of infection of the penthouse guinea-pigs breathing air from the tuberculosis ward containing such patients [26]. This would accord with studies from Baltimore [38], Madras [39] and expert opinion [40] that most, if not all, contacts of patients with tuberculosis are infected prior to the initiation of effective chemotherapy. Most physicians now consider, on the basis of these findings, that after 1 or 2 weeks of effective chemotherapy the risk of transmission of tuberculosis is minimal, even from a smear-positive patient.

### Prevention of transmission in hospitals

From the point of view of hospital practice, the 1967 recommendations of the National Tuberculosis Association [41] have now been complemented by advice from the American Centers for Disease Control [42] and the British Thoracic Society [33] as well as from the International Union Against Tuberculosis and Lung Disease and the Tuberculosis Programme of the WHO [43]. These authorities accept the droplet nucleus mechanism of transmission and rely principally on chemotherapy to prevent transmission of disease. Isolation of patients suspected of having tuberculosis who are hospitalized is recommended

until three sputum smears are known to be negative for *M. tuberculosis* and the patient therefore non-infectious. Immunosuppressed patients (e.g. those with AIDS) should not be admitted to a tuberculosis ward until tuberculosis is confirmed and treatment has begun.

Patients with sputum smear-positive pulmonary tuberculosis, i.e. those who are infectious, should ideally be isolated from all other non-tuberculous patients until they have negative sputum smears and certainly until they have been treated for 2 weeks. Patients with HIV infection and tuberculosis or those in whom infection with drug-resistant organisms is suspected should be isolated until sputum is negative for acid-fast bacilli. Healthcare staff need to be educated about tuberculosis and those who are known to be HIV positive should not work with tuberculous patients.

Isolation rooms should be well ventilated to the outside and special precautions are required during cough-inducing procedures. Infectious patients who are being transported to other areas of the hospital should wear tight-fitting masks that filter particles 1–5 µm in diameter. Surgical masks may prevent dissemination from coughing patients but do not protect staff from inhalation of droplet nuclei. Following the occurrence of outbreaks of multidrug-resistant tuberculosis in the USA, the introduction of high-efficiency particulate air filter respirators was recommended; an analysis from Virginia, USA showed that, in one hospital, this intervention would only prevent one case of occupationally acquired tuberculosis at a cost of \$US1.3–18.5 million [44]. Such highly efficient interventions are not generally required.

## Pathology

Deposition of tubercle bacilli in the alveoli of the lungs is followed by vasodilation and an influx of polymorphonuclear leucocytes and macrophages to the area. After several weeks the polymorph numbers diminish and macrophages predominate. The macrophages develop pale foamy cytoplasm rich in lipid and crowd together as epithelioid cells to form the tubercle or unit lesion of tuberculosis (Fig. 16.2). Some mononuclear cells fuse to form the multinucleated or Langhans' giant cell. Lymphocytes surround the outer margin of the tubercle and in the centre of the lesion a zone of caseous necrosis may appear that may subsequently calcify.

Primary infection is usually evident as a subpleural tubercle (the primary or Ghon focus), which may be in any lung zone and which drains via lymphatics to hilar lymph nodes to form the primary complex. Most primary infections heal with or without calcification of the primary complex, although haematogenous spread probably occurs via the lymphatics in the majority of infected subjects, resulting in the seeding of tubercle bacilli to other parts of the lung as well as other organs [45]. Studies with

radioactive bacille Calmette–Guérin (BCG) suggest that within an hour of the bacilli reaching the lung they reach the lymph glands and often the bloodstream [46].

The infection is usually contained at extrapulmonary sites, as it is in the lung, but the potential for reactivation of infection at all sites is always present. The primary lesion sometimes progresses and the pathological changes are then similar to those seen in reactivation tuberculosis. Reactivated pulmonary tuberculosis is most often seen in the upper lung zones and is limited in extent, most frequently to the posterior segment of the upper lobe or the apex of the lower lobe. The high ventilation–perfusion ratios, with alveolar  $PO_2$  elevated relative to other zones, is believed to predispose to reactivation at these sites [45]. Proliferation of tubercle bacilli in the caseous centres is followed by softening and liquefaction of the caseous material, which may discharge into a bronchus with resultant cavity formation. Whereas  $10^4$  bacilli per gram are found in caseous tissue, up to  $10^9$  organisms may be harboured within a single cavitary lesion [47]. Fibrous tissue forms around the periphery of such tuberculous lesions but is usually incapable of limiting extension of the tuberculous process. Haemorrhage may result from extension of the caseous process into vessels within the cavity walls. Spread of caseous and liquefied material through the bronchial tree may disseminate the infection to other lung zones with or without the development of a vigorous inflammatory exudate or tuberculous pneumonia.

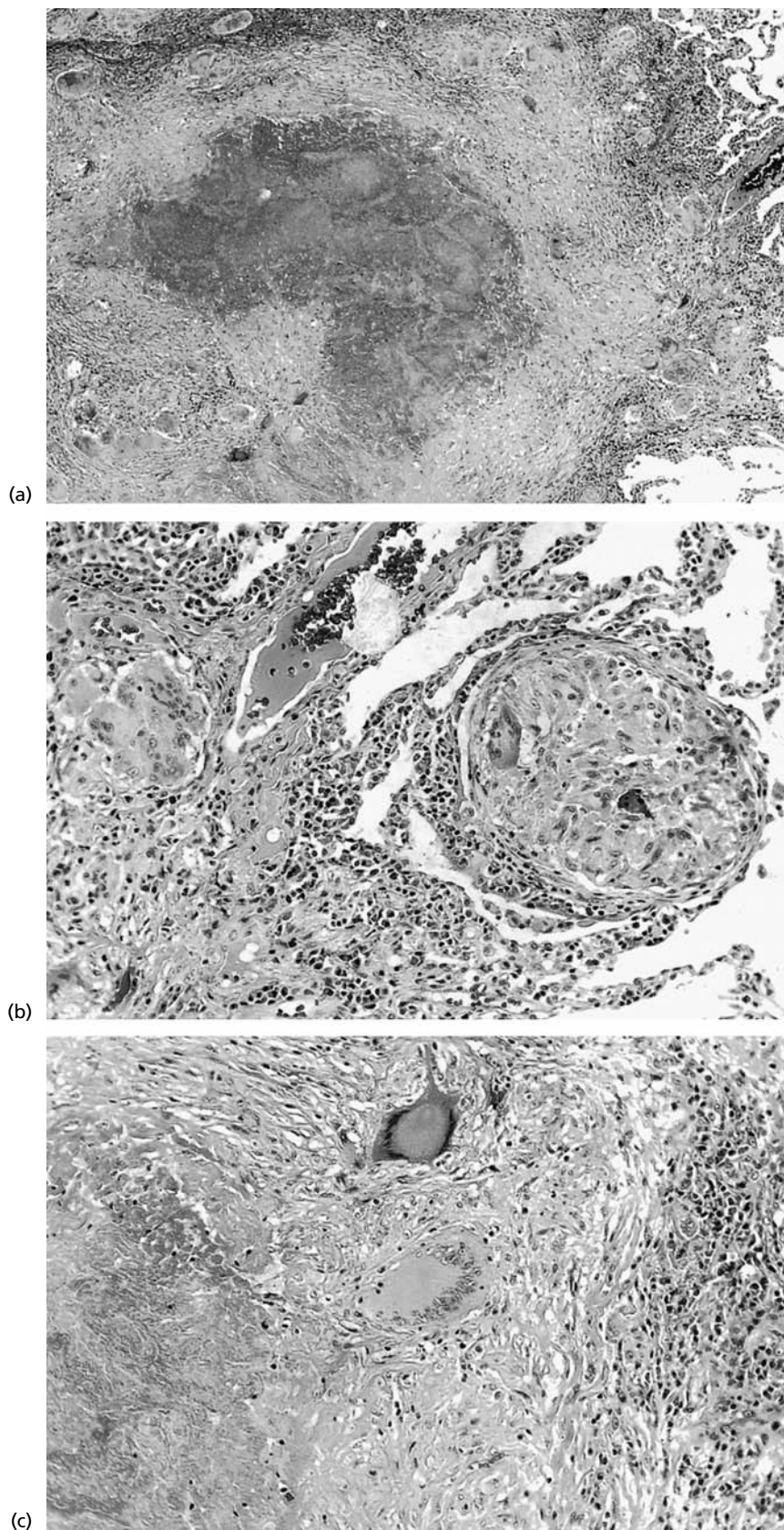
Rupture of a caseous pulmonary focus into a blood vessel may result in miliary (*milia*, a seed) tuberculosis, with the formation of multiple 0.5–2 mm tuberculous foci in the lung and in other organs of the body. Encroachment on bronchi of pulmonary or lymph node caseous material may give rise to tuberculous bronchitis. Rupture of caseous glands into trachea or major bronchi causes collapse of lung or even sudden death by suffocation in young children.

## Immunology [48]

Koch first described the reinfection phenomenon that still bears his name [49]. Primary infection in guinea-pig skin was associated with a slowly progressive, well-localized, granulomatous response with lymph node involvement. Subsequent infection with the same organism led to the development of an early localized indurated lesion that peaked at 72 h followed by rapid healing. A similar secondary response could be induced in the skin of tuberculous patients by the intradermal injection of heat-killed tubercle bacilli or an extract of this organism (tuberculin). The true nature of this diagnostic reaction was elucidated some 30 years later [50].

A positive skin reaction to tuberculin cannot be transferred to tuberculin-negative recipients by means of hyperimmune serum. It can be transferred to non-infected





**Fig. 16.2** (a) Large caseous granulomatous lesion of tuberculosis showing central necrosis, a surrounding zone of epithelioid cells and giant cells, and a peripheral ring of lymphocytes and fibroblasts (haematoxylin & eosin  $\times 35$ ). (b) Same lesion showing small epithelioid cell granuloma with giant cells (haematoxylin & eosin  $\times 110$ ). (c) Another area of the same lesion showing Langhans-type giant cells and epithelioid cells centrally, necrosis to the left and lymphocytes and fibroblasts to the right (haematoxylin & eosin  $\times 110$ ).

individuals by an infusion of lymphoid cells from tuberculin-hypersensitive donors [51]. In mice the same procedure results in the transfer of antituberculous immunity [52]. Immunity and hypersensitivity are now known to be mediated by a population of immunocompetent T lymphocytes originating in the thymus-dependent areas of the spleen and lymph nodes [53], and in the naturally infected host both hypersensitivity and immunity are believed to develop simultaneously [54].

Lurie [55] was the first to demonstrate in rabbits that the immune or antimycobacterial response of previously infected animals to subsequent mycobacterial challenge was mediated by a population of mononuclear phagocytes that ingested and killed tubercle bacilli at an increased rate compared with normal macrophages. The essentially cellular nature of the antituberculous immune response was subsequently confirmed [56,57], leading to the concept that cell-mediated immunity alone was responsible for this acquired resistance.

The immunity transferred by an initial infection is today utilized in the form of vaccination with BCG. BCG is derived from a virulent strain of *M. bovis* initially attenuated by cultivation on a potato–glycerine–bile medium for 230 serial transfers [58], thus achieving immunogenicity without pathogenicity. BCG confers immunity by activation of macrophages within the reticuloendothelial organs of the immunized host, with resultant limitation of mycobacterial growth on subsequent challenge [59]. The immune host (whether protected by previous infection or BCG) is not protected from subsequent infection [60] but in such a host the rate of growth of *M. tuberculosis* is slowed compared with that seen in non-immunized controls [61].

As already mentioned, acquired immunity is mediated by T cells, almost certainly Th1 cells [62], which reach the tubercle from the spleen and lymph nodes [53]. On contact with antigen processed by macrophages in the tubercle, lymphokines such as interleukin 2 and interferon  $\gamma$  [62] are released and activate blood-derived monocytes entering the lesion. These activated macrophages show structural, enzymatic and metabolic changes [63] and phagocytose and kill tubercle bacilli at a markedly enhanced rate compared with unstimulated cells. The central role of T cells in mediating this antituberculous response can be seen in the inability of T cell-depleted mice to develop tuberculin hypersensitivity or resistance to tuberculous infection following challenge with tubercle bacilli [64].

The positive tuberculin skin test is the earliest indicator of infection with tuberculosis [65]. It is not a universal finding in patients with clinical tuberculosis and it is critical to note that a negative tuberculin test does not exclude tuberculosis [66,67]. Numerous reports have documented the occurrence of negative tuberculin tests in patients with tuberculosis, particularly in those with miliary tuberculosis [68], cryptic miliary tuberculosis [69–72] and extensive

disease [73] and in older patients [74,75]. The presence of anergy may be due to the activation of suppressor lymphocytes [76] or the presence of a population of adherent cells, presumably macrophages, with suppressor properties [77,78]. Alternative explanations include defects in lymphokine production and compartmentalization of sensitized lymphocytes [79]. As a rule, tuberculin anergy, whatever its cause, disappears after successful treatment of the underlying disease [66,80,81].

It has been suggested that tuberculosis, like leprosy, is a disease with a wide immune spectrum [82]. Most patients, for example those with tuberculoid leprosy, develop disease characterized by granuloma formation and cellular hypersensitivity documented by a positive tuberculin test. A few patients, for example those with cryptic miliary tuberculosis, present with a pattern of disease akin to lepromatous leprosy where bacillary multiplication is uncontained and skin tests are negative. These patients are anergic, both *in vivo* and *in vitro* (when cultured lymphocytes are stimulated by either antigen or mitogen), and have augmented B-cell antibody-mediated responses [83,84]. Lenzini *et al.* [85] have attempted to correlate the immune with the clinical spectrum of tuberculous disease. Although the extremes of their spectrum (UU, unreactive; RR, reactive tuberculosis) are readily recognizable in the terms described above, their intermediate categories (RI, reactive intermediate; UI, unreactive intermediate) are less convincing on clinical grounds. Nevertheless, the classification draws attention to unreactive disease, which is likely to be increasingly prevalent in developing countries as reactivation occurs in an ageing population.

### Patterns of presentation: the timetable of tuberculosis

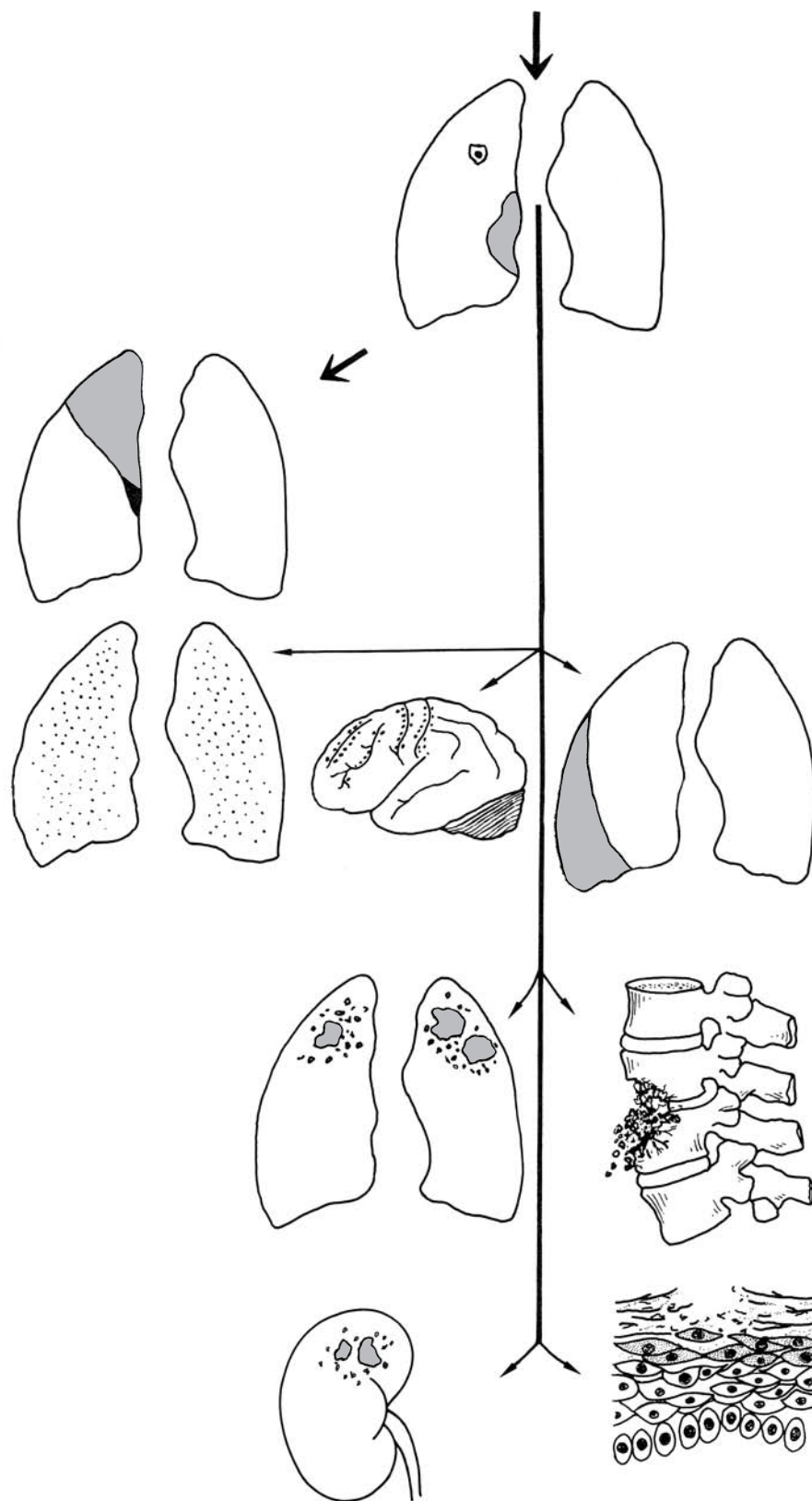
Most primary tuberculous infections heal spontaneously and are contained by the body defences described above. There may be no residua visible on the chest film or there may be variable calcification of the primary lesion and complex. In some patients there may be sequelae to the primary tuberculous infection and, in general, these tend to conform to a 'timetable of tuberculosis' (Fig. 16.3). Wallgren [86] described this timetable in Sweden in 1948 in the era before chemotherapy or BCG when the majority of cases of tuberculosis occurred in the young; for example in Scotland in 1949, 50% of pulmonary and 74% of extrapulmonary notifications were aged under 25 years [87]. The timetable is presumably still largely applicable to the high-prevalence countries of the developing world but should be applied with caution to manifestations of tuberculosis in the developed world, for example in Scotland in recent years only 12% of tuberculosis cases were aged less than 25 years and 38% were over 65 years [88]. These elderly cases of tuberculosis probably represent reactivation disease developing many decades removed from the

Tuberculin test becomes positive.  
Minority of those infected experience  
febrile illness and erythema nodosum.

Miliary and meningeal tuberculosis  
common in children under 5 years:  
pleural effusion rare in children.  
Usually within 6–12 months, after  
primary infection.

Adult (post-primary) disease and skeletal  
disease commonly occurs 1–5 years later.

Genito-urinary and skin lesions are  
late manifestations after 5–15 years.



**Fig. 16.3** Natural history of untreated primary tuberculosis: the timetable of tuberculosis. See text for explanation.



primary infection and occur with both pulmonary and non-pulmonary disease [89–91]. These cases, as well as cryptic miliary disease [91], could be described as 'stations further along the line' on Wallgren's timetable [88].

In children especially, enlarged hilar lymph nodes may compress or erode bronchi with resultant lobar consolidation and collapse, a phenomenon formerly called epituberculosis. Miliary tuberculosis and tuberculous meningitis, which was frequently associated with miliary tuberculosis, occurred usually within 6 months of the primary infection and were especially common in children under 5 years. Meningitis is also sometimes a terminal event in cryptic miliary disease in the elderly. Pleural effusion, presumably due to seeding of the pleura from a lung focus, also occurred early, usually within 6–12 months, and was commoner in young adults and unusual in small children. In young adults the primary disease could progress, with increasing infiltration and cavitation evident 1–2 years or even later after the primary infection. This type of disease was labelled progressive primary or postprimary disease and occurred most commonly at puberty. Skeletal tuberculous lesions, most commonly of the spine, could also present 1–5 years after the primary infection. Lesions of the genitourinary tract [92] and the skin made their appearance much later, commonly 5–15 years after the primary infection. The most common type of disease seen in developed countries today, postprimary or reactivation disease of late middle age or the elderly, is due to reactivation of apical pulmonary foci that were seeded at the time of the primary infection, have lain dormant and then present with progressive cavitating pulmonary disease many decades after the initial primary infection. Finally, cryptic miliary tuberculosis or anergic tuberculosis of the elderly is an extreme variant of reactivation tuberculosis that also presents late in life and may be associated with an entirely normal chest radiograph.

Important information is available on the development of clinical tuberculosis following primary infection acquired during adolescence, based on the British Medical Research Council's tuberculosis vaccines trial [93,94]. There were 54239 participants in this trial aged 14–15.5 years on entry in 1950–52. Of the 32282 participants who were tuberculin negative (to 100 tuberculin units, TU) with a normal chest film, 12867 chosen at random were left unvaccinated and were followed by means of periodic tuberculin tests and chest films for about 10 years; cases of tuberculosis developing among them were recorded for a total of 20 years. Taking 8 mm of induration or more to 3 TU as indicative of infection with tuberculosis (a fairly strict criterion), 1335 of the 12867 participants were infected and 108 cases of clinical tuberculosis (or 8.1% of those infected) developed in the 10 years following the primary infection. In total 243 cases of tuberculosis developed among all the initially tuberculin-negative partici-

pants within 15 years of entry [93]. Of these 243 cases, 54% had developed disease within 1 year and 80% within 2 years of infection as shown below [94]:

First year, 54%

Second year, 24%

Third year, 9%

Fourth year, 5%

Fifth and sixth years, 3%

Seventh and eighth years, 3%

Ninth year and above, 1%.

The greatest risk of disease following primary infection was therefore within the first 2 years. The nature of disease in those with clinical tuberculosis is shown in Table 16.1. The striking feature is the high incidence of cavitary disease in these progressive primary lesions. The high incidence of pleural effusion and low incidence of non-pulmonary tuberculosis are also of interest. Further analysis of these data [94] demonstrated the interval from infection to onset of disease for the different forms of the disease (Table 16.2). These findings are in keeping with Wallgren's timetable [86], with more miliary tuberculosis or meningitis occurring in the first year than the pulmonary forms of the disease and relatively less of the other non-pulmonary tuberculosis occurring in the first year. With tuberculosis, as with any other disease, there are of course no absolute rules of behaviour, but these figures illustrate in general terms much of what was known about the natural history of the disease before specific interventions were applied.

## Epidemiology

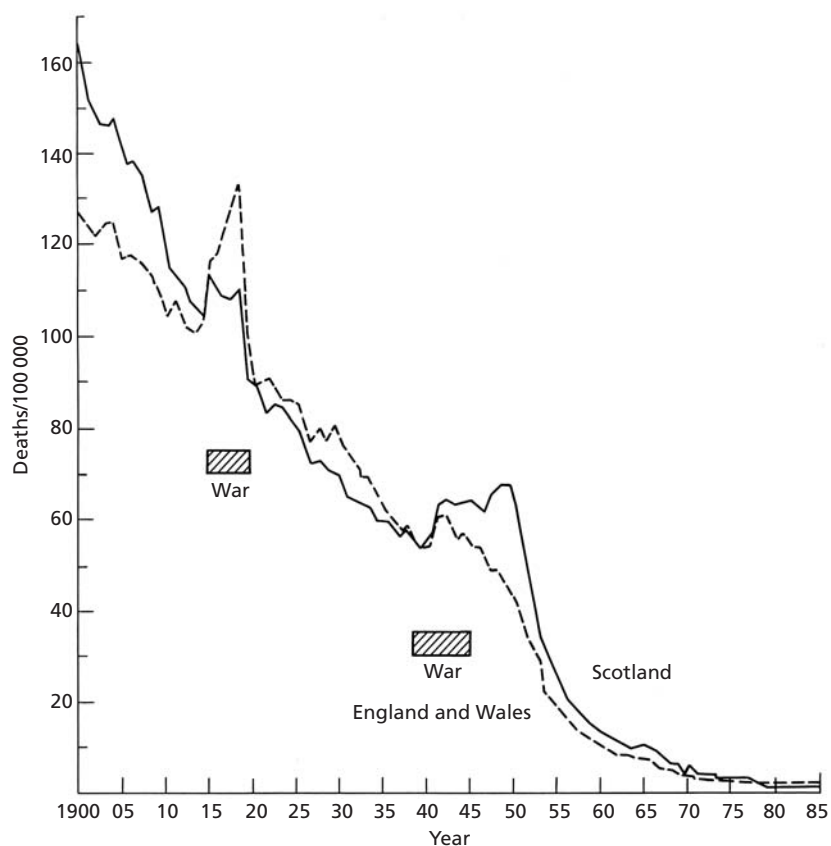
Keeping track of tuberculosis is not easy but not impossible. Historically, death rates from tuberculosis were the obvious indicators; however, at present, mortality from tuberculosis is less common in developed countries and though common in developing countries is poorly recorded. In both situations the mortality rate from

**Table 16.1** Nature of disease developing in the 243 initially tuberculin-negative patients followed for 15 years in the British Medical Research Council vaccines trial. (From Medical Research Council [93] and Sutherland [94].)

	No.
Tuberculous meningitis	5 (2%)
Pulmonary tuberculosis	
Miliary	5 (2%)
Non-miliary with cavitation	52 (21%)
Non-miliary without cavitation, extensive lesions	11 (5%)
Non-miliary without cavitation, less extensive	100 (41%)
Pleural effusion	51 (21%)
Non-pulmonary tuberculosis	19 (8%)

	Total no.	Cases in first year	
		No.	Percentage
Miliary tuberculosis, meningitis	10	7	70
Pleural effusion	51	28	55
Pulmonary tuberculosis: no cavitation	111	59	53
Pulmonary tuberculosis: cavitation	52	30	58
Non-pulmonary	19	8	42
Total		132	54

**Table 16.2** Form and timing of disease onset in the 243 cases of tuberculosis reported in the British Medical Research Council vaccines trial. (From Medical Research Council [93] and Sutherland [94].)



**Fig. 16.4** Death rates for respiratory tuberculosis in Scotland and in England and Wales 1900–85.

tuberculosis is not the appropriate parameter by which to judge the prevalence of tuberculosis.

### Mortality rates

In the past, mortality figures were recorded and had value. Even before the tubercle bacillus was isolated in 1882 the reported mortality from tuberculosis in England and Wales was falling by about 1% annually between 1861–65 and 1876–89 [95]. The rate of fall increased in subsequent years in developed countries in the absence of any specific form of intervention. The fall has been attributed to changes in social circumstances, with improvements in nutrition and more particularly alleviation of overcrowding. Mortality from tuberculosis in Scotland and England

and Wales is shown in Fig. 16.4. The continuing decrease in mortality with time is only partly attributable to the introduction of adequate chemotherapy in the early 1950s. Adverse social influences are seen in the documented increases in mortality during the two world wars; favourable social influences, though unquantifiable, have undoubtedly operated since and these, along with improvements in case detection and chemotherapy, have improved the mortality figures.

Deaths still occur from tuberculosis in developed countries [96]. In the USA almost 10% of patients with tuberculosis in 1983 were recorded as dying from the disease [97]; in the UK 15% of white patients with tuberculosis died, although review of death certificates revealed that only half of these patients actually died from, rather than with,

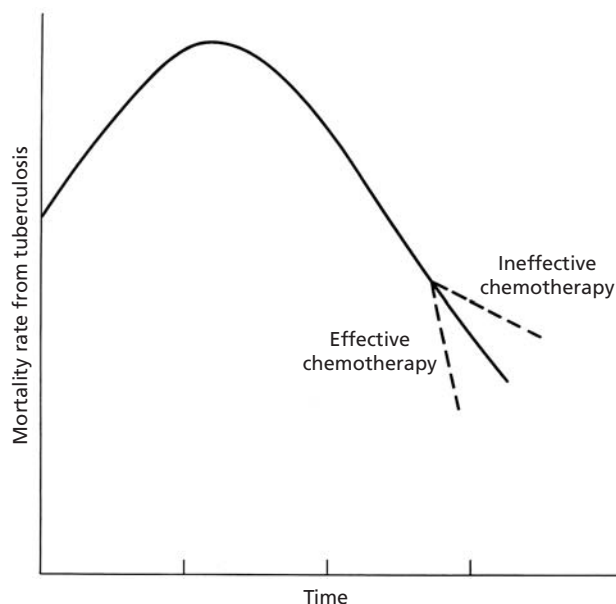
tuberculosis [12,98]. Patients who die in developed countries tend to be older and to have reactivated pulmonary tuberculosis; often there is delay in diagnosis to the extent that it may only be made at autopsy [96–98].

Gryzbowski [99] has outlined his view of the impact of a tuberculosis epidemic on a population (Fig. 16.5). An initial soaring increase in mortality eventually reaches a plateau and subsequently declines without intervention. This may be due to the elimination of susceptible individuals and natural selection. The decline in mortality will continue and can be accelerated by effective chemotherapeutic intervention; ineffective chemotherapy may actually slow the rate of decline by generating a population of infectious individuals who transmit drug-resistant bacilli to the population at large. The possibility that the ineffective application of chemotherapy in the epidemic of HIV-associated tuberculosis in the developing world may exacerbate the tuberculosis problem via this mechanism is one of the reasons why the WHO declared tuberculosis a global emergency in 1993 [100].

The characteristics of an epidemic of tuberculosis at its height are:

- 1 high rates, such as 1% mortality per annum, 1–2% incidence and an annual risk of infection of 15–25%;
- 2 no high-risk groups, although young adults are most often affected;
- 3 most disease is due to recent infection.

This contrasts with countries where tuberculosis is in decline, which are characterized by low rates and high-risk groups such as older men, where disease is due to reactivation rather than recent infection. Alaska is an



**Fig. 16.5** Impact of a tuberculosis epidemic on mortality from tuberculosis in a population. See text for explanation. (From Gryzbowski [99].)

example of a population in which tuberculosis mortality reached a plateau during the period from the 1920s to the 1950s with a death rate of 650 per 100 000, tuberculosis accounting for 35% of all deaths among Eskimos [101,102]. Case finding and treatment have since made a dramatic impact on these figures [103], thus emphasizing what can be achieved if chemotherapy and public health measures are properly utilized.

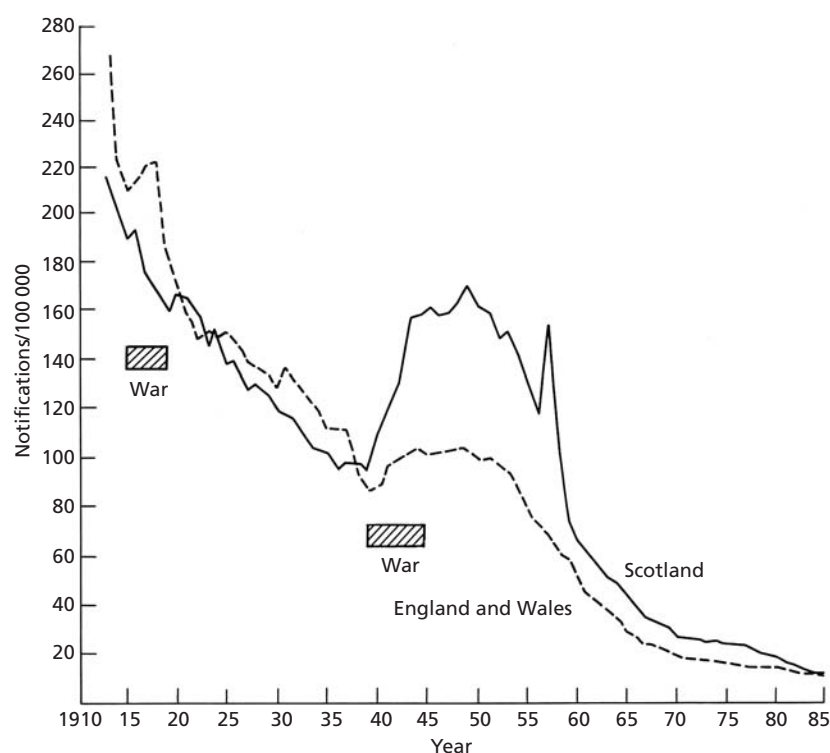
### Notification rates

If death rates are of little value in assessing the epidemiological behaviour of tuberculosis, then what of notification rates? Notification of tuberculosis has been compulsory in most developed countries for over half a century but is not yet reliably established on a national basis in most developing countries. Notification rates mirror mortality rates, with a decline well established before the introduction of chemotherapy and corresponding increases in rates during the two world wars. Local notification practices vary, making comparison even within, and certainly between, countries difficult. The author's own experience of patients notified as having pulmonary tuberculosis confirms the finding that 50–60% of patients have positive cultures to support the diagnosis [104]. Many have suggestive pulmonary lesions, positive tuberculin tests and an appropriate response to chemotherapy although bacteriologically negative. A few have primary tuberculosis and negative bacteriology and some are notified because they have only a positive tuberculin test and are contacts of an infectious case. The latter should not be included in notification rates. Notification rates are not necessarily the most reliable indicators of the extent of tuberculosis in the community but where practices of notification are consistent they may well be the most easily obtained indices of trends of disease. As the result of an initiative by the International Union Against Tuberculosis and Lung Disease and the WHO, the definitions of cases of tuberculosis to be notified and utilized for the purpose of surveillance have recently been clarified and are given in Table 16.3 [105].

The trends of notification rates with time for Scotland and England and Wales are shown in Fig. 16.6. In both

**Table 16.3** Case definitions for tuberculosis recommended for surveillance purposes. (From Rieder *et al.* [105].)

Definite case: culture-confirmed disease due to <i>Mycobacterium tuberculosis</i> complex
Other than definite cases: must meet both of the following criteria:
Clinical judgement that the patient's clinical and/or radiological signs and/or symptoms are compatible with tuberculosis
Clinical decision to treat with a full course of antituberculosis chemotherapy



**Fig. 16.6** Notification rates for respiratory tuberculosis in Scotland and England and Wales 1913–85.

Region	People infected (millions)	New cases	Deaths
Africa	171	1 400 000	660 000
Americas*	117	560 000	220 000
Eastern Mediterranean	52	594 000	160 000
South-East Asia	426	2 480 000	940 000
Western Pacific†	574	2 560 000	890 000
European and other industrialized countries‡	382	410 000	40 000
Total	1722	8 004 000	2 910 000

\* Excluding USA and Canada.

† Excluding Japan, Australia and New Zealand.

‡ USA, Japan, Australia and New Zealand.

**Table 16.4** The global toll of tuberculosis, 1989–90. (From Anon. [2].)

countries a downward trend of 8–10% per annum continued from the 1950s until the mid-1980s, when tuberculosis notifications plateaued [106,107]. A similar phenomenon has been observed in other European countries [108] as well as in the USA [109]. The reasons for this reversal of the downward trend in notifications varies for each country: in Holland and Switzerland, for example, immigrants and refugees form a significant proportion of notifications [110]; in the USA, HIV and a decline of tuberculosis control services has been implicated [8]. In Scotland, immigration and HIV are not causes, although more tuberculous disease among the growing numbers of an increasingly elderly older population may be a factor [111]. In England and Wales, the picture is less clear but urban overcrowd-

ing, immigration and deprivation may all be factors [112,113].

The global toll of tuberculosis in terms of new cases (or estimated notifications) and deaths is given in Table 16.4 and the estimated worldwide notification rates are shown in Fig. 16.7. Notification rates of greater than 100 per 100 000 are almost universal in Africa and Asia and are also found in parts of South America. Finally, Fig. 16.8 shows the relationship of notification rates to age and sex for a rural south Indian population and the white and non-white population in the USA [114,115]. Male and female rates are much the same from childhood through young adult life. Thereafter male rates become increasingly greater than female rates. In the USA, non-white

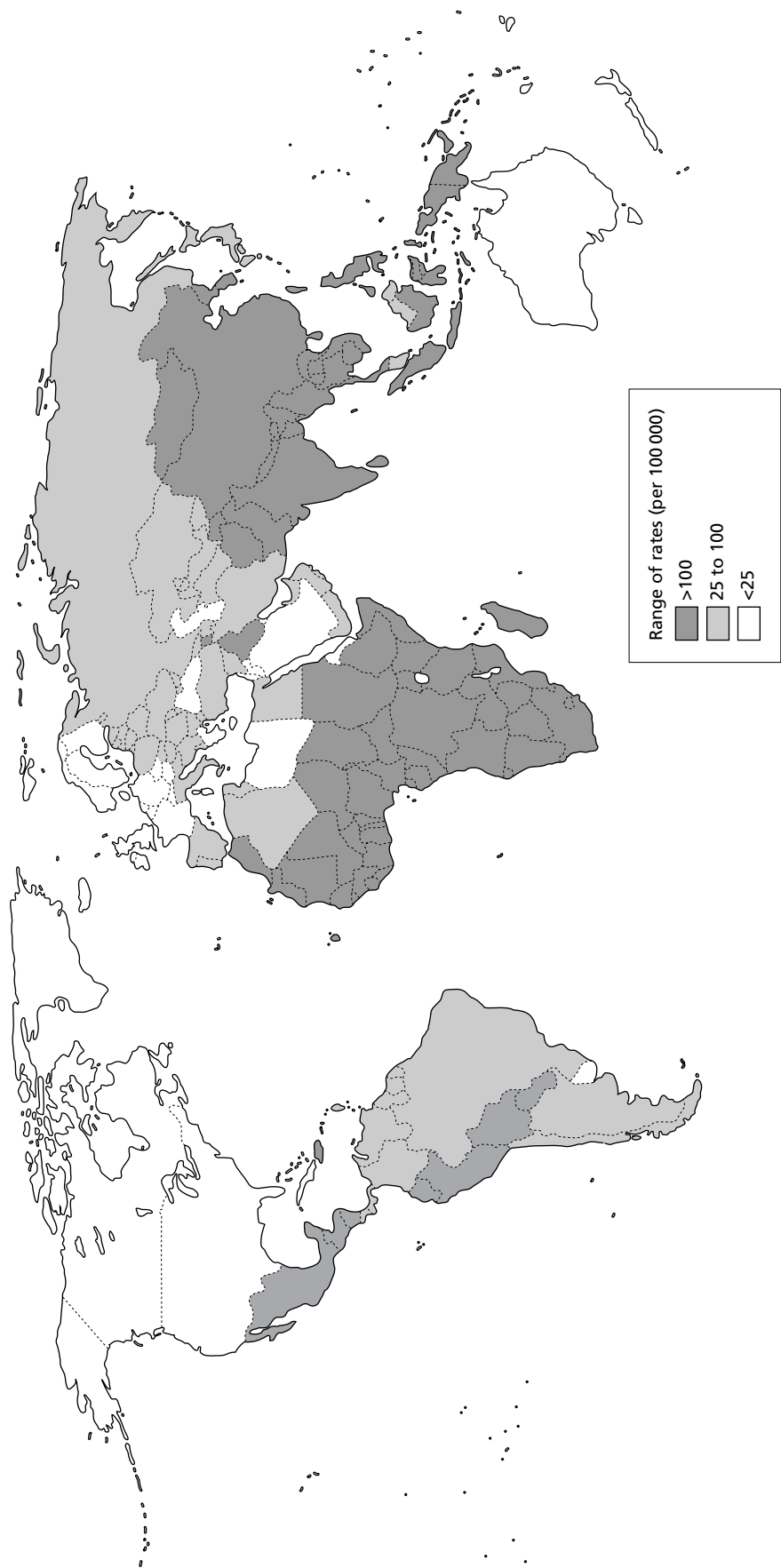


Fig. 16.7 World estimated tuberculosis notification rates 1990. (From WHO.)

rates for both sexes are consistently higher than those for whites.

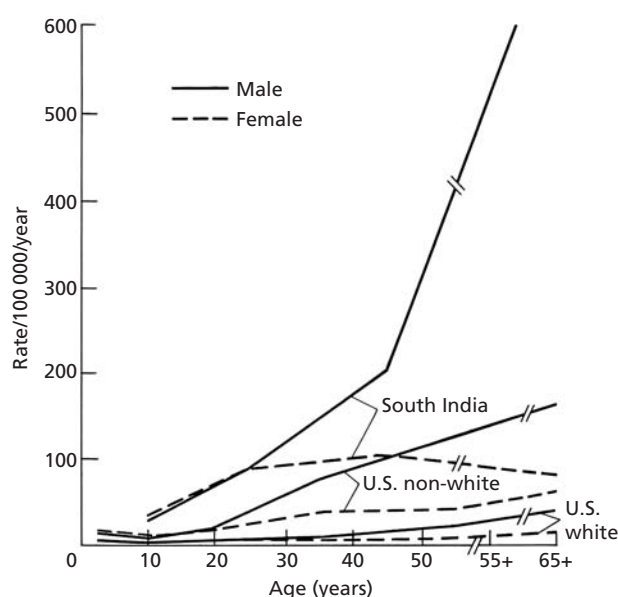
### Risk of tuberculous infection

The annual tuberculosis infection rate or annual risk of infection is the best single indicator of the status and trend of tuberculosis in both developed and developing countries. It indicates the proportion of the population that will be primarily infected or reinfected in the course of 1 year and is usually expressed as a percentage. The rate is derived from the results of tuberculin testing (see later) [116–118], and to obtain reliable estimates of rates and changes over a particular period several tuberculin

surveys are required at intervals in representative samples of non-BCG-vaccinated subjects of the same age who are tested by the same technique. In countries with high rates of infection, only a small sample of children, say 4000 aged 10 years, would be needed to estimate the rate. Where the prevalence of tuberculous infection is low, a larger sample of older children would be needed.

The risk of tuberculous infection in developed countries is now very low, being less than 0.5% per annum in the majority, 0.1–0.3% in most and less than 0.1% in a few countries [119]. The risk of tuberculosis in these countries continues to decline by about 10% per year, studies from The Netherlands suggesting that the trend in risk has closely followed an exponential decline for the last 25 years [120].

In developing countries much higher rates are found. The annual risks of infection for the richest and the poorest countries are shown in Table 16.5 [2]. In most industrialized countries the annual rate of infection is now below 0.1% and continues to decline by 10% per annum. In sub-Saharan Africa, the annual risk of infection may be as much as 2.5% or more, and in the present context of increasing tuberculosis notifications due to the HIV epidemic is increasing rather than decreasing. The most striking decrease in the risk of tuberculous infection ever recorded is that seen in the native population of Alaska between 1950 and 1970 when the rate fell from 25% to 0.3% [121], a valuable illustration of the impact that efficient antituberculosis measures can have even in high prevalence areas.



**Fig. 16.8** Tuberculosis notification rates by sex and age, south India, 1961–68; and by race, sex and age, USA, 1978. [From National Tuberculosis Institute Bangalore [114] and Centers for Disease Control [115].]

### Trends in the pattern of tuberculous infection

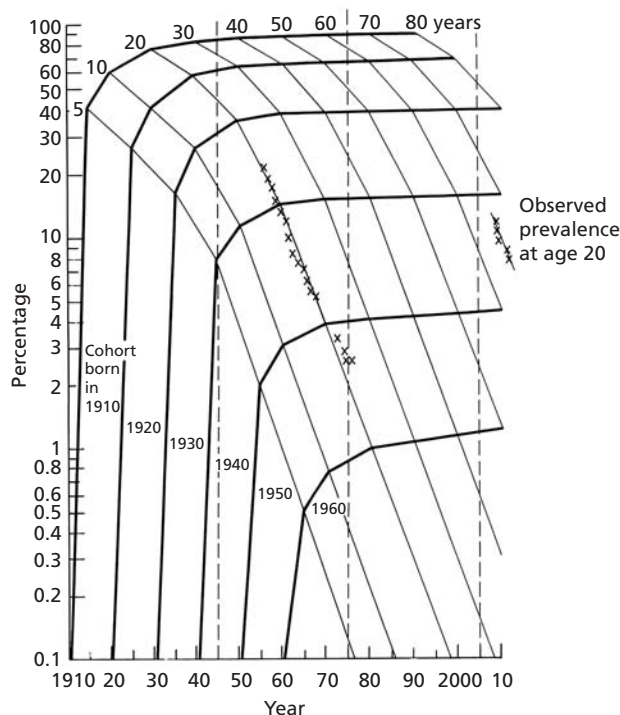
#### Developed countries

Styblo [122] has estimated the number of persons infected annually with tubercle bacilli in the decades from 1910 to 1975 in The Netherlands; this fell from 11 310 per 100 000 in 1910 to 25 per 100 000 in 1975, a decrease of 99.88%. This

Areas	Annual risk of infection		Health resource availability
	Current level (%)	Annual decline trend (%)	
Industrialized	0.01–0.1	>10	Excellent
Middle income in Latin America, West Asia and North Africa	0.5–1.5	5–10	Good
Middle income in East and South-East Asia	1.0–2.5	<5	Good
Sub-Saharan Africa and Indian subcontinent	1.0–2.5	0–3	Poor

**Table 16.5** The epidemiological pattern of tuberculosis: annual risks of tuberculosis infection 1989–90. (From Anon. [2].)

dramatic change in the risk of tuberculous infection in The Netherlands (and by implication in other developed countries) has led to profound changes in the prevalence of infection in the indigenous population. The estimates of prevalence of tuberculous infection in the cohorts born in the year 1910 and succeeding decades for those aged 5, 10, 20, 30, . . . , 80 years are shown in Fig. 16.9. For individual cohorts each curve is similar, in that it rises steeply during childhood, less steeply during adolescence and after about 25 years of age is very nearly flat. The prevalence of tuberculous infection at individual ages has changed substantially during the 50 years. For example, the prevalence of infection at age 20 years was 77% for the cohort of 1910 but had decreased to 3.8% for the cohort of 1950 and would have decreased to about 1% for the cohort of 1960 (in 1980). The prevalence rates have also fallen steeply for 30–40 year olds but in 50-year-olds they remained unchanged at about 85% until the 1960s when they reached their 'turning point', with the present rate now being about 50%. For 70 year olds it is possible to calculate from the figure that it will take about 30 years before an infection rate of only 20% will be achieved. These estimates are clearly useful in illustrating how the pattern of infection changes with time by age cohorts in a developed country and allow one to forecast the extent of tuberculous infection in the future, assuming that the present pattern of declining risk continues. At present, in most developed

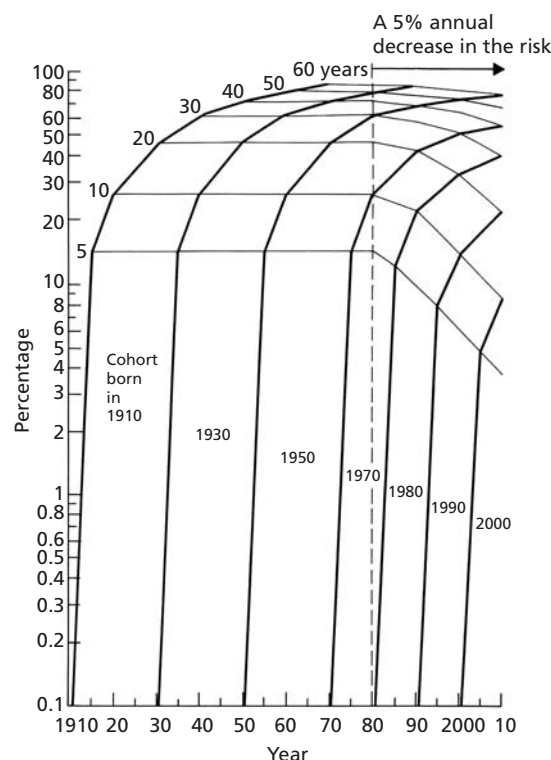


**Fig. 16.9** Estimated prevalence (%) of tuberculosis infection in cohorts born 1910–60 in 1945, 1975 and 2005, The Netherlands. See text for explanation. (From Styblo [122].)

countries, any rise in tuberculosis notifications secondary to HIV infection has not influenced trends in annual risk of tuberculous infection.

### Developing countries

With certain assumptions, estimates of prevalence with a similar pattern can be derived for the developing countries. Assuming an average annual infection rate of 3% and a 5% annual decrease in risk from 1981 to 2010 (an optimistic assumption in the light of the impact of the HIV epidemic), it is possible to illustrate how tuberculous infection might behave in the future in a developing country (Fig. 16.10). Up to 1980 the prevalence of infection remains constant for all age groups; however, with the assumption of a 5% decrease in the annual risk of infection, decreases in prevalence are seen so that, for example, only 14% of 10-year-old children born in 1990 will be infected in 2000 compared with 26% of the cohort born in 1970. It can be calculated that a 5% annual decrease in the risk of tuberculous infection would reduce the overall risk of infection from 3% in 1980 to about 0.7% in 2010, thus beginning to approach the situation currently found in developing countries. The value of estimating not only the



**Fig. 16.10** Calculated prevalence (%) of tuberculous infection in a developing country for cohorts born in 1910, 1930, 1950, 1970, 1980, 1990 and 2000 at ages 5, 10, . . . , 60 years assuming a constant decrease in risk between 1981 and 2010. See text for explanation. (From Styblo [122].)



risk of tuberculosis in developing countries but also its trend, both as a measure of the impact of antituberculosis programmes and as a predictor of the future extent of tuberculous infection in the community, is thus seen.

### Risk of disease after infection

Time trends in the risk of developing tuberculosis after infection are difficult to ascertain because of differences in tuberculin testing methods, criteria for a positive reaction and the age structure of the populations. However, among untreated tuberculin-positive household contacts of active cases the annual new case rate was 1220 per 100 000 in the first year, falling to 310 per 100 000 for the next 2 years and finally to 160 per 100 000 in the sixth and seventh years [123]. This finding confirms the observation in the British Medical Research Council study that the majority of cases occur in the first year after infection [93,94].

Geographic variation in the extent of disease after infection is well recognized and largely unexplained. In untreated tuberculin-positive Eskimo reactors, attack rates of over 1500 per 100 000 were recorded in the first year of observation [123]. This compares with attack rates of 101 per 100 000 in south India [114], 61 per 100 000 in Georgia and Alabama [124] and only 29 per 100 000 in Denmark [125].

Case rates among tuberculin reactors vary markedly with age [123,126,127], being high in the early years of life, troughing at 10–12 years of age and peaking again in late adolescence and early adult life. Thereafter case rates decrease to a relatively low level that persists into old age.

### Impact of HIV infection on the epidemiology of tuberculosis in developing countries

HIV infection is remarkably common in the developing world [6]; surveys of apparently healthy blood donors and other subjects have shown prevalences of HIV positivity as high as the 23.5% of women in the Rakai district of Uganda [128]. In the developing world the principal mode of transmission of HIV infection is heterosexual [128] so that the young and sexually active are infected; the WHO has calculated that over 9 million adults were infected with HIV in Africa by December 1993, 2.5 million in Central and South America and 2 million in South-East Asia and the Western Pacific [6]. Since most (82%) of the 1700 million infected worldwide with tuberculosis are found in the developing world, a substantial minority, if not a majority, of those acquiring HIV infection will already have been infected with tuberculosis [3]. The relative risk of developing active tuberculosis in those dually infected lies between 6 and 100 [129] and is over 20 in two studies of Zairean and Rwandan women [130,131]; in Haiti the risk ratio was 16 [132].

Most disease occurring in the dually infected is believed to be due to reactivation of pre-existing tuberculosis infection, although evidence is mounting that, especially in high-prevalence areas, disease due to new or reinfection with tuberculosis may occur in those infected with HIV [133–135]. On the basis of available information it is possible to calculate on a conservative basis that tuberculosis cases will increase by 50–60% in sub-Saharan Africa by the year 2000 [136]; this is borne out by reports of annual notifications from several of these countries (Fig. 16.11) and is being monitored by measuring the annual risk of infection in Tanzania [137]. Surveys of HIV infection in tuberculosis patients in Zambia [138], Kenya [139] and Uganda [140] have shown HIV seropositivity in 27–50% of patients. HIV-associated tuberculosis is no more infectious than non-HIV-associated tuberculosis [141].

The clinical features of HIV-associated tuberculosis are given in Chapter 17 and the treatment of HIV-associated tuberculosis is discussed in Chapter 19. Preventive therapy for HIV-positive patients is discussed later in this chapter under chemoprophylaxis.

### Measurement of infection: tuberculin skin testing

Tuberculin, a broth culture filtrate of tubercle bacilli, was first prepared by Robert Koch in 1880 and wrongly promoted as a cure for tuberculosis [142]. Subcutaneous injection of tuberculin into patients with tuberculosis resulted in severe systemic upset whereas non-tuberculous individuals showed few or no symptoms. The original preparation of old tuberculin was used until the 1930s when Seibert prepared a purified protein derivative (PPD). This

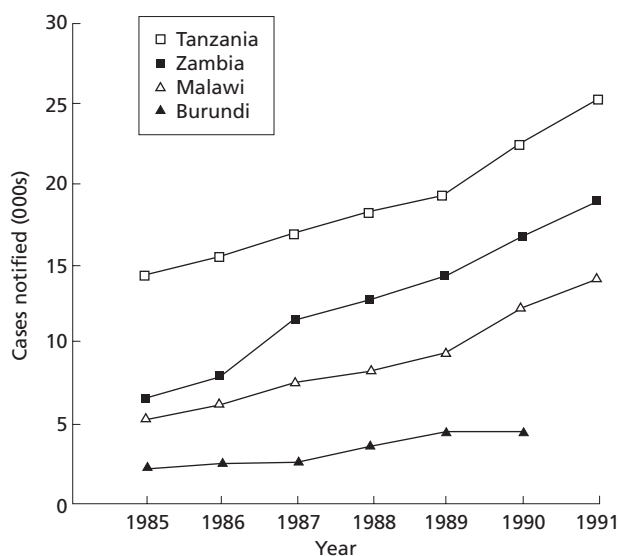


Fig. 16.11 Rise in annual notifications of all forms of tuberculosis in four African countries 1985–91 (WHO, unpublished data).

proved to be a potent, stable tuberculin without sensitizing properties and in 1941 a single large lot of PPD from a single strain of the human tubercle bacillus was made [143] and deposited as the International Standard for Purified Protein Derivative of Mammalian Tuberculin to be known as PPD-S. Other standard PPDs include PPD-RT23 prepared in Denmark for international use and the British Standard preparation known as PPD-Weybridge. Problems with the adsorption of tuberculin to glass and plastic surfaces that resulted in false-negative reactions have been resolved by the addition of small quantities of the detergent Tween 80 to the solution. The use of the tuberculin test has been reviewed extensively [144–47].

### Specific and non-specific tuberculin skin reactions

The early days of tuberculin skin testing were plagued by the problem of false-positive skin reactions [144]. In 1941, a study of quantitative tuberculin skin sensitivity in various Ohio and Minnesota populations was published [148]. This study found that almost everyone would react to tuberculin if sufficiently high doses were used for testing. However, patients with tuberculosis and many of their contacts reacted to a relatively low dose of PPD, whereas those without tuberculosis or lacking contact reacted only to higher doses. It was concluded that high-dose reactions were probably 'not due to infection with the tubercle bacillus'. As a result of this and other corroborating studies the dose of 0.1 µg of PPD or 5TU became accepted in North America as the dose most likely to distinguish true from false positives. Application of the 5-TU skin test and a 250-TU skin test to student nurses throughout the USA confirmed the value of the test [149]. The nurses were divided into three groups on the basis of their tuberculosis contact status: no contact, intermediate contact and close contact. Positive reactions to 5TU increased from 10% in those with no contact to 41% in those with close contact, whereas similar numbers in all three groups had positive reactions to 250 TU. The positive findings with 5TU were similar in both northern and western states and in south-eastern states. However, positive reactions to 250 TU were 29% in northern and western states but 67% in south-eastern states, leading to the con-

clusion that the sensitivity elicited by high doses of PPD-S represented infection by a different but antigenically related organism that was highly prevalent in some geographical areas (south-eastern USA) and apparently was not pathogenic for humans.

Using the Mantoux technique with 5TU of PPD-S or its equivalent, surveys of tuberculosis patients throughout the world have shown a remarkable degree of concordance in the size of skin reactions [150]. There is a normal distribution of reactions, with a mean ranging from 12.8 mm in south India to 18.8 mm in the Sudan (Fig. 16.12). In the general population the problem of how to interpret the size of the skin reaction to 5TU remains and is well illustrated by reference to studies in tuberculous patients and US Navy recruits [151–153]. In the patients with tuberculosis, with the exception of a few who failed to react, the distribution of reactions to 5TU is essentially normal with a single mode at induration sites of 16–17 mm in diameter (Fig. 16.13a). In US Navy recruits with household exposure to tuberculosis the distribution of reaction sizes is bimodal (Fig. 16.13b), with the right-hand portion similar to reaction sizes of tuberculosis patients but at a much lower level. In Navy recruits who deny household exposure to tuberculosis there is no evidence of bimodality of reaction sizes, with a majority of low reaction sizes (Fig. 16.13c). However, it is possible to sketch in the hidden right-hand portion of the distribution caused by tubercu-

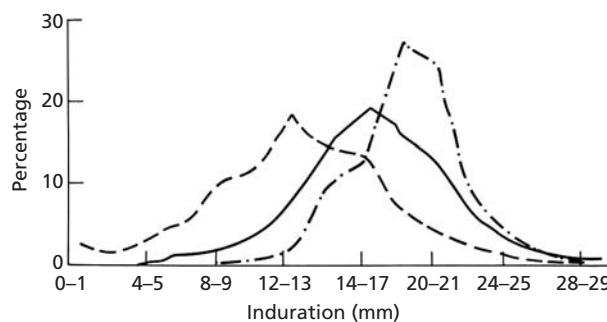
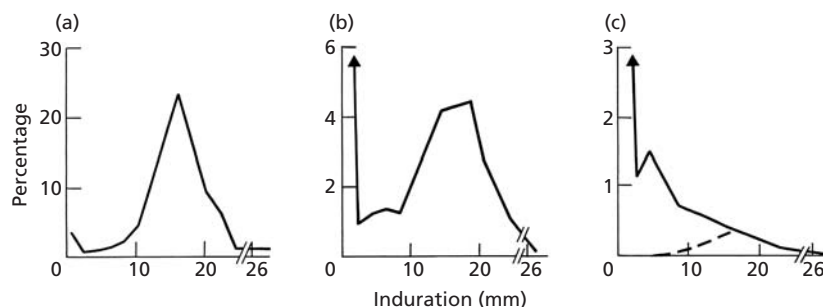


Fig. 16.12 Frequency curves of sizes of reactions to 5 TU of PPD for patients in tuberculosis hospitals in Sudan (—•—), south India (---) and averaged for all countries (—). (From WHO Tuberculosis Research Office [150].)

Fig. 16.13 Percentage distribution of diameters of induration to 5 TU of PPD-S: (a) tuberculous patients with positive sputum cultures; (b) white male US Navy recruits, 17–21 years of age, with a history of contact with tuberculosis; (c) white male US Navy recruits, 17–21 years of age, with no history of contact with tuberculosis (note different scales on y axes). (From Comstock *et al.* [152], Rust & Thomas [153] and American Thoracic Society [154].)



lous infections. From these studies it is clear that if the level of positivity for the 5TU test is set at 10mm, most cases of tuberculous infection or specific skin test reactions will be included. However, there is an overlap at 5–10mm of induration of non-specific and specific tuberculin reactions. This has led to the recommendation that where the index of suspicion for tuberculous infection is high, as in close contacts of tuberculosis or in those with chest X-ray changes consistent with tuberculosis, then a reaction size of 5mm should be used to separate non-significant from significant tuberculin skin test reactions. If this is done, few persons infected with tuberculosis are classified as having insignificant reactions and few persons not infected with tuberculosis are classified as having significant reactions [145,154,155].

The cause of the non-specific or weak tuberculin reactivity clustered in the south-eastern USA is now thought to be infection with environmental atypical mycobacteria such as the *M. avium-intracellulare/scrofulaceum* complex organisms [156,157]. Skin testing of Navy recruits with PPD-S, PPD-B (an antigen prepared from the Battey bacillus, *M. intracellulare*) and PPD-G (an antigen prepared from the 'Gause' strain of *M. scrofulaceum*) showed that the geographical distribution of reactors to PPD-S was quite different to that of reactors to the atypical antigens [158]. PPD-S reactors were concentrated in large metropolitan areas, in Appalachia, along the Mexican border and in a few other isolated areas. In contrast, reactors to the atypical antigens were concentrated in the south-eastern USA.

Bimodal distributions of tuberculin reactions have now been reported from many countries [150,159,160], with considerable geographical variation. Non-specific sensitivity ranged from less than 10% in Denmark and northern USA to over 90% in the Philippines, the Sudan and Vietnam. It was relatively high (70–80%) in some parts of India and relatively low (20–30%) in England and Mexico.

### Techniques and interpretation of tuberculin tests

Tuberculin skin testing may be performed by the intradermal injection of PPD (Mantoux test) or with multiple puncture devices utilizing Old Tuberculin (Heaf and Tine tests).

#### Mantoux test

The Mantoux test is performed by intradermal injection of 0.1 mL of PPD containing 5 TU into the volar surface of the forearm using a 27-gauge needle with a plastic or glass syringe. The injection should be made just beneath the surface of the skin and produce a wheal of 6–10mm in diameter. The test is read at 48–72 h. The reaction consists of erythema and induration. The erythema should be dis-

regarded and the diameter of the induration measured in millimetres. Induration of greater than 10mm is virtually diagnostic of past or present tuberculous infection. Lesser degrees of induration may be due to non-specific sensitivity, but where the index of suspicion for tuberculosis is high (as discussed above) reactions above 5mm should be considered positive.

Where skin tests are performed in contacts of infectious cases of tuberculosis, subjects with initial skin test reactions of less than 10mm should be retested at 6 weeks, when an increase in reaction size to greater than 10mm and by an increase of at least 6mm is taken to indicate skin test conversion due to recent infection [161]. The classification and interpretation of skin reactions to 5 TU of tuberculin is shown in Table 16.6 [145].

In the UK, the Mantoux test has traditionally been performed with 10 TU of PPD. Induration of greater than 5 mm is considered to be significant and more than 15 mm to represent definite tuberculous infection (cf. Table 16.6). BCG vaccination is still universally employed in the UK and vaccinated individuals usually have positive Mantoux tests, with induration ranging from 5 to 14 mm. Induration greater than 15 mm in response to a Mantoux 10-TU test in a previously BCG-vaccinated individual should be considered to represent tuberculous infection (usually presumed subsequent to the BCG vaccination) [162].

**Table 16.6** Interpretation of skin-test reactions to the 5-TU Mantoux test. Reactions in the following categories of patients should be considered significant and indicative of tuberculosis infection.

---

#### *Induration >5 mm*

HIV-infected persons or persons with risk factors for HIV and unknown HIV status  
Persons who have had close recent contact with an infectious case of tuberculosis  
Persons who have chest radiographs consistent with old healed tuberculosis

#### *Induration >10 mm*

Persons with risk factors for tuberculosis other than the above, including the following:  
Foreign-born persons from high-prevalence countries  
Intravenous drug users  
Socially deprived or ethnic minority groups  
Residents of long-term care facilities  
Persons with medical conditions predisposing to tuberculosis, e.g. silicosis, gastric surgery, chronic renal failure, diabetes mellitus and immunosuppressive therapy  
Other high-risk populations

#### *Induration >15 mm*

Considered positive in all persons (including those who have had previous BCG vaccination)

---

### Heaf test

The multipuncture test of Heaf is carried out with an instrument (gun) that carries a small plate to which are fixed six short steel needles. A disposable head is available that performs favourably in comparison with the original fixed-head Heaf gun and its use avoids the need for sterilization [163]. On release of a spring the needles puncture the skin to a depth of 2 mm or, by adjustment, to a depth of 1 mm in children. Penetration of the tensed skin takes place through a thin film of applied solution, either PPD in a strength of 2 mg/mL or pure Old Tuberculin to each 1 mL of which one drop of 1:1000 epinephrine (adrenaline) has been added. The test is best read between 3 and 7 days, can be read and self-reported by the patient [164], and is graded as follows (Fig. 16.14).

Grade I: at least four separated papules.

Grade II: the papules are confluent to form a ring.

Grade III: the ring is filled in at the centre with induration that may spread outwards from the ring.

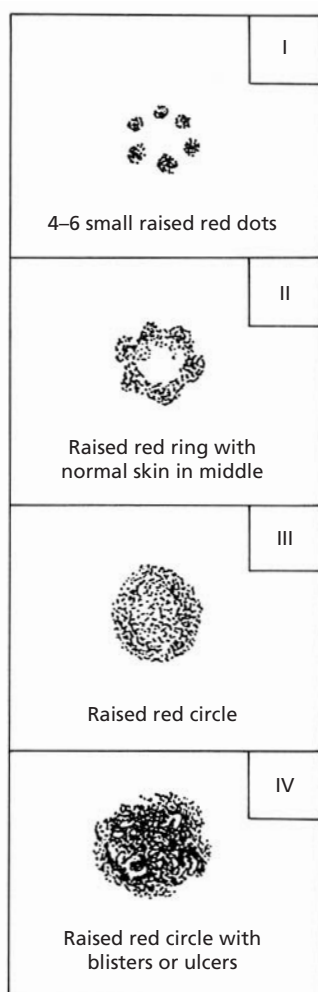


Fig. 16.14 Typical Heaf test reactions, grades I-IV.

grade IV: as for grade III with vesiculation or ulceration of the skin and extended induration.

Grade III and IV Heaf reactions are usually indicative of past or present tuberculous infection. Grade I and II reactions are not usually associated with infection by human tubercle bacilli and may be due to other mycobacteria [165]. In populations vaccinated with BCG most individuals develop Heaf grade I or II rather than grade III or IV reactions [166] (Fig. 16.15).

### Booster effect or phenomenon

Repeated tuberculin testing of non-sensitized individuals does not sensitize them to tuberculin [167]. Delayed hypersensitivity to tuberculin, once established by mycobacterial infection, may gradually wane over the years. A recent study in Edinburgh showed 55% Heaf grade III or IV reactors in the age group 45-65 years but only 37% positive at the same level in those aged over 65 [168], reflecting the gradual waning of skin-test reactivity with passing years [169]. Reaction to a tuberculin skin test many years after original infection may not be significant, although a subsequent test may prove to be positive, the lymphocytes having been 'switched on' by the initial test, giving an apparent 'conversion' or development of tuberculin hypersensitivity. This may be wrongly interpreted as a 'skin-test conversion' and hence primary tuberculous infection. As implied by the Edinburgh observations [168], the booster phenomenon is most likely to occur in middle or advanced age [169]. It can be seen as soon as 1 week after the initial stimulating test and can persist for 1 year

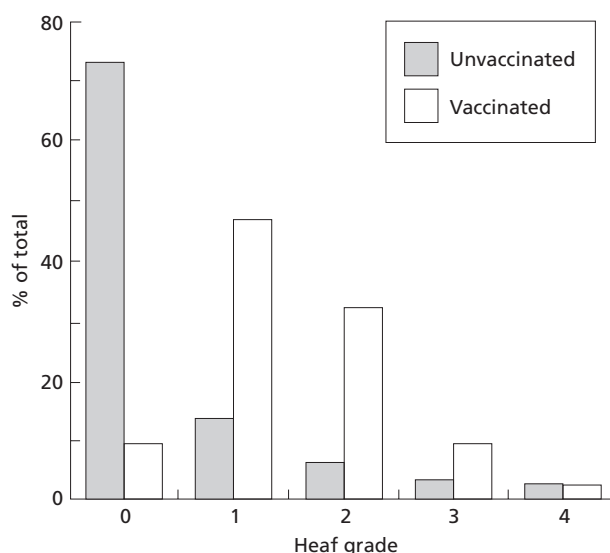


Fig. 16.15 Histogram showing percentage of reactions by Heaf grade in groups of children before and after receiving BCG vaccination. (From Davies & Leitch [147].)

or more [170]. Where repeat tuberculin tests are used in surveys (most commonly with hospital employees in the USA), it is important to eliminate this effect. Where employees are young (mean age 26) Valenti *et al.* [171] have shown that boosting (i.e. conversion of skin test at 1 week) does not occur. Where there is a wide range of ages in employees, apparent skin-test conversion is age related [172], reflecting the booster phenomenon; if boosters are eliminated, converter rates fall from 9% to 3% [173]. These conversion rates are still too high but err on the side of safety. A further study found a 5-year conversion rate of 7.1%. However, conversion was commoner in non-white 46–64 year olds of low social class and was considered to represent largely a contribution from boosting and, possibly, an indeterminate contribution from exposure in the community at large [174].

The booster phenomenon presents a real problem of interpretation in contacts. Should an elderly person in contact with a smear-positive case with an initially negative reaction to 5TU or to the Heaf test be considered to have converted (and therefore developed primary infection) if they are subsequently positive? The author's own policy is simply to observe for 1 year with chest films if the second tuberculin test is positive (they have probably boosted) and to treat for tuberculosis if the chest film is positive. If all tuberculin-positive contacts in Edinburgh were given chemoprophylaxis, a substantial minority of the contact population would be exposed to drug therapy [168].

Causes of false-negative tuberculin tests

As already discussed, patients with active tuberculosis do not invariably have positive tuberculin skin tests. False negatives are most commonly seen in those with overwhelming disease, miliary or cryptic miliary disease and tuberculous meningitis. Many other factors relating to the patient and also to the performance of the test may be implicated and these are listed in Table 16.7. The subject has recently been reviewed [67].

Control and prevention

The most powerful weapons for controlling and preventing tuberculosis are case finding and treatment with a view to preventing the spread of *M. tuberculosis* from smear-positive cases. Prevention of infection by *M. bovis* can be achieved by the establishment of tuberculosis-free herds and the pasteurization of milk [175]. Rarely, measures may have to be taken against other animals, as in the south-west of England where wild badgers became heavily infected with *M. bovis* and were believed to be responsible for reinfecting cattle [176]. Transmission of disease due to *M. bovis* has also been recorded from farmed elk in Canada [177–179] and in marine park seals

Table 16.7 Potential causes of false-negative tuberculin reactions.

<i>Patient-related factors</i>	
Infections	
Viral, e.g.	mumps, measles, chickenpox, influenza, HIV
Bacterial, e.g.	typhoid, brucellosis, typhus, leprosy, pertussis, overwhelming miliary or cryptic miliary tuberculosis, tuberculous meningitis
Fungal, e.g.	South American blastomycosis
Live virus vaccinations, e.g.	
measles, mumps, polio	
Metabolic disease, e.g.	
chronic renal failure	
Nutritional defect, e.g.	
protein malnutrition	
Lymphoid disease, e.g.	
Hodgkin's disease, lymphoma, lymphocytic leukaemia, sarcoidosis	
Drugs, e.g.	
corticosteroids and immunosuppressive agents	
Age, e.g.	
newborns and elderly	
Miscellaneous, e.g.	
stress, surgery, burns, graft-versus-host reaction	
<i>Tuberculin-related factors</i>	
Improper storage (exposure to light and heat)	
Improper dilution	
Chemical desaturation	
Contamination	
Adsorption (add Tween 80)	
<i>Method of administration factors</i>	
Injection of too little antigen	
Injection too deep	
<i>Reading and recording factors</i>	
Inexperience in reading	
Bias in reading	
Error in recording	

in Australia [180]. BCG vaccination and chemoprophylaxis also make important contributions to the control of tuberculosis.

Case finding

Developed countries

It is now recognized that mass screening of the general population by X-ray examination, although identifying cases of tuberculosis, makes no substantial impact on the number of new cases arising in that population [181]. The evidence for this observation is derived principally from studies in Kolin in the former Czechoslovakia [36,182], where 95% of the population over 14 years old had chest radiography at 3-year intervals between 1961 and 1972. All identified cases were treated. The number of infectious (smear-positive) cases did not differ significantly from year to year between 1960 and 1972, i.e. despite repeated 'cleaning-up' of the population by radiographic detection of disease and treatment, new cases of smear-positive disease developed in the years between the screenings. The methods of discovery of smear-positive cases in Kolin



**Table 16.8** Mode of detection of smear-positive tuberculosis cases in Kolin, Czechoslovakia, 1961–69 and The Netherlands, 1951–67. (From Meijer *et al.* [183].)

Country or area	Period of observation	Number of smear-positive cases	Percentage of smear-positive cases discovered by			
			Symptom cases	Chest clinic check-ups	Mass radiography	Other
Kolin study	1961–69	193	45	21	25	9
Netherlands	1951–55	6027	58	12	14	15
	1956–61	3823	57	15	13	14
	1962–67	2460	54	17	15	13

and also in The Netherlands, where screening by mass miniature radiography was also carried out, are shown in Table 16.8 [183]. In both studies the commonest method of discovery was presentation with symptoms. Smaller numbers were detected by chest clinic check-ups (e.g. contacts, recent converters and those with ‘fibrotic’ lesions) and by mass radiography. Therefore case finding in the general population most frequently results from X-ray and sputum examination of patients presenting with symptoms. Although mass radiography is not indicated as a case-finding method in the population at large, there are clear indications for the screening of selected populations. Such selected populations may be divided into high-yield and danger groups.

### High-yield groups

#### *Symptom group*

This consists of patients who have symptoms suggestive of tuberculosis, for example patients presenting with a cough that fails to respond to conventional treatment; such patients should be referred for a chest radiograph. In Edinburgh it has proved extremely valuable to have a facility to which general practitioners can easily refer patients for X-ray examination. Delays in referral for investigation, though common, are infrequently reported [184,185].

#### *Contacts*

It is most important following notification of a case of tuberculosis that appropriate contact procedures be initiated with a view to identifying other associated cases of tuberculosis. If the first notified or index case is one of primary tuberculosis, then a source case is sought; if the index case has postprimary tuberculosis then, although a source may still be searched for, the concern is that other contacts may have been infected by the index case. Studies in the UK [186–193] have shown that up to 10% of all new cases of tuberculosis are diagnosed by contact-tracing procedures, although these may be less rewarding in areas where the incidence of tuberculosis is low [194,195].

Contacts should be screened by tuberculin testing and chest film. Negative skin reactors should be retested at 6 weeks to exclude the possibility of recent primary infection. Skin-test conversion merits chemoprophylaxis. Priority should be given to household and close family contacts of smear-positive cases of pulmonary tuberculosis [196,197] where 5–14% of contacts have been found to have disease [186,193,198–201]. The extent of screening may be determined by the infectivity of the index case; if evidence of infection is found in close contacts the search should be extended, the ‘stone in the pond’ principle [202]. Screening of close contacts of all other cases of tuberculosis with a single chest radiograph, though less productive, is nevertheless recommended [32,33]. Screening should be extended to casual contacts of smear-positive cases but is not necessary for casual contacts of smear-negative or non-respiratory tuberculosis. Tuberculin-positive contacts with normal chest films should have further films taken at intervals for 1 year, a practice that detects further cases in the UK [33]. In the UK, it is usual to offer BCG vaccination to tuberculin-negative contacts [33]. In the USA, it is usual to offer chemoprophylaxis to tuberculin-positive disease-free contacts [32]; in the UK, this is recommended for those aged under 16 years [33].

Recent developments in DNA fingerprinting of *M. tuberculosis* [203] have allowed more detailed examination of patterns of tuberculosis transmission in communities in North America [204,205] and Switzerland [206]. Such studies have revealed the limitations of conventional contact tracing procedures and will undoubtedly continue to yield valuable epidemiological information [207].

#### *Inhabitants of lodging houses, prisons and mental institutions and the homeless*

Tuberculosis is more common in the population variously referred to as the homeless or ‘down and outs’ and in lodging-house or hostel dwellers, among whom alcohol and drug abuse are often commonplace [208–214]. Incidence rates of active tuberculosis may be as high as 2000 per 100 000 [215]. The advent of HIV infection among intravenous drug abusers in this population has led to a further increase in tuberculous disease [216] and has

focused attention on the marked deficiencies in the public health services offered them [217,218]. These individuals are notoriously unreliable, frequently moving address and usually hostile to, and suspicious of, the attentions of the health services. In the USA, skin-testing programmes with chemoprophylaxis for skin test-positive individuals have been suggested [219] and successfully implemented [220]. The threshold of suspicion for tuberculosis in this population should be set low, with early bacteriological and radiological investigation followed by supervised or directly observed treatment of disease [221]. The use of BCG vaccine has been suggested [222]. Staff working with this population should be protected by BCG vaccination or annual tuberculin testing, with chemoprophylaxis for converters. In either case they should be educated to present early for radiographic examination if they develop symptoms.

Homelessness apart, it is increasingly obvious that social deprivation in the so-called developed world continues to be a major contributor to the burden of tuberculosis cases [223] as exemplified by recent reports from Leeds [224,225] and London [226], as well as from England and Wales as a whole [113].

The increasing prevalence of HIV infection has focused attention on the possible consequences to the prison service of incarcerating individuals with dual tuberculous and HIV infection who are predisposed to the risk of developing active tuberculosis, with all the attendant risks of transmission of tuberculosis to other inmates and staff [227]. Clear guidelines have been issued in both the UK [33] and the USA [228] to address this situation. A report from Spain, where prisoners had a high prevalence of HIV infection (30%), found that 2.7% of prisoners had active tuberculosis on admission to prison [229].

Residential facilities, such as homes for the mentally ill or the handicapped, are also potential sites for the spread of tuberculous infection and disease. Radiological screening of such patients in the UK ceased many years ago as it proved unproductive, almost certainly reflecting the overall decrease in tuberculous infection. The occasional identified case leads to prompt and usually unproductive contact screening, which is nevertheless reassuring to all concerned. Chemoprophylaxis of the resident population has been successfully employed in the past [230].

#### *Immigrants and refugees*

In 1993 tuberculosis notifications rates in England and Wales were 4.3 per 100 000 for whites, 115 per 100 000 for the Indian ethnic group and 135 per 100 000 for the Black African group [231]. Similarly in the USA, in comparison with whites tuberculosis was four times more common in Hispanics, five times more common in Amerindians, six times more common in Blacks and 11 times more common

in Asians and Pacific Islanders [232–237]. Recent immigrants from high-prevalence areas should therefore be screened by chest radiography and/or tuberculin testing in order to detect cases of active tuberculosis and permit the prescription of chemoprophylaxis where it is deemed appropriate [110]. Tuberculosis rates so determined have been found to be high in, for example, recent Asian immigrants [238] and South-East Asian refugees [239]. The effects of war are well known [240].

Ideally, screening should be undertaken at the port of entry where this is possible, as in Switzerland [241]; in many countries, including the UK [242], such screening is incomplete and it is essential that the port authorities pass information on all new immigrants to the relevant authorities in the district of intended residence. Such official information on new immigrants can be supplemented by local intelligence [33] and allow the prompt implementation of screening and prevention interventions [243]. The ethical considerations of relevance to managing tuberculosis in immigrant and refugee groups have recently been discussed in detail [244].

#### *Elderly in nursing homes*

It has been suggested that the elderly are not only at risk from endogenous reactivation of tuberculosis but also of exogenous reinfection, particularly in nursing homes [245]. Outbreaks of tuberculosis among the elderly in nursing homes have been reported [246] and subsequent studies of such chronic care populations have shown as much as a 5% annual rate of tuberculin skin-test conversion in elderly residents [247,248], with the development of significant disease in those not given isoniazid [248]. The skin-test conversion rate was twice as high in Blacks as whites [249]. Hopewell [250,251] has suggested, on the basis of his own studies of nursing home residents, that these skin-test conversions are apparent rather than real, simply representing an extension of the booster phenomenon. This would be in keeping with reports from Canada [252] and the UK [253] that do not indicate an increased risk of tuberculosis among the institutionalized elderly. Common sense dictates that an awareness of chest radiological status, and the need for bacteriological investigation for tuberculosis where indicated, be promoted in residential institutions for the elderly.

#### *Medical laboratory workers*

The incidence of tuberculosis is five times higher in medical laboratory workers than in the general population and particularly high in those working in pathology departments [254,255]. Such workers may be offered annual screening chest films or, in countries where BCG is not routinely employed, annual tuberculin testing.



### *Danger groups*

Among those whose work is liable to predispose them to tuberculosis and/or bring them into contact with susceptible individuals are the following.

#### *Schoolteachers and those working with children.*

The important consideration in this group is the detection of active pulmonary tuberculosis by medical examination and appropriate investigation of those about whom there is any suspicion at the pre-employment assessment or at any time thereafter [33].

#### *Hospital employees, including doctors, dentists, nurses and other healthcare workers working with patients*

All healthcare staff in regular contact with patients and laboratory workers handling specimens are potentially at risk of contracting tuberculosis, especially those who work with tuberculosis patients or specimens. Pre-employment screening should exclude symptoms of tuberculosis, determine details of BCG immunization and scar status, and include skin testing for those who have not had BCG. Unvaccinated tuberculin-negative workers should receive BCG [33]. Unvaccinated tuberculin-positive workers should only have radiography if they are symptomatic [254]. It is uncommon in the UK for hospital staff to acquire infection from patients [255] and routine periodic chest radiography is not required, except possibly for some categories of pathology and bacteriology laboratory staff. More realistically, such staff, as well as others concerned about contact with an infectious case, should be educated and advised to report early if suggestive symptoms develop. In the UK, guidelines for the occupational health services within the National Health Service have been published [33] and are necessary [256] since cases of tuberculosis still occur in hospital doctors [257–259], some of whom have evaded screening. Such individuals may transmit infection to patients [260]. In the USA, the practice of annual tuberculin testing of hospital employees, with chemoprophylaxis for skin-test converters, is likely to continue [261].

Reports from the USA have indicated a risk to staff of contracting tuberculosis, including multidrug-resistant strains, from patients with HIV infection. In the UK, all such exposed staff must be protected by BCG vaccination or must be known to be tuberculin positive before working with HIV-infected tuberculosis patients [33]. The author, faced with the prospect of contact with multidrug-resistant tuberculosis, would prefer to have had BCG vaccination even though protection is not complete (see below); such a policy has yet to be adopted in the USA.

### **Developing countries**

In the developing countries, where expense precludes the universal availability of chest X-ray facilities, the most rewarding method of case finding is by direct smear examination of sputum from symptomatic cases. This can be done in rural as well as urban areas by suitably trained personnel [262] and has the advantage of identifying the most infectious cases of tuberculosis.

### **BCG vaccination**

BCG was originally a bovine strain of tuberculosis that was attenuated by 230 passages through media containing glycerine and ox bile and was first used in France in the 1920s as an oral vaccine and subsequently as an intradermal injection. It does not prevent infection with tuberculosis but limits multiplication and dissemination of mycobacteria following infection [263].

### **Types of vaccine**

Numerous strains of vaccine are currently available [264,265] and they must be carefully standardized. If the vaccine is too 'virulent', there is a higher incidence of complications; if it is too weak, the tuberculin test conversion rate may be decreased and efficacy impaired. The vaccine must also be given under carefully controlled conditions as the organisms are very susceptible to daylight or sunlight. For many years the standard vaccine was a liquid that was freshly prepared and had to be given within 14 days or less of preparation. Freeze-dried vaccine has now been developed, with the great advantage that it can be kept for longer periods provided it is stored at a temperature of less than 6°C. Deterioration may occur within a day or two at temperatures of 37°C and above, as in very hot climates [266–268].

### **Evidence for efficacy**

The first trial to demonstrate the efficacy of BCG was carried out by Aronson *et al.* [269] on North American Indians in 1936–38 and showed a protective efficacy against death from tuberculosis of 82% for 18–20 years. The second trial by Rosenthal *et al.* [270] in Chicago infants in 1937–48 gave 74% protection over 12–23 years. The British Medical Research Council [93,271,272] controlled trial in urban school leavers showed a 79% reduction in tuberculosis in the vaccinated group over 20 years. Protection was not related to the degree of tuberculin sensitivity induced [273]. In south India, Frimodt-Moller *et al.* [274] obtained a 62% reduction in attack rate.

Less satisfactory results were reported by the United States Public Health Service from controlled trials carried

out in Puerto Rico and the southern USA [275,276]. More recently an extensive trial in south India has demonstrated no protective effect of BCG [277,278]. Whether the failures of these trials are due to differences in vaccine, the high prevalence of possibly protective atypical mycobacterial sensitization in these areas or to study design has not yet been resolved [265,279]. However, numerous additional studies do provide support for a substantial beneficial influence of BCG vaccination [280–284], including a recent meta-analysis [285] that suggested a 50% protective effect.

### Indications for vaccine

In the UK, BCG is still given to schoolchildren aged 13–14 who are Heaf grades 0 or 1 or who show less than 5-mm induration to 10 TU on Mantoux testing [162,284]. In 1989 it was estimated that 4000 vaccinations are given to prevent one case of tuberculosis. The need for universal BCG vaccination of schoolchildren is likely to be reviewed in the near future as the risk of infection and hence the number of cases prevented by BCG diminishes [286].

Other categories of individuals currently offered tuberculin testing, and BCG vaccination if negative, include health service workers, contacts of cases of tuberculosis and those planning to reside in high-prevalence countries. Children and newborns of Asian families in the UK who have an increased risk of exposure to tuberculosis should also be vaccinated.

In developing countries with a high incidence of tuberculosis, the WHO has recommended administration of BCG to neonates or as early as possible to children [287]. The main reason for this recommendation is that BCG has always shown a protective effect in studies in young children [288] and the south India study did not produce any contradictory evidence.

### Techniques of administration

The vaccine is best given by intradermal injection of 0.1 mL (0.05 mL for those <3 months old) in the lower deltoid area. A papule appears in 3–4 weeks that usually remains for a number of weeks and may ulcerate slightly and discharge. There is sometimes slight enlargement of the draining lymph nodes. The tuberculin test should become positive within 3 months. It has been shown that no untoward reaction occurs if tuberculin-positive individuals are vaccinated [289]. This enables mass vaccination to be carried out in a developing country without the necessity for a return visit to have a tuberculin test read.

### Complications

Complications of BCG are very few [290]. Local secondary infection is the commonest and this occasionally gives rise to an abscess or swollen tender draining lymph nodes.

Cold abscess of the draining glands may occur [291]. Short courses of erythromycin or isoniazid are equally effective in the treatment of these local complications [292–294]. Local lupoid reactions may occur, most often under an occlusive dressing. Ultraviolet light is sometimes effective in hastening healing of local lesions. Erythema nodosum and urticaria have occasionally been recorded. Disseminated BCG, which may be fatal, is exceedingly rare and most usually seen in those with disturbances of immunity. BCG should not be given to such individuals or to patients with extensive dermatosis [291,295].

### Chemoprophylaxis

Chemoprophylaxis is the administration of chemotherapy to prevent the development of tuberculous disease [123,296,297]. Primary chemoprophylaxis involves giving chemotherapy to individuals who have not so far been infected. Secondary (or disease) chemoprophylaxis is chemotherapy for individuals with a positive tuberculin test who have been infected in an endeavour to prevent development of disease. These individuals may have a normal chest film or it may show evidence of previous tuberculous infection.

### Mass chemoprophylaxis

Combinations of both primary and secondary chemoprophylaxis or mass chemoprophylaxis have been used in communities with a high prevalence of tuberculosis, with isoniazid treatment applied to the whole population [127,298,299]. Such mass prophylaxis resulted in diminution of the amount of tuberculosis in the treated group when special care was taken to ensure that a high proportion of the population took their medication. In the Greenland trial [298], prophylaxis with isoniazid for 1 year resulted in a 60% disease reduction that persisted for at least 5 years. Isoniazid-resistant strains were not a feature in those subsequently developing disease. In a smaller-scale Canadian controlled trial in Eskimos who are particularly susceptible to the disease, where isoniazid and ethambutol were used three times a week under supervision for 18 months, there were no cases in the treated group over 3 years compared with an annual attack rate of 1.8 per 1000 in the controls [300]. The same regimen of ethambutol and isoniazid thrice weekly for 18 months applied to those with previous tuberculosis or a strongly positive tuberculin test with or without previous BCG resulted in an incidence of tuberculosis of 0.1% per annum in the treated group compared with 1% per annum in the untreated group over a period of 10 years [301]. Though effective in populations with a high prevalence of tuberculosis, such interventions are enormously expensive and therefore inappropriate for developing countries.

### Primary chemoprophylaxis

The use of isoniazid to prevent disease in individuals who have not previously been infected is based on the value of the drug in preventing disease in experimental animals [302–306]. It is infrequently employed, since individuals at risk of infection following exposure to tuberculosis are usually simply tuberculin tested and if negative retested at 6 weeks, when converters are treated and non-converters offered BCG (see p. 495). It is not known whether starting chemotherapy with isoniazid at the time of the first negative tuberculin test is of greater benefit than starting therapy should the tuberculin test convert to positive. In the situation where a suckling child cannot be separated from a tuberculous mother because of the risk of malnutrition or for emotional reasons, it may be justified to give the infant isoniazid until the mother is considered non-infectious; if the tuberculin test becomes positive then isoniazid should be continued; if negative, then BCG should be given [33,307,308].

### Secondary chemoprophylaxis

The recommended dose of isoniazid for chemoprophylaxis is 300 mg daily for adults and 5 mg/kg up to a maximum of 300 mg in children, with a total duration of therapy of 1 year. The current American recommendations for secondary chemoprophylaxis and the relevant contraindications are outlined in Table 16.9 [296,309]. Needless to say, there are differences in the fervour with which these recommendations are applied and these are discussed below.

The first group for whom chemoprophylaxis is recommended includes household and other close contacts of cases of tuberculosis. If the contact procedure outlined

above is followed, isoniazid chemoprophylaxis is not required for tuberculin-negative contacts in this situation. Tuberculin-positive children are likely to have been recently infected and qualify for chemoprophylaxis. Tuberculin-positive adults are common in contact clinic populations, particularly the middle-aged [168]; in the UK at least, chest X-ray surveillance of these individuals for 1 year is recommended rather than chemoprophylaxis [33], since the majority of positive tuberculin tests in this category represent remote rather than recent infection. This avoids unnecessary exposure of individuals to the risks of isoniazid therapy (see below) while ensuring that tuberculous disease that develops is detected. Chemoprophylaxis (or even combination chemotherapy) is essential for contacts who are tuberculin skin-test converters, although in the older age groups apparent conversion may simply be a manifestation of the booster phenomenon.

The second group comprise tuberculin skin-test reactors with an abnormal chest film suggestive of inactive tuberculous disease. In the studies by the United States Public Health Service, the reduction in tuberculous morbidity in this category by isoniazid chemoprophylaxis was slight [123]. In a recent study of 27 830 20–65-year-old individuals with well-delineated radiographic lesions of probable tuberculous origin that had been stable for 1 year [310,311] the following observations were made: 3 months of isoniazid produced only a small reduction in tuberculosis compared with placebo; 6 months of isoniazid produced a 65% reduction in cases of tuberculosis; 1 year of isoniazid produced a 75% reduction in cases of tuberculosis and in those with proven good compliance for 1 year on isoniazid there was a 93% reduction in cases. Hepatitis developed in 0.46% of the treated group compared with 0.1% of the control group, with fatalities only occurring in those who took isoniazid after hepatitis developed. At least one worker questions the value of this kind of intervention [312], feeling that to halve the number of cases developing is simply not worth while viewed against the numbers who have to be treated to achieve this effect. The author's view is that individuals in this category should not receive isoniazid but should be advised to seek medical advice if they develop symptoms suggestive of tuberculosis.

The third category of patients with positive tuberculin tests in special clinical situations includes those receiving steroid or immunosuppressive therapy, those with blood and reticuloendothelial diseases such as leukaemia and Hodgkin's disease, those with diabetes mellitus, silicosis or renal transplants and those with the surgical interventions of gastrectomy or ileal bypass. One reviewer deems chemoprophylaxis unnecessary for patients receiving moderate doses of long-term corticosteroids (such as used in asthma) for respiratory disease [313]. Whether or not all of these patients receive chemoprophylaxis, a high index of suspicion of the development of tuberculous disease must be maintained throughout.

**Table 16.9** Current American recommendations for secondary chemoprophylaxis with isoniazid. (From American Thoracic Society [310].)

Indications	Contraindications
Household members, other close contacts of newly diagnosed patients and newly infected persons	Progressive tuberculous disease (combination chemotherapy required)
Positive tuberculin skin-test reactors with an abnormal but inactive chest X-ray	Adequate course of isoniazid previously completed
Positive tuberculin skin-test reactors with special clinical situations	Severe adverse reaction to isoniazid previously
Other positive tuberculin skin-test reactors up to age 35	Previous isoniazid-associated hepatic injury, acute liver disease

The fourth category recommended for chemoprophylaxis, tuberculin-positive skin-test reactors under the age of 35, is the most contentious. Treating 1000 symptomless reactors aged 35 for 12 months with isoniazid as recommended [219] would prevent 23 cases of tuberculosis or one case every 2 years [312]. An American analysis has suggested that the risk of such individuals developing active tuberculosis over 20 years is 0.56–1.3%, whereas the risk of isoniazid-induced hepatitis is 0.3–1.1% [314]. Isoniazid could therefore prevent 108–109 cases per 100 000 over 20 years but there would be 300–1100 cases of hepatitis as a consequence of the treatment. More recently, the conclusion that you can 'take it or leave it' has been arrived at [315], although individual authorities continue to promote isoniazid chemoprophylaxis in the under 35 age group most strongly [316,317] as part of the campaign to eliminate tuberculosis [318]. That chemoprophylaxis fails in this respect is known and the reasons for failure have been analysed but are not immediately amenable to solution [319]. Some therefore disagree with the recommendations of the American Thoracic Society and the Centers for Disease Control [154,219].

The risk of hepatitis from isoniazid therapy is small but real. In a trial in the USA there were eight deaths among 14 000 participants. The likelihood of toxicity increased with age and alcohol intake and was particularly high among Orientals [320]. In the USA, the reports of deaths due to isoniazid-associated hepatitis that continue to appear [321,322] have led to a cogent and reasoned pronouncement from an experienced physician that the time to promote isoniazid chemoprophylaxis as part of the programme for the elimination of tuberculosis is long since past [323].

The debate about when and where to implement chemoprophylaxis will continue. There is no doubt that in all categories currently recommended for chemoprophylaxis such intervention is effective, albeit at low levels, in reducing the subsequent numbers of active cases of tuberculosis. The difficulty is that so many healthy people have to be treated to prevent so few cases, especially with a disease eminently curable by current chemotherapy should it develop. The contribution to the public health in preventing transmission of disease is not known but is unlikely to be large. If chemoprophylaxis were to be restricted to those likely to have been recently infected, e.g. tuberculin-positive contacts of highly infectious cases, and all other tuberculin-positive reactors advised to present for chest radiography should symptoms develop, then it seems unlikely that the pattern of active disease in the community would differ from that seen now. Unnecessary isoniazid consumption would certainly decline dramatically.

Those infected with HIV and with positive tuberculin tests fit the third category of qualifiers for chemoprophylaxis but merit separate comment.

There is now good evidence that those who are dually infected with tuberculosis and HIV have a 5–10% per annum chance of developing tuberculosis [324,325]. Whether the tuberculosis is due to reinfection or reactivation [326] is not relevant since chemoprophylaxis of all such individuals who have greater than 5 mm induration to 5 TU has been shown to be effective in preventing the development of tuberculous disease [327], and is now recommended by the International Union Against Tuberculosis and Lung Disease [328].

## Antituberculosis campaign

### Developed countries

In economically developed countries the aim should be the eradication of tuberculosis [329]. In summary, the following measures should be employed.

- 1 Control of infection from cows' milk by pasteurization and tuberculin testing of herds.
- 2 Effective treatment of all patients with disease, especially infectious individuals.
- 3 Identification of all infectious or potentially infectious individuals, mainly by radiography.
- 4 BCG vaccination, although as discussed above this may eventually make an insignificant contribution.

Tuberculosis should be continuously monitored on a national level and periodic assessment of the distribution of disease in different community groups by age, sex and ethnic origin is of value in ensuring that appropriate progress is being made and for redirecting, as required, appropriate control measures [330]. Defects in notification practices [107,331,332] and provision of clinical services [333,334] need to be remedied.

### Developing countries

Where limitation of money and staff is present the main emphasis should be placed on the following.

- 1 BCG vaccination at birth or as early as possible with revaccination in later childhood.
- 2 Case finding, with the emphasis being placed on the detection of highly infectious cases by the application of inexpensive direct sputum smear examination to symptom groups.
- 3 Chemotherapy: standard short-course directly observed chemotherapy is now recommended by WHO throughout the developing world [335], although it has been employed for many years in some countries, e.g. Tanzania [336]. The potential for the development and dissemination of multidrug-resistant strains of tuberculosis in such a scenario, where chemotherapy may be abused, is avoidable if the national tuberculosis programme is organized efficiently [337].

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# PULMONARY TUBERCULOSIS: CLINICAL FEATURES

A. GORDON LEITCH

This chapter is principally concerned with describing the clinical features of primary and postprimary or reactivation pulmonary tuberculosis. Congenital, classical miliary and cryptic miliary tuberculosis are also described. Extra-pulmonary tuberculosis, including pleural tuberculosis, accounted for 21% of tuberculosis notifications in white and 53% of notifications in Indian subcontinent patients in Scotland in 1993 [1] and clinical aspects of these manifestations of tuberculous disease are given in Chapter 18. Tuberculous pleural effusion is considered in Chapter 43.

## Congenital tuberculosis

### Pathogenesis

Congenital tuberculosis is a very rare condition, with fewer than 300 cases reported in the literature [2]. Tuberculous disease in the mother is invariable but may not be clinically obvious, for example miliary disease of the endometrium. Three possible modes of infection of the fetus have been proposed: haematogenous infection via the umbilical vein or fetal aspiration/inhalation of infected amniotic fluid resulting in primary lesions in the liver or lungs respectively. To satisfy the criteria for congenital tuberculosis the disease must be bacteriologically proven and present *in utero*, at birth or within the first few days of life [3]. Recently, phage typing has been used to establish the common identity of mycobacteria isolated from both mother and infant [4,5].

### Clinical features and diagnosis

The disease is usually widespread, with multiple organ involvement, and the baby is often premature. Presentation within a few days of birth is usual, often with respiratory distress due to extensive bronchopneumonia or miliary disease. Fever, hepatosplenomegaly and lymphadenopathy are common. Obstructive jaundice due to glands in the porta hepatis may occur. Presentation may simply be as failure to thrive. Positive smears may be

obtained from gastric washings, liver, lymph node or lung biopsy [6], or from tracheal aspirates. The tuberculin test is commonly negative.

### Treatment and prognosis

Treatment should be initiated with three drugs including rifampicin in appropriate dosage (see Chapter 19). Corticosteroids may be given empirically if the baby is very ill. The prognosis is poor, with only 54% of 26 treated cases surviving in a recent study [7].

### Prevention

The only hope of preventing this rare but often fatal condition lies in the screening of high-risk groups, e.g. immigrant women, and appropriate treatment of those found to be suffering from tuberculosis [2,5,8].

## Primary pulmonary tuberculosis

The first infection with the tubercle bacillus is known as primary tuberculosis and usually includes involvement of the draining lymph nodes in addition to the initial lesion [9–11]. All lobar segments are at equal risk of being seeded by inhaled infected droplets and in 25% of cases there may be more than one primary focus [12]. Probably within days the infection spreads to regional lymph nodes, with enlargement of hilar, mediastinal or subcarinal nodes. A left-sided pulmonary focus may lead to bilateral adenopathy, whereas right-sided lesions only result in right-sided adenopathy [13]. The combination of the primary (Ghon) focus and the draining lymph nodes is known as the primary complex. All other tuberculous lesions are regarded as postprimary and are not, at least in whites, accompanied by major involvement of the draining lymph nodes.

Although primary tuberculosis was formerly relatively common in the intestine or tonsil, due to infection from milk, and may occur in various other unusual sites [14], in

the great majority of cases the route of infection is by inhalation and consequently the primary lesion is pulmonary. The pathology of primary pulmonary tuberculosis has been described in Chapter 16.

### Clinical features

The great majority of primary tuberculous infections are probably symptomless, at least in young adults and adolescents [11,15,16], the infection being overcome without the individual being aware of it. A proportion may experience a brief febrile illness at the time of tuberculin conversion that is indistinguishable from the many febrile illnesses of childhood. Most children are symptom-free and are discovered only when they are investigated as contacts of an adult case. Occasionally, typical primary tuberculosis may occur in elderly people who have lost their tuberculin sensitivity.

In most cases there are no detectable physical signs. However, in a few cases, perhaps those with more severe infection or low host resistance, the child may be unwell with loss of appetite, fretfulness and failure to gain weight. Cough is not usual but may occur, and may mimic the paroxysms of whooping cough when lymph nodes or tuberculous granulation tissue impinge on the bronchial wall [17]; wheeze may be a result of the same process. Sputum production is rare in children. Auscultation of the

chest is usually unrewarding but occasionally crepitations may be heard over an extensive primary focus. More obvious physical signs may be present if there is segmental or lobar exudation or collapse (see below).

### Radiological features

Radiological changes are found at the time of tuberculin conversion in 7–30% of young adults, being higher in those exposed to a known source of infection [15,18]. The prevalence of radiological changes in children varies in different populations: in a Nigerian series, 79% had lymphadenopathy and 68% had a parenchymal lesion [19] (Fig. 17.1); in a Canadian series, 94% had lymphadenopathy [20]. The hilar lymph node was most commonly involved but the paratracheal node was also frequently enlarged and a substantial minority had enlargement of both hilar and paratracheal nodes. Occasionally, especially in Asians, bilateral hilar adenopathy may be seen. In adults the lung component of the primary complex is usually more obvious and the nodal component may not be seen, whereas in children often only an enlarged hilar or paratracheal node is seen. There may be radiological evidence of segmental or lobar consolidation or obstructive emphysema (see below). Radiological abnormality persists in a majority 6 months after diagnosis but complete resolution is usual after 2 years [20].

In due course, usually after a year or more but rarely earlier, the lung or nodal component of the primary complex or both may calcify. Calcification may occur in the absence of any chest radiographic changes in the acute stage. In some cases the calcification may eventually disappear [21,22].

**Fig. 17.1** (a) Chest radiograph of an Asian child with primary tuberculosis showing hilar and paratracheal lymph gland enlargement. (b) Later film showing tuberculous consolidation of right upper lobe ('epituberculosis').



(a)



(b)

## Diagnosis

The clinical manifestations of primary pulmonary tuberculosis are by no means specific but the disease should always be borne in mind when there is vague ill-health, particularly if there is a history of contact with an infectious case of tuberculosis. By the time there is clinical or radiological evidence of tuberculosis the tuberculin test is usually strongly positive, a negative test making the diagnosis unlikely. The radiological changes outlined above are more helpful in diagnosis, although where there is doubt about a parenchymal lesion a trial of non-tuberculous chemotherapy may be helpful in distinguishing a simple pneumonic process from tuberculosis: simple pneumonia usually improves after 2 weeks, while a tuberculous process will be unchanged.

Sputum is rarely produced by children with primary pulmonary tuberculosis and gastric washings are more frequently obtained for mycobacterial examination [23]. Smears positive for acid-fast bacilli are uncommon and positive mycobacterial cultures can be expected in only 20–25% of cases [20]. Attempts to improve diagnostic returns by employing serological [24,25] or mycobacterial DNA amplification [26] techniques are in their infancy and cannot be recommended as routine at present.

## Complications

### Collapse/consolidation

The term 'epituberculosis', coined by Eliasberg and Neuland [27,28] to describe the development of dense homogeneous shadows in the lungs of children with tuberculosis, has now properly been abandoned. These radiological appearances are due to lobar or segmental consolidation/collapse (Fig. 17.2), are associated with enlarged tuberculous lymph nodes at the hilum and, as in Fig. 17.2, may rarely occur in elderly subjects who have lost their tuberculin sensitivity. The middle lobe is most often affected. Segmental lesions are seen in 43% of infected infants, 25% of those aged 1–10 years and 16% of those aged 11–15 years [11].

The radiographic appearances may be due to collapse, inflammatory exudation, caseous pneumonia or any combination of these three. Collapse is produced by pressure of the lymph node on the bronchus, by the spread of tuberculous granulation tissue into the bronchus with resultant stenosis or by discharge of caseous material from the lymph node through the bronchial wall [29–31]. Later the bronchial lesion may heal with residual scarring or fibrous stenosis. The available pathological evidence suggests that the commonest cause for the appearance is inflammatory exudate, either monocytic or polymorphonuclear. Epithelioid tubercles may also be present [22]. The

exudate is probably due to the discharge of caseous material into the bronchial lumen, with aspiration into a segment or lobe and a resultant exudative hypersensitivity reaction to the contained tuberculo-protein. It is not possible on purely radiological grounds to distinguish this appearance from caseous pneumonia, although the latter may be inferred from the absence of clinical illness and the later development of calcification. Actual caseous pneumonia appears to be very unusual, although small areas of caseation may occur [32].

Clinically, there is a greater likelihood of wheeze or paroxysmal cough. Dullness to percussion, diminished air entry, bronchial breathing or crepitations may be found. In infants and young children sudden asphyxia resulting in death may occur.

Treatment does not differ from that for primary tuberculosis, except that corticosteroids are utilized on the basis that a hypersensitivity reaction is often involved [33,34]. The daily dose should be equivalent to prednisolone 1–2 mg/kg and this should be continued for 4–6 weeks with a gradual reduction thereafter. Steroid therapy may need to be resumed if there is any subsequent radiological or febrile relapse. Steroid therapy may reduce the rate of residual bronchiectasis following this complication of primary pulmonary tuberculosis [33]. Rarely, surgical resection of nodes may be necessary in infants because of the threat of asphyxia.

### Bronchiectasis

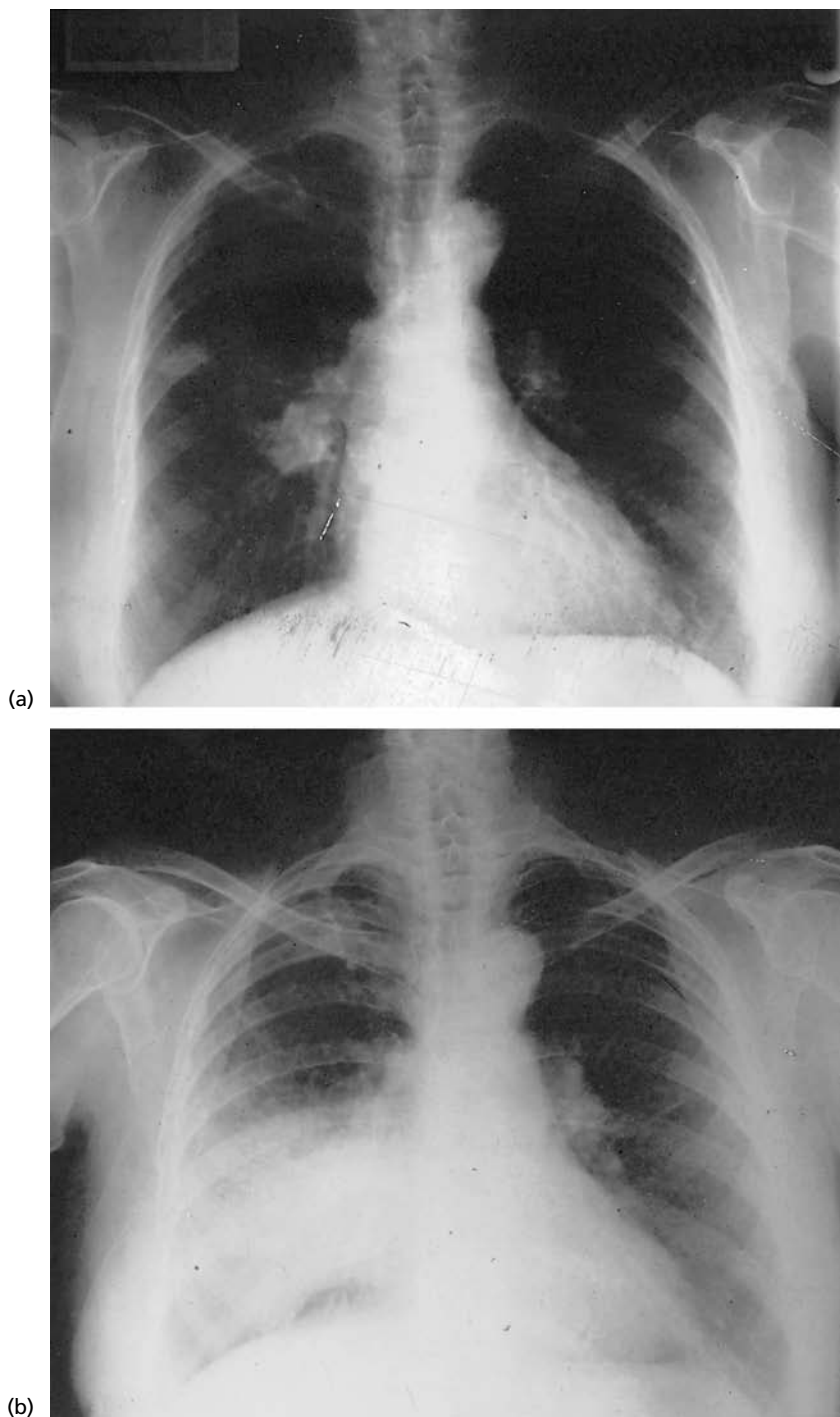
Distension by mucus, caseous tissue or secondary infection beyond a bronchial stenosis may result in bronchiectasis, especially following lobar or segmental lesions [35]. The incidence is reduced by prompt chemotherapy and the use of corticosteroid drugs [33].

### Obstructive emphysema

Occasionally a bronchus is compressed in such a way that a valve action results, with air being admitted to a portion of lung on inspiration but unable to escape on expiration. This results in distension of a segment or lobe, often with depression of the horizontal fissure or diaphragm and deviation of the mediastinum on expiration. The phenomenon is best shown on a chest film taken on expiration. The condition is rare but is commoner in children under the age of 2 years [11,36]. It usually resolves with chemotherapy and may be an indication for the use of corticosteroid drugs.

### Broncholith

Calcification in a primary focus, or more commonly in a lymph node, may later be extruded into a bronchus as a 'broncholith', which may declare itself with haemoptysis.



**Fig. 17.2** Chest radiograph of 70-year-old Asian lady with primary tuberculosis showing (a) peripheral focus and enlarged right hilar nodes and (b) consolidation of right middle lobe 1 week later. The diagnosis was made following bronchial biopsy, carcinoma having been suspected originally.

Such broncholiths may be seen through the bronchoscope but are best left well alone.

### **Erythema nodosum**

Erythema nodosum has been reported to have accompanied primary tuberculous infection in 1–2% of British [15,37] and 5–15% of Scandinavian [38] cases. It is rare below the age of 7, with an increase in frequency up to

puberty. It is commoner in girls than boys at all ages and after puberty 80–90% of cases are in females [38].

Tuberculin conversion is said to precede the eruption by a few days to a few weeks in most cases, although erythema nodosum may also occur later in primary or even postprimary disease. The rash is probably a manifestation of the Arthus phenomenon, as in erythema nodosum leprosum, where local deposits of immunoglobulin, complement and soluble mycobacterial antigen have been



demonstrated [39]. The characteristic feature of erythema nodosum is the presence of tender, dusky-red slightly nodular lesions on the anterior surfaces of the legs (Fig. 17.3), although lesions are occasionally also found on the anterior surfaces of the thighs, the extensor surfaces of the forearms and rarely on the face and breasts. The nodules are usually 5–20 mm in diameter, have ill-defined margins and may become confluent. They usually resolve over a week or two, the red colour fading to purple and then brown, the brownish pigment often persisting for several weeks. Recurrent crops of lesions may occur.

The amount of systemic reaction varies greatly. Fever may precede the eruption by days or weeks and usually resolves with clearing of the lesions. Occasionally a high fever persists for several weeks in association with recurrent crops of nodules. Arthralgia is common in adults, affecting the larger joints, wrists, elbows, knees or ankles, and joints may sometimes be hot, swollen and tender, mimicking acute rheumatic fever. The erythrocyte sedimentation rate (ESR) is usually high and there may be a leucocytosis. The tuberculin test is virtually always strongly positive. A negative tuberculin test suggests a non-tuberculous cause such as sarcoidosis.

Chemotherapy for tuberculosis is of course indicated in the presence of a chest radiograph suggesting primary



Fig. 17.3 Legs of patient with erythema nodosum.

tuberculosis but should also be given if the tuberculin test is strongly positive even when the chest film is normal, as postprimary tuberculosis is more likely to develop when erythema nodosum complicates first infection. The fever and eruption usually respond well to chemotherapy and failure to respond suggests that the diagnosis should be reviewed. The systemic manifestations of erythema nodosum are also usually adequately controlled with non-steroidal anti-inflammatory drugs. Occasionally corticosteroids may be indicated.

### Phlyctenular conjunctivitis

This condition also reflects hypersensitivity to the tubercle bacillus but, unlike erythema nodosum, is not necessarily confined to the first weeks of infection. It usually occurs within the first year [40], is most often seen in children and is said to be commoner in those with poor social backgrounds and in non-European communities in Africa and America [11].

The lesion is usually seen in one eye but may occur in both either simultaneously or successively. It begins with irritation, lacrimation or photophobia. The characteristic finding is of a small 1–3 mm shiny yellowish or grey bleb at the limbus, with a sheaf of dilated vessels running out towards it from the edge of the conjunctival sac. The reaction subsides in a week or so but multiple crops may occur, either successively or at intervals.

Any underlying tuberculosis should be treated by chemotherapy. Locally the pupil is dilated with atropine, and 1% hydrocortisone drops rapidly relieve the symptoms. If attacks continue to occur in spite of chemotherapy, desensitization to tuberculin may be effective [41].

### Pleural effusion

Pleural effusion may sometimes accompany primary pulmonary tuberculosis in children under the age of puberty [19,20]. Such effusions are usually small and transient, resolving with chemotherapy. Larger effusions are commoner after puberty and are discussed in Chapter 43.

### Miliary tuberculosis

Miliary tuberculosis is produced by acute dissemination of tubercle bacilli via the bloodstream. The term 'miliary' derives from the radiographic picture of diffuse, discrete, nodular shadows about the size of a millet seed (2 mm) that are characteristic of the classical disease. Although the overt case is relatively easily diagnosed, cryptic forms are not at all uncommon. In communities where tuberculosis is now greatly decreased, these cryptic forms in older people contribute an important proportion of cases of miliary tuberculosis and are sometimes diagnosed only at

postmortem. In one report serious miliary disease was not recognized until postmortem in 15 of 21 patients, most of whom were over 70 [42]. Other studies have emphasized failure to consider the diagnosis with resultant delays in initiating therapy and death [43–47]. In Edinburgh in the 1980s the mean age of all patients with miliary tuberculosis was 74 years and 40% had cryptic miliary disease [46]. Since the disease is almost always fatal without adequate treatment and recovery is the rule if proper chemotherapy is given, the importance of making the diagnosis needs no emphasis.

### Pathogenesis

When tuberculosis was widespread in the community the majority of cases of miliary tuberculosis closely followed the primary tuberculous infection in young children, more than one-third in one series being aged less than 3 years [48]. If the initial infection is overwhelming or the patient's defences are poor due to malnutrition, intercurrent disease or corticosteroid or immunosuppressive drug therapy, then the haematogenous phase of the primary infection may give rise to acute miliary tuberculosis. Seeding of bacilli into vessel walls may cause a caseous vasculitis of the intima, with subsequent discharge of bacilli into the bloodstream. Such lesions are said to be commoner in the large veins and the thoracic duct but less so in the arterial system, aorta or endocardium [49]. Miliary dissemination may also follow recrudescence of an old primary lesion, which may discharge itself into a vessel wall. Vascular invasion presumably also occurs from other active postprimary lesions, thus explaining the now relatively more frequent occurrence of miliary tuberculosis in the middle-aged and elderly.

### Pathology

In the commonest or classical form of miliary tuberculosis, the millet seed-sized lesions consist of clumps of epithelioid cells, lymphocytes and Langhans' giant cells with or without central caseation in which acid-fast bacilli are seen. The distribution of the lesions in the body is variable but the lungs are virtually always affected, sometimes only microscopically. Involvement of other organs varies from case to case. Lesions may occur in any of the serous sacs with resultant effusions.

A variant pathological type known as 'non-reactive' is almost only seen in adult cases and in immunosuppressed children. Here the lesions are mainly necrotic, with no obvious tuberculous histology, and are teeming with tubercle bacilli. The spleen and liver may be enlarged and studded with irregular necrotic foci, usually less than 1 cm in diameter or only visible microscopically. Any organ may be affected.

## Clinical features

### Acute or classical miliary tuberculosis

The disease is most common in infants and young children [50]. In children, the onset may be associated with an acute or subacute febrile illness [11,48,51] but often, especially in adults [44,52–54], the onset is insidious with gradual development of vague ill-health, malaise, anorexia, weight loss and fever. Cough, breathlessness, haemoptysis and night sweats are less common. Headache as a feature suggests associated tuberculous meningitis, which is found in an appreciable proportion of cases.

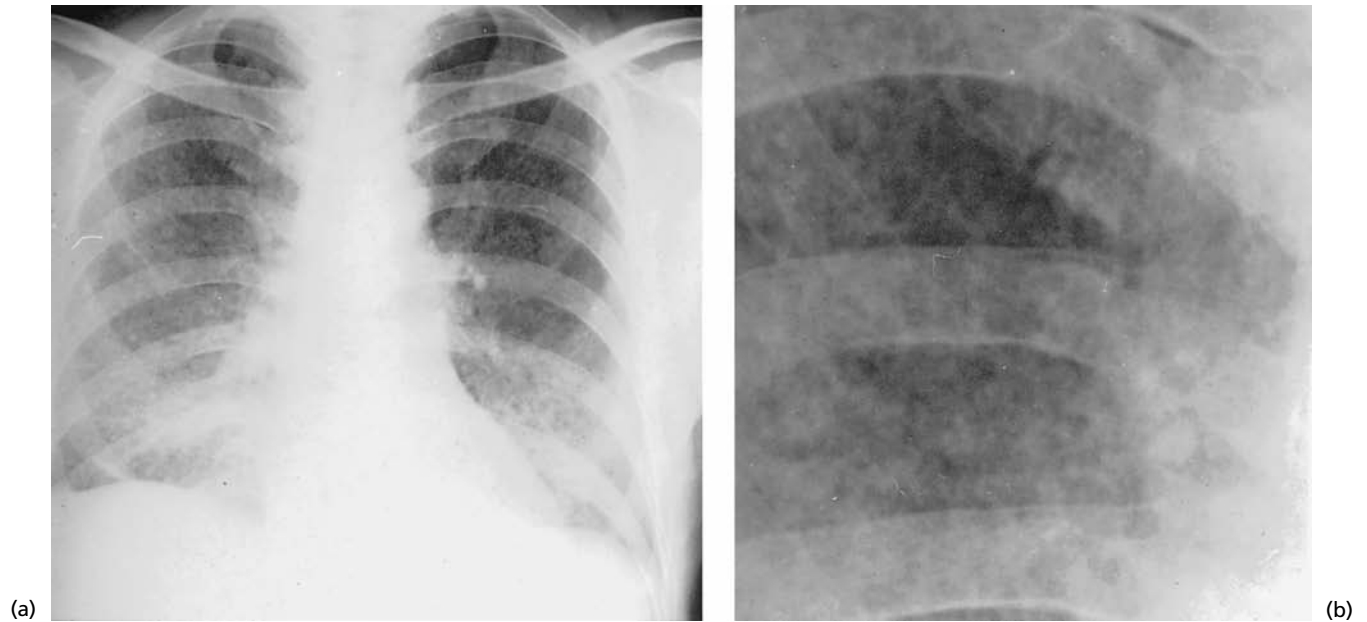
Apart from fever there may be no physical signs; in particular, the chest is frequently normal on auscultation, although crepitations may develop in the later stages. Hepatomegaly, nuchal rigidity, lymphadenopathy and splenomegaly may be found in a proportion of cases [52,53,55–57]. Choroidal tubercles are found in over 90% of children with miliary tuberculosis but less commonly in adults [48,58]. A search of the fundus is difficult in an irritable ill child and if it is important from a diagnostic point of view the pupils should be dilated and the child given an anaesthetic [58]. The lesions are usually less than one-quarter of the diameter of the optic disc. They are initially yellowish, a little shiny and give the impression of being slightly raised. Later they become flatter and may be very white in the centre and ultimately pigmented. There may be only one or two lesions or they may be very numerous. Miliary lesions of the skin are very occasionally seen and may take the form of macules, papules, vesicles or purpuric lesions [59].

### Cryptic miliary or disseminated tuberculosis

The cryptic form of disseminated disease is increasingly being seen in the elderly [46], where it may be difficult to diagnose since the chest film may be normal, choroidal tubercles are absent and the tuberculin test may be negative. The most common presentation [60,61] is with the insidious onset of weight loss, malaise and a fever of unknown origin. Anaemia is usual and the ESR is often elevated. A variety of blood dyscrasias, including leucopenia, pancytopenia, aplastic anaemia, leukaemoid reactions leucoerythroblastic anaemia and polycythaemia, have been seen [62–71]. The liver function tests are commonly disturbed, with elevation of transaminases and alkaline phosphatase. Hyponatraemia and hypokalaemia are also commonly seen [72,73].

### Radiology

It is important to recognize that the chest radiograph may be quite normal in the presence of miliary tuberculosis,



**Fig. 17.4** (a) Chest radiograph showing miliary tuberculosis. (b) Magnified view of the lung periphery in miliary tuberculosis.

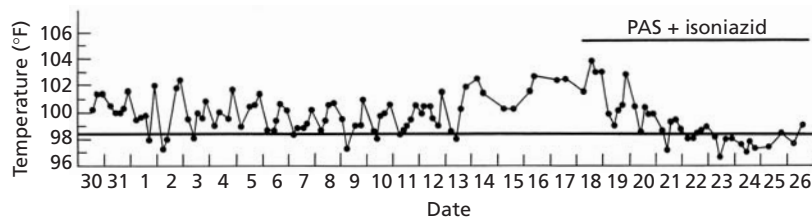
since the lesions are too small to be seen. When abnormal shadows are present they are usually fairly evenly distributed and may vary from faint shadows 1–2 mm in diameter to large dense shadows up to 5 or 10 mm. Usually the shadows are all a similar size (Fig. 17.4) but, as the disease progresses, larger coalescent shadows may develop. Evidence of a primary tuberculous complex, complicating segmental lesion or a postprimary lesion may be seen. Bilateral pleural effusion may occur. Rarely the appearance may be reticular, with a network of thin dense lines that has been shown to be due to lymphatic involvement, hence its description as lymphangitis reticularis tuberculosa [74]. The author has seen an 80-year-old patient die from presumed bronchopneumonia with a radiograph confidently reported as showing diffuse interstitial pulmonary fibrosis; in fact, she had non-reactive miliary tuberculosis. Following initiation of treatment the radiographic lesions clear slowly, taking up to 3–4 months on average but sometimes longer. There may be residual miliary calcification.

### Diagnosis

Diagnosis in the classical case with a febrile onset, miliary shadows on the chest film and perhaps with choroidal tubercles and an enlarged spleen is not difficult. The tuberculin test may be positive but this is not invariable and direct smear of fluid obtained by gastric lavage or

sputum if present may confirm the diagnosis. If necessary, transtracheal aspirates or fiberoptic bronchoscopic biopsy or lavage specimens can be obtained for microbiological examination [75]. The differential diagnosis of fever with miliary shadows includes bronchopneumonia due to haemolytic *Streptococcus*, *Staphylococcus* and *Mycoplasma pneumoniae*. If reasonable doubt exists, then the patient should be treated for both conditions until a firm diagnosis can be reached. Non-mycobacterial pneumonia clears much more rapidly than miliary tuberculosis. There has been a report of disseminated histoplasmosis simulating miliary tuberculosis, even to the extent of exhibiting choroidal lesions [76].

If there is no microbiological evidence of tuberculosis in an ill patient with a pyrexia of unknown origin, even if the chest film is normal and the tuberculin test negative, a therapeutic trial of specific antituberculosis chemotherapy is indicated and this should be started whether or not biopsies of liver and bone marrow have been taken for culture of acid-fast bacilli [77,78]. In proven cases, such biopsies will be positive on culture in the majority of patients [61]. While the cultures are awaited, the patient should be treated with isoniazid plus ethambutol in standard dosage, since these drugs act specifically on *Mycobacterium tuberculosis*, and the effect on the pyrexia and the haematological and biochemical abnormalities monitored. Improvement is usually seen within a few days (Fig. 17.5), after which standard chemotherapy should be introduced. Failure of the pyrexia to respond within 2 weeks makes the diagnosis of tuberculosis unlikely but not impossible. No patients with pyrexia of unknown origin, particularly those who are elderly,



**Fig. 17.5** Cryptic miliary tuberculosis: temperature chart of a 70-year-old man presenting with pyrexia and normocytic anaemia but a negative tuberculin test and normal chest radiograph. The pyrexia and anaemia responded to treatment with para-aminosalicylic acid and isoniazid.

immunosuppressed or immigrants, should be allowed to deteriorate and die undiagnosed without having such a trial of antituberculosis therapy.

## Complications

### Adult respiratory distress syndrome

Miliary tuberculosis may present with all the features of the adult respiratory distress syndrome or the syndrome may even develop after treatment has been initiated [79,80]. Therapy should be directed to both conditions.

### Immune complex nephritis

Immune complex nephritis complicating miliary tuberculosis has been described [81].

## Postprimary pulmonary tuberculosis

Postprimary pulmonary tuberculosis is by far the most important type of tuberculosis, partly because it is much the most frequent and partly because smear-positive sputum is the main source of infection responsible for the persistence of disease in the community. The pathology and pathogenesis are considered in detail in Chapter 16.

### Pathogenesis

Postprimary pulmonary tuberculosis may arise in one of three ways: (i) direct progression of a primary lesion; (ii) reactivation of a quiescent primary or postprimary lesion; and (iii) exogenous reinfection.

### Progression of the primary lesion

This is most likely to occur if the primary infection has occurred around the time of puberty [82,83]. This is true particularly for those of European stock, although progressive primary lesions can occur before puberty in Africans and Asians.

### Reactivation of the primary or postprimary lesion

This can occur at any time in a patient's life. The original lesion need not necessarily be visible radiographically and

the only evidence that it has occurred may be a positive skin test. It is probable that the great majority of middle-aged and elderly men who develop postprimary pulmonary tuberculosis do so as a result of a reactivation of lesions contracted many years previously. Waning of an individual's defences at any time of life may result in the development of postprimary pulmonary tuberculosis. Examples of predisposing factors are given below.

### Nutrition

Malnutrition is believed to predispose to tuberculosis. Evidence from the two world wars is suggestive: during the blockade of Germany in 1914–18, mortality from tuberculosis rose more in Saxon and Russian industrial towns, where food shortage was severe, than in rural Bavaria; also in the last year of the Second World War, there was an enormous rise in mortality in the occupied area of The Netherlands where the population was starving. One of the most impressive pieces of evidence regarding the effect of nutrition was the sudden increase in mortality due to tuberculosis in French prisoners of war in Germany after the cessation of Red Cross food parcels in 1944, following the invasion of France by the Allies.

### Housing/homelessness

Poor housing conditions with overcrowding, such as still exist in many common lodging houses [84,85], may contribute to disease, although other factors such as nutrition, smoking, alcohol consumption and human immunodeficiency virus (HIV) infection are also important in this context. Tuberculosis in this population may be due to reactivation disease in one individual and reinfection or new infection in others [86,87]. Incidence rates may be several hundred times higher than in the population at large [87].

### Occupation

Workers in occupations giving rise to pulmonary silicosis, such as masons, quarry workers, knife-grinders and coal-miners, have a greater risk of developing tuberculosis [88]. Silica appears to have a specific effect in lowering resistance to the disease, perhaps through a toxic effect on pulmonary macrophages [89]. Tuberculosis is commoner

among the health-service professions due to an increased risk of exposure to the disease [90,91].

### *Alcoholism*

Tuberculosis is common in alcoholics, contributory factors probably being malnutrition, adverse social factors and a direct effect of alcohol on host defences [92,93].

### *HIV infection*

The association of HIV infection with tuberculous disease is now well recognized and is described in detail in Chapter 16.

### *Cigarette smoking*

In patients of both sexes over the age of 30 suffering from pulmonary tuberculosis it has been shown that there is a highly significant deficiency of non-smokers and light smokers and an excess of moderate and heavy smokers compared with controls of the same age suffering from other diseases [94,95]. Mortality from pulmonary tuberculosis among doctors has been shown to increase significantly with the number of cigarettes smoked [96], and a similar effect has been found among US veterans [97]. These findings may be related to the higher alcohol consumption of smokers [92].

### *Steroid and other immunosuppressive drugs*

Reactivation of tuberculosis may occur in patients receiving corticosteroid or other immunosuppressive drugs for the treatment of disease or for the suppression of transplant rejection. The disease being treated may also contribute to such reactivation [98].

### *Other diseases*

Diseases associated with impaired cellular immunity, such as Hodgkin's disease, leukaemia, lymphoma and AIDS, may predispose to reactivation [99–103]. Gastrectomy probably predisposes to tuberculosis, particularly in patients with low weight/height ratios or malabsorption syndrome [104]. Diabetes mellitus may predispose to tuberculosis and also lead to a significant increase in cavity and smear-positive disease [105,106].

### *Exogenous reinfection*

Most tuberculin-positive individuals have sufficient immunity to control an episode of reinfection with tubercle bacilli and prevent the development of disease. However, such reinfection may lead to disease (as has been confirmed by DNA fingerprinting studies [107,108]),

although this is probably an uncommon cause of disease in developed countries. Disease from reinfection may be more common in populations with a high prevalence of tuberculosis, as was once the case with Eskimos [109]. Most cases of pulmonary tuberculosis arise either from a progressive primary lesion (in young people) or from reactivation of a dormant primary or postprimary lesion (in the middle-aged or elderly) [110].

### **Clinical features**

In the developed countries, the majority of patients with postprimary pulmonary tuberculosis are middle-aged or elderly, the trend towards increasing age (and also increasing numbers of alcoholics) being significant in comparison with 20 years ago [111]. In Scotland in 1993, 64% of white patients with tuberculosis were aged over 55 years; in comparison, 85% of Asian patients were under 55 years [1]. In developing countries, the age distribution is strikingly different (Fig. 17.6), with a preponderance of young and young middle-aged patients [112].

### **Symptoms**

Active disease may be present with no symptoms at all, while mild debility may be so gradual in onset that patients do not notice it and may feel so much better after chemotherapy that only subsequently do they realize they were unwell. There is little that is specific about the symptoms of tuberculosis but one of the points in the history that may make tuberculosis a possibility is the gradual onset of symptoms over weeks and months. Clearly,

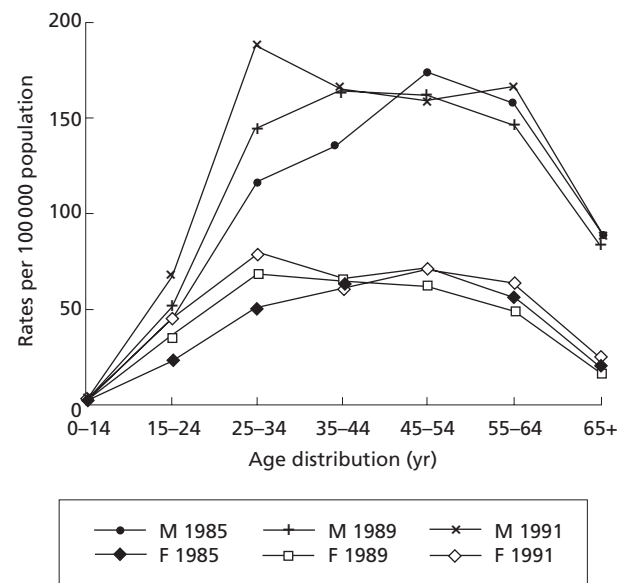


Fig. 17.6 Age and sex distribution in the National Tuberculosis and Leprosy Programme in Tanzania.

middle-aged or elderly patients with carcinoma of bronchus may give a similar history.

Many patients with tuberculosis present with general symptoms, such as tiredness, malaise, loss of appetite, weakness or loss of weight. In advanced cases, febrile symptoms may be reported and night sweats, a classic symptom of tuberculosis, are still commonly admitted by patients with extensive disease. Symptoms are most frequently related to the respiratory system, with cough as the outstanding manifestation. Cough is such a common finding among cigarette smokers that many patients ignore it; however, anyone who develops a cough, or an exacerbation of cough, persisting for more than 3 weeks, even if attributed entirely to cigarette smoking, should have a chest radiograph. Sputum may be mucoid, purulent or blood-stained. Many patients simply admit to cough productive of mucoid or purulent sputum, again often attributed to chronic bronchitis. Haemoptysis is a classic symptom of pulmonary tuberculosis and may vary from mere blood-staining of the sputum to the rarer occurrence of sudden eruption of half a litre or more of blood, occasionally immediately fatal. Massive haemoptysis is usually due to erosion of a bronchial artery, which bleeds at systemic pressure. Chest pain is common and may vary from a dull ache or tightness to pleuritic pain. Coughing may result in 'soreness' of the chest and occasionally a cough fracture. With extensive pulmonary disease, breathlessness may be a feature and endobronchial tuberculosis, although uncommon, may result in localized wheeze [113–118].

It is not uncommon for a patient to present with a history of recurrent colds for a number of months. On close questioning these usually prove to be exacerbations of cough. Patients may occasionally present with an apparent acute pneumonia, the diagnosis of tuberculosis only being made on routine examination of sputum or because of failure of clinical or radiological resolution with broad-spectrum antibiotics. Finally, amenorrhoea may be a presenting symptom, usually in severe tuberculosis.

In summary, the following are the common presentations:

- 1 symptom-free, discovered on routine radiography;
- 2 persistent cough with or without sputum;
- 3 general malaise;
- 4 weight loss;
- 5 recurrent colds;
- 6 pneumonia which proves to be tuberculous;
- 7 haemoptysis.

### Physical signs

There may be no physical signs in pulmonary tuberculosis even with relatively advanced disease, although there may be pallor, a hectic flush or cachexia in severe disease.

In the UK, most patients are afebrile at the time of diagnosis but with more extensive disease there may be a varying degree of fever and the respiration rate may be increased with advanced disease. Finger clubbing is unusual even in chronic disease and in the UK suggests another diagnosis, in particular carcinoma of the bronchus. Severe clubbing has been reported in Africa in association with advanced disease [119].

In the chest there may be no physical signs whatever in spite of extensive radiological changes. The most common early abnormality consists of post-tussive crepitations in the upper zones or apices. With advanced or pneumonic disease there may be signs of consolidation. In chronic disease, deviation of the trachea may occur due to fibrosis. The classical physical signs of a cavity are seldom found even when large cavities are evident on the chest film. Localized wheezes may occasionally be heard if the patient has severe endobronchial tuberculosis.

In general, examination of the chest contributes relatively little to the diagnosis or assessment of postprimary tuberculosis. Sputum examination and chest radiography are much more important. However, it is essential to conduct a general examination of the patient as there may be additional tuberculous lesions outside the chest.

### Radiology

A normal chest film almost, although not completely, excludes pulmonary tuberculosis. There are two provisos. First, it has been shown in a number of studies that small radiological lesions are easily missed [120–123]. Such observer error may be reduced by double reading by two independent observers or even by the same observer on two separate occasions. Second, it is possible for a patient to have localized postprimary endobronchial tuberculosis with a positive sputum and a normal chest film [118].

### Appearances suggestive of tuberculosis

It is seldom possible to make a completely confident diagnosis of pulmonary tuberculosis on radiological grounds alone, as almost all the manifestations of tuberculosis can be mimicked by other diseases. The following characteristics of a chest radiograph favour the diagnosis of tuberculosis:

- 1 opacities mainly in the upper zone(s);
- 2 patchy or nodular opacities;
- 3 presence of a cavity or cavities;
- 4 presence of calcification;
- 5 bilateral opacities especially if in upper zones;
- 6 opacities that persist after several weeks (and thus are less likely due to acute pneumonia).

In appropriate areas, such as North America, all these appearances can be found in histoplasmosis and most of them in coccidioidomycosis (see Chapter 21).

### Characteristic radiographic appearances

Pulmonary tuberculosis can mimic almost all other pulmonary diseases in much the same way that syphilis mimics most neurological diseases.

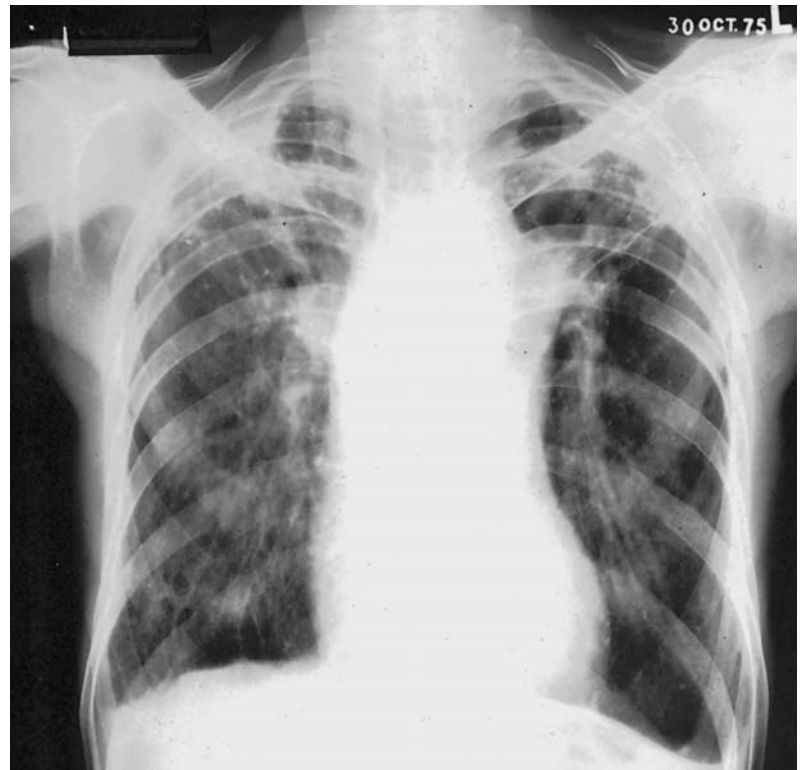
Soft confluent shadows alone suggest an exudative process and may be difficult to distinguish initially from a simple pneumonia. There may be different foci in the lungs. Linear shadows, especially if they produce distortion of fissures, trachea, mediastinum or diaphragm, suggest fibrosis; bilateral upper zone fibrotic shadows, with shrinkage of the upper lobes and elevation of the pulmonary hila, is a common picture (Fig. 17.7). The presence of calcification suggests healed disease, although activity is impossible to determine solely on radiographic grounds, in many cases reactivation occurring on a background of an old calcified lesion. Linear and soft shadows may coexist. Tuberculous disease is usually located in the posterior or apical segments of the upper lobe but, exceptionally, may be restricted to the anterior segment of the upper lobe [124].

Cavitation results from a valvular process in a draining bronchus. Cavities in a mass of caseous material may initially have irregular walls that later become smoother and thinner as caseous material is coughed up or absorbed (Fig. 17.8). A cavity may become 'blocked' and fill with purulent or caseous material, so-called tuberculoma (Fig. 17.9), but with effective chemotherapy such lesions

usually resolve satisfactorily [125]. However, cavities may persist permanently even after effective chemotherapy and eventually be colonized by *Aspergillus* to produce an aspergilloma (see later). Tuberculous cavities may be differentiated from non-tuberculous cavities on the basis of a longer history of illness and the presence around them and in other parts of the lungs of patchy or nodular infiltrates and atelectasis. Non-tuberculous cavities more often have putrid sputum, associated leucocytosis and fluid levels [126]. CT may sometimes be used to confirm the presence of cavities and may also be useful in detecting calcification in a suspicious lesion; this, and the presence of satellite lesions on such tomographic studies, make the diagnosis of tuberculosis more likely.

Bronchiectasis may be suggested by elongated translucent areas in the upper zones and can be confirmed by bronchography, although this does not affect management. If such a bronchus becomes blocked and fills with caseous material, a so-called 'bronchial cold abscess' may form and show as a solid-looking elongated dense shadow, sometimes scalloped.

Enlargement of hilar or paratracheal lymph nodes is unusual in European adults but more frequent in Asians or Africans [127]. The lymphadenopathy and pyrexia in the presence of a positive tuberculin test may be the only manifestations of tuberculous disease. Tuberculosis limited to the lower zones of the lung is uncommon but does occur [128,129].



**Fig. 17.7** Chest radiograph showing bilateral apical fibrosis with calcification and upper lobe shrinkage with elevation of the hila.





**Fig. 17.8** Extensive bilateral tuberculosis with cavity formation at right apex.

### **Radiological classification of disease extent**

For clinical and research purposes the classification of the National Tuberculosis Association of the USA has proved useful [130].

#### ***Minimal***

Minimal lesions include those that are of slight to moderate density but which do not contain demonstrable cavitation. They may involve a small part of one or both lungs, but the total extent, regardless of distribution, should not exceed the volume of lung on one side that occupies the space above the second chondrosternal junction and the spine of the fourth or the body of the fifth thoracic vertebra.

#### ***Moderately advanced***

Moderately advanced lesions may be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight to moderate density that may extend throughout the total volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one-third the volume

of one lung; total diameter of cavitation, if present, must be less than 4 cm.

#### ***Far advanced***

Lesions more extensive than moderately advanced.

### **Other investigations**

#### **Sputum examination**

Sputum examination is of great value in making the diagnosis of pulmonary tuberculosis and in following the patient's response to treatment. If sputum production is difficult, it may be induced by inhalation of nebulized saline. Sputum should first be examined by direct smear using the Ziehl–Nielsen stain. The fluorescence method allows large numbers of specimens to be examined rapidly [131]. Quantitative grading of smears is of value in following progress especially in research [132,133]. Sputum smear examination is usually positive in advanced disease but may be negative in less advanced disease. Sputum smear examination had a sensitivity of about 50% and a specificity of greater than 99% in two reported studies, with a positive predictive value of



**Fig. 17.9** Chest radiograph showing large tuberculoma in right mid-zone, originally thought to be a coincidental carcinoma in patients with extensive upper lobe tuberculosis.

91–98.5% [134,135]. In one study, smears were positive in 52% of patients with cavitating disease but in only 32% with non-cavitating disease [135]; the same study found that 96% of patients with cavitating disease had positive cultures compared with only 70% with local infiltrates. In Edinburgh in 1993, 60% of notified cases of postprimary pulmonary tuberculosis were bacteriologically positive. Comparable figures for European countries are shown in Table 17.1. The considerable variations between European countries for positive mycobacteriology findings has led to recommendations for uniform case definitions and standards of reporting to facilitate international comparisons [137].

Growth is visible on culture only after 3–8 weeks. Guinea-pig inoculation of the sputum is probably more sensitive than a single culture but is now very rarely carried out since multiple cultures are as sensitive as inoculation. Rapid diagnosis is now possible within 2–6 days using a radiometric culture system, the Bactec system [138]. This is particularly valuable for early determination of the resistance characteristics of mycobacteria. In any patient in whom the diagnosis is in doubt,

**Table 17.1** Proportion of cases of pulmonary tuberculosis bacteriologically confirmed in Europe in 1983. (From Horne [136].)

Country	Percentage positive
Belgium	59
Czechoslovakia	55
Denmark	73
England and Wales	56
Federal Republic of Germany	43
Finland	69
France	57
German Democratic Republic	56
Greece	88
Hungary	47
Iceland	83
Luxemburg	52
Netherlands	69
Norway	73
Poland	54
Portugal	60
Sweden	83
Yugoslavia	44
Mean	52

repeated smear and culture examinations should be carried out.

Sputum is sometimes both smear and culture negative even when there are well-marked radiological opacities, symptoms and a subsequent appropriate response to anti-tuberculosis chemotherapy. Such patients may still demonstrate radiographic resolution following antituberculosis chemotherapy consistent with the diagnosis [139]. Direct smear is occasionally negative even in a patient with far advanced disease and, rarely, cultures are also negative. By contrast, it must be remembered that an unexpected positive smear or culture in a patient whose clinical characteristics do not otherwise suggest tuberculosis may be due to a laboratory error (such as a mistake about a name or contamination); alternatively, a neoplastic or infectious process in the lung may have eroded an old tuberculous focus. A single unexpected positive in an inappropriate clinical situation should not be given great weight unless repeated. The possibility of opportunistic mycobacterial infection (see Chapter 20) should be borne in mind. Sputum examination, like all other examinations, must be considered in the total clinical context.

Following the initiation of modern chemotherapy (Chapter 19) sputum cultures become negative most quickly in smear-negative culture-positive disease, less quickly in direct smear-positive cases and least quickly in direct smear-positive cases with far advanced disease, where 8% still have positive cultures after 3 months of therapy [140]. With modern chemotherapy, it is not unusual for organisms to be coughed up and visible on smears but not to grow in culture; this smear-positive culture-negative phenomenon has been observed in 20% of cases for a few weeks after the start of therapy [140].

#### **Bacteriological examination of samples other than sputum**

##### ***Gastric aspirate***

Sputum, especially if not abundant, is frequently swallowed rather than coughed up. In such a situation aspiration of early-morning gastric secretions may reveal acid-fast bacilli on staining [141,142]. The secretions should also be cultured.

##### ***Laryngeal swabs***

Laryngeal swabs are an alternative to gastric aspiration and are simpler to perform and less uncomfortable for the patient [142,143]. The operator should be gowned and masked and the swabs taken in pairs. The first swab usually makes the patient cough and the second often collects the better specimen.

##### ***Fibreoptic bronchoscopic specimens***

Where the conventional methods of obtaining bacterial confirmation of suspected tuberculosis have failed, flexible fibreoptic bronchoscopy may be utilized to provide direct smear or culture-positive specimens from bronchial washings, bronchial brushings or trans-bronchial biopsies [130,144–147].

##### ***Transtracheal aspirate***

This procedure may also yield positive specimens when sputa are negative [148] but the author considers bronchoscopic specimens more productive of results.

##### ***Fine-needle aspiration biopsy***

Where this procedure is being employed to obtain cytology from a doubtful lesion in the lung, if tuberculosis is a possibility then both direct smear and culture of the specimen may yield positive results [149].

##### ***Mediastinoscopy***

Occasionally, mediastinoscopy may be necessary in patients (usually Asians) to provide mediastinal lymph node specimens for pathological and bacteriological examination [150].

#### ***Newer diagnostic techniques***

##### ***Serological diagnosis of tuberculosis***

Serodiagnosis of tuberculosis has been under investigation for some years [151–157], although there is no evidence that serological diagnosis provides any more diagnostic information than can be made available from conventional microbiological investigation. Serodiagnosis using enzyme-linked immunosorbent assay does not add to diagnosis in cases where sputum smears are available [155] and results so far in patients with negative sputum smears have been disappointing [153].

##### ***Polymerase chain reaction***

Diagnostic polymerase chain reaction (PCR) is theoretically capable of detecting a single organism in a specimen of sputum [151,158]. To date its role in clinical practice is not clear. For example, one study reported sensitivity and specificity for sputum PCR of 92 and 99%, although there were only 12 cases of active tuberculosis among the 108 patients studied and PCR failed to detect the one patient with smear-negative culture-positive tuberculosis [159]. In contrast, Walker *et al.* [160] found positive PCR tests even in patients with a past history of tuberculosis or of

tuberculosis exposure. It would seem that this technique still needs evaluation and at the present market prices it is unlikely to displace conventional microbiology.

## Haematology and biochemistry

### *White blood cell count*

In general, a normal total white blood count in the presence of extensive pulmonary shadowing on a chest radiograph favours a diagnosis of tuberculosis (or atypical pneumonia) rather than acute pneumonia or lung abscess. Exceptions to this rule are frequent.

### *Haemoglobin*

A normochromic normocytic anaemia is common in pulmonary tuberculosis but the more bizarre blood dyscrasias characteristic of miliary tuberculosis are unusual and, if present, most likely imply severe disease with cryptic miliary spread.

### *Liver function tests*

It is not uncommon to find abnormalities of liver function tests in moderate or advanced tuberculosis. Since many of the chemotherapeutic agents are hepatotoxic, it is therefore important to determine baseline values for liver function before initiating chemotherapy.

### **Tuberculin testing**

Most patients with postprimary pulmonary tuberculosis have a strongly positive tuberculin test (see Chapter 16).

### **Gallium scanning**

Gallium scanning [161] is of no value in the diagnosis of tuberculosis.

### **Assessment of activity**

Abnormal chest radiographic opacities due to pulmonary tuberculosis are very common, especially in older people in developed countries and at all ages in developing countries. It is often difficult to decide whether a particular lesion should be treated or whether it merits further follow-up to assess activity. The following may give some guidance.

- 1 Bacteriologically positive sputum indicates activity and is an absolute indication for treatment.
- 2 The presence of symptoms such as cough, haemoptysis, tiredness or loss of weight is suggestive that a lesion demonstrated radiologically is active.

- 3 The presence of crepitations on auscultation, especially if persistent, is in favour of activity.

- 4 Certain radiological appearances suggest activity: a cavity (unless there has been previous effective treatment); soft shadows, especially if widespread; and shadows that extend on serial chest films.

Unless the lesion has calcified there is a risk of reactivation of pulmonary tuberculosis, although the risk varies with age and the type of lesion [162–164]. The more extensive the lesion, the younger the patient and the softer the opacity, the more likely is relapse with active tuberculosis. The risk of reactivation is 10 or more times greater than the same risk in tuberculin-positive patients with a normal chest film and can be diminished by chemoprophylaxis [165–168]. Nevertheless, most clinicians in the UK would not treat or give prophylactic isoniazid to such patients, who have no symptoms suggesting activity, have stable chest films and are bacteriologically negative. They should be advised to present themselves for radiography should they develop new respiratory or systemic symptoms suggestive of activity. In the author's experience, annual chest films for such patients are uneconomic and largely unproductive, since patients who do reactivate usually present with symptoms between attendances, like those who relapse following chemotherapy [169].

### **Clinical features in the HIV-positive patient**

The clinical features of tuberculosis in the HIV-positive patient depend on whether tuberculosis is developing early or late in the course of HIV infection [100,170–178]. Tuberculosis tends to occur earlier in the course of HIV infection and in this situation the clinical, radiological and bacteriological findings do not differ substantially from those found in HIV-negative patients. The disease is predominantly pulmonary, located in the upper lobes and cavitation occurs. Tuberculin tests are usually positive and sputum smear positivity is not decreased.

When tuberculosis occurs later in the course of HIV infection or in patients with AIDS the features are more often atypical: pulmonary disease may occur in atypical sites, e.g. lower zone or diffuse consolidation, mediastinal adenopathy is more common and involvement of extrapulmonary sites such as brain, pericardium, bones and the gastrointestinal tract is found [179–181]. Cavitation of pulmonary lesions and tuberculin positivity are less common. Sputum smear negativity may be more common [182].

### **Differential diagnosis of pulmonary tuberculosis**

The most important conditions from which tuberculosis has to be distinguished are pneumonia, carcinoma of the bronchus, lung abscess and pulmonary infarct. In certain regions of America coccidioidomycosis, and histoplasmosis in both America and parts of Africa, have to be consid-

ered. In the developed world as tuberculosis declines, disease due to atypical mycobacterial infection may cause confusion.

### Pneumonia

A segmental pneumonia with soft upper zone opacities may mimic pulmonary tuberculosis. In contrast to tuberculosis, where symptoms may be absent or prolonged, the acute pneumonic patient usually has symptoms of fairly recent onset. A history of contact with tuberculosis may suggest this diagnosis in young people. The diagnosis of tuberculosis is made by sputum examination and tuberculin testing. If the patient is symptomatic, an oral antibiotic should be prescribed and if the radiographic opacities have not cleared or improved in 2–3 weeks then tuberculosis is more likely.

Acute bacterial pneumonia requiring hospital admission sometimes proves to be tuberculous and it is wise to bear this possibility in mind should response to antibiotics not occur. With pneumonia refractory to standard treatment, especially if the white cell count is normal, repeated sputum specimens should be examined for acid-fast bacilli.

### Carcinoma of the bronchus

This differential diagnosis arises in the middle-aged and elderly age groups. Consolidation distal to a proximal carcinoma, particularly in the upper zone, may be cavitated and closely mimic tuberculosis. Occasionally, primary tuberculosis in the elderly presents with a peripheral lesion and enlarged hilar nodes, closely mimicking carcinoma (see Fig. 17.2). Sputum examination for malignant cells and acid-fast bacilli may differentiate the two but bronchoscopy may be required to make the diagnosis. If no tumour is seen and the sputum is negative on direct smear, bronchoscopic specimens should be obtained for direct smear and culture for acid-fast bacilli. Both conditions may of course coexist.

With isolated solid pulmonary opacities, the presence of satellite lesions or calcification, perhaps only detectable on CT, suggests tuberculosis. If bacteriologically negative, it may be possible to establish a diagnosis by transbronchial biopsy or fine-needle aspiration but if this fails then thoracotomy is mandatory, assuming the patient is fit enough for this procedure. If there is any doubt about the lesion, a positive tuberculin test should not delay thoracotomy.

Isolated cavities may also give rise to difficulties. Irregularity of the wall or polypoid protrusions into the interior suggest carcinoma, while satellite lesions or calcification favour tuberculosis. Bilateral shadows suggest tuberculosis. If sputum examination and biopsy attempts are unrewarding, thoracotomy should be considered to establish the diagnosis.

### Lung abscess

Lung abscess due to *Staphylococcus pyogenes* or *Klebsiella pneumoniae* is usually an acute severe illness with marked leucocytosis and the organism readily isolated from blood or sputum. There may be multiple abscesses. With cavitary tuberculosis the sputum is usually, but not always, positive on direct smear.

### Pulmonary infarction

Upper zone pulmonary infarcts, especially if bilateral and/or cavitating, may give rise to diagnostic difficulty. Routine investigations, evidence of deep vein thrombosis and serial chest films that show rapid change in pulmonary infarction usually readily distinguish the two conditions.

### Other pulmonary diseases

Tuberculosis enters into the differential diagnosis of many other pulmonary diseases and sputum examination and tuberculin testing are essential in the investigation of abnormal pulmonary shadows. Atypical mycobacterial disease is a frequent source of diagnostic confusion (see Chapter 20).

## Complications

### Pleurisy

Pleurisy occurs commonly in pulmonary tuberculosis. A classical pleural rub may be heard (see Chapter 43).

### Tuberculous empyema

Tuberculous empyema was commonly found following artificial pneumothorax therapy. It still presents as many as 30 years after initial infection [183]. It is now rare but may be seen in association with pleural effusion complicating severe pulmonary disease or as the result of rupture of a cavity into the pleural space [184]. The diagnosis is made by the demonstration of acid-fast bacilli on direct smear in pus from the pleural space. Chemotherapy and tube suction may resolve the situation but further surgical procedures such as decortication may be indicated [184,185].

### Tuberculous laryngitis

This is seen in patients with positive sputum and relatively severe disease. It causes hoarseness progressing to pain on swallowing. Lesser lesions, such as oedematous arytenoids, may be detected on laryngoscopic examination [186]. Biopsy is important in establishing the diagnosis.

### Tuberculosis of other organs

Tuberculosis may not be confined to the lung. In the male the testes should be examined routinely, and routine examination of the urine for tubercle bacilli is advisable.

### Chronic obstructive airways disease

There is no doubt that a clinical pattern of disease almost indistinguishable from that of chronic bronchitis and emphysema with severe airways obstruction may result in patients with severe fibrotic pulmonary disease following tuberculosis [187–189].

### Cor pulmonale

A logical extension of chronic obstructive airways disease is that some patients develop cor pulmonale secondary to extensive fibrotic disease, with distortion of pulmonary parenchyma, emphysema and airways obstruction. Early treatment obviates this late complication of pulmonary tuberculosis.

### Amyloidosis

This complication is now rare but may still be seen in association with a tuberculous empyema. Diagnosis may be made by the staining of rectal, mucosal, liver or kidney biopsies.

### Aspergillomas

Infection of tuberculous cavities by *Aspergillus fumigatus* is well recognized (Fig. 17.10). Most give rise to no major problems apart from occasional haemoptysis from which sudden death rarely occurs. Surgical resection of lesions causing major problems (i.e. massive haemoptysis) may be feasible [190,191] provided pulmonary function is adequate (see Chapter 21).

### Carcinoma of the bronchus

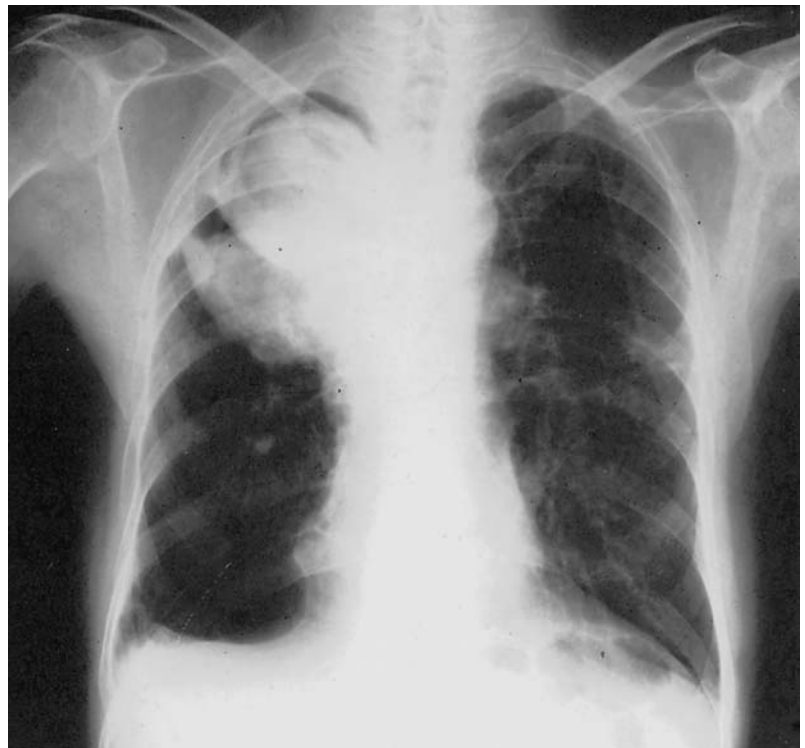
There is no definite evidence that carcinoma of the bronchus is more common in patients with inactive tuberculous disease. However, both are common in cigarette smokers and may occur together. The concept of 'scar carcinoma', although attractive, has never been fully established [192].

### Adult respiratory distress syndrome

The adult respiratory distress syndrome may complicate postprimary tuberculosis [193].

### Pulmonary tuberculoma

Tuberculoma presents occasionally as an incidentally discovered solitary pulmonary nodule. If there is any doubt about the nature of the lesion, then it is best resected since



**Fig. 17.10** Aspergillomas in old tuberculous cavities: the upper cavity contains an aspergilloma and shows the classical air crescent sign; the lower cavity has a fluid level with an aspergilloma protruding above it.

the principal differential diagnosis is from bronchogenic carcinoma [194].

### Poncet's disease

Finally, and scarcely a complication but an accompani-

ment of postprimary pulmonary tuberculous disease, mention must be made of Poncet's tuberculous polyarthritides [195]. First described in 1897, and reiterated as recently as 1984 [196], this polyarthritides, resembling rheumatic fever, may occur in association with postprimary pulmonary tuberculosis. It resolves with treatment.

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# EXTRA-PULMONARY TUBERCULOSIS

R. ANDREW SEATON

Tuberculosis is an increasing problem for the developed world, particularly among the economically deprived [1], the growing immigrant population and elderly, debilitated or frankly immunosuppressed patients. Human immunodeficiency virus (HIV) infection is a well-recognized risk factor for both activation of initial infection and reactivation of latent infection. In the USA, patients with AIDS are 54 times more likely to have tuberculosis than the rest of the population and patients with tuberculosis are 204 times more likely to have AIDS [2]. The incidence of extrapulmonary features tends to increase with advancing immunosuppression in HIV-infected persons. However, the burden of both HIV infection and tuberculosis is greatest in sub-Saharan Africa; in Zambia, 49% of patients with pulmonary tuberculosis are HIV-antibody positive and the incidence of HIV infection increases to 84% when extrapulmonary sites are involved [3]. Similar trends can be expected to develop in Asia, where tuberculosis is already endemic, as HIV seroprevalance grows [4]. In other developing countries, such as India and Papua New Guinea, a failure of local control programmes has meant that tuberculosis remains a major public health problem despite relatively low HIV seroprevalance rates. Despite this, tuberculosis is emerging as a significant cause of morbidity in the increasing HIV-infected population [5]. This chapter is primarily concerned with describing the clinical features of extrapulmonary disease, which worldwide comprises approximately 10–50% of all tuberculosis presentations in HIV-negative patients [6,7] and 35–80% in HIV-infected patients [2,7,8]. In Scotland in 1993, extrapulmonary tuberculosis accounted for approximately 21% of tuberculosis notifications in the Caucasian population and 53% of such notifications in the Indian subcontinent population [9]. The commonest manifestations of extrapulmonary tuberculosis are superficial lymphadenitis, genitourinary disease, pleural disease, miliary disease, bone and joint disease and abscesses of the soft tissues (Table 18.1). Pericardial disease is of particular importance in HIV-infected patients in the developing world and mycobacterial bacteraemia may be detected

in most HIV-infected patients with tuberculosis. Most forms of extrapulmonary tuberculosis are readily diagnosed and treated, provided a high index of suspicion is maintained. However, there is evidence through autopsy surveillance that extrapulmonary tuberculosis is underdiagnosed in both the developed and underdeveloped world. In the USA, 18% of miliary, meningeal and peritoneal tuberculosis is diagnosed after death [10]; in HIV-infected patients in Italy, only 70% of autopsy-proven extrapulmonary tuberculosis is diagnosed clinically [11]. In African patients with HIV-related 'slim disease' (patients previously thought to be wasted due to chronic enteric infections), autopsy studies have shown that disseminated tuberculosis is significantly correlated with wasting [12].

When diagnosed, the presence of extrapulmonary features may have important implications with respect to management, particularly in considering the use of adjuvant therapies such as corticosteroids and surgery, but all forms require standard antituberculous treatment as described in Chapter 19. Pulmonary tuberculosis and pleural disease are covered in Chapters 17 and 43. Where appropriate, special mention is made of therapy in organ-specific tuberculosis.

## Central nervous system tuberculosis

Central nervous system (CNS) tuberculosis is a particular problem in infants and children, in whom disease occurs as a complication of primary infection, but it also complicates miliary disease in both adults and children. In patients with tuberculosis and HIV infection there is a significantly greater risk of meningeal disease than in the non-HIV-infected tuberculosis population [13].

## Pathology

The most common manifestation of CNS tuberculosis is meningitis. The meninges are presumably infected at the time of disease dissemination and it is the breakdown of

**Table 18.1** Distribution of extrapulmonary tuberculosis in Lothian, Scotland in 1993. (Adapted from Leitch *et al.* [9].)

Site of tuberculosis	Percentage
Lymphatic	37.5
Genitourinary	23.4
Pleural	12.5
Miliary	8.6
Bone and joint	5.5
Cold abscess	4.7
Gastrointestinal	3.1
Meningitis	3.1
Pericardial	0.8
Skin	0.8

meningeal granulomas with seeding of the cerebrospinal fluid (CSF) and extension of the process that leads to the clinical manifestations. The basal meninges are usually covered with a gelatinous exudate that contains lymphocytes, fibrin and caseating granulomas. This inflammatory process may extend into the cerebrum or cerebellum, where larger collections, or tuberculomas, are formed. Alternatively, and possibly more commonly, tuberculomas may arise from blood-borne dissemination of infection and may present as mass lesions. The most frequent site for operatively proven intracerebral tuberculomas is the posterior fossa, where 67% of all mass lesions are found. Multiple lesions occur in about 16% of patients. Coexistent meningitis is relatively rare in the presence of intracerebral tuberculoma in non-HIV-infected patients [14]. Involvement of the basal meninges commonly leads to cranial neuropathies and the exudative process may also cause obstruction of CSF flow, leading to hydrocephalus. Arteritis may also develop and lead to cerebral and brainstem infarction [15]. Encephalitis with oedema and gliosis of brain tissue is also recognized and increased intracranial pressure may result in tentorial herniation of the brainstem. Cerebral tuberculous abscesses are histologically distinct from the more common cerebral tuberculomas and depend on the finding of macroscopic pus in the abscess cavity with acute inflammatory changes within the abscess wall associated with *Mycobacterium tuberculosis*. Abscesses are thought to arise because of haematogenous spread from a pulmonary focus; they tend to be solitary and progress more rapidly than tuberculomas [16].

### Clinical features

These are usually insidious and take the form of malaise, fever, weight loss, headache, diplopia, altered consciousness and meningism. Cranial neuropathies, particularly involving the abducens, oculomotor and facial nerves, are common and sensorineural deafness is also recognized. In infants, failure to thrive and bulging fontanelles may be

presenting features and late presentation may result in severe neck retraction. Focal neurological signs, such as hemiparesis, monoparesis, quadriparesis and cerebral paraplegia, may occur when tuberculomas are present [15] or indeed may arise as a result of arteritis and infarction. A variety of other neurological syndromes have also been described, including tremors (generalized or parkinsonian), hemiballismus, myoclonic jerks and cerebellar ataxia [15]. Symptoms and signs of raised intracranial pressure, such as coma, generalized convulsions, systolic hypertension and papilloedema, may also be present. Symptoms and signs in HIV-positive patients are similar, although other opportunistic infections commonly coexist [13] and other CNS diseases should also be excluded whenever possible [16,17].

### Differential diagnosis

As this depends on the mode of presentation, the site of the tuberculous lesions, the presence or absence of HIV infection and the origin of the patient, the differential diagnosis is wide. Tuberculous meningitis must be differentiated from bacterial and fungal meningitis, particularly cryptococcal meningitis which occurs in approximately 5% of AIDS patients in the UK [18] and in 10% of those in the USA [19], where it is one of commonest life-threatening opportunistic infections. In immunocompetent patients in some tropical settings, cryptococcal meningitis is commoner than tuberculous meningitis [20] but can be easily differentiated by positive serum or CSF cryptococcal antigen assays or by india ink staining and culture of CSF. Viral meningitis may be rarely confused with tuberculous meningitis owing to the relative lymphocytosis in CSF.

The differential diagnosis of a space-occupying lesion includes primary or secondary brain tumours and particularly medulloblastomas in the posterior fossae of children. Intracerebral cysticercosis must also be differentiated in endemic areas [21].

### Investigations

The majority of CNS tuberculosis is diagnosed in the developing world where resources are often poor. Therefore a high index of suspicion should be maintained in all neurological syndromes in endemic areas and often the response to empirical antituberculous therapy is the most valuable diagnostic tool.

The examination of CSF is mandatory in any suspected case of tuberculous meningitis and characteristically demonstrates pleocytosis (>20 cells and >60% lymphocytes) on direct microscopy, although early in the disease process polymorphonuclear cells may predominate. CSF protein concentration is usually raised (>500 mg/L) and CSF glucose is usually less than 60% of corresponding

blood sugar. In some, but particularly HIV-positive patients, CSF protein concentrations may be normal; less frequently CSF may be acellular [13,22]. CSF parameters may also vary depending on the level from which the specimen is retrieved. A patient with hydrocephalus seen recently demonstrated normal CSF in a ventricular sample but examination of a lumbar sample revealed a marked lymphocytosis. The diagnosis is established by demonstrating acid-fast bacilli following Ziehl–Nielsen staining or by fluorochrome staining of CSF, which is slightly more sensitive. However, microscopy may only be positive in one-quarter of patients. Culture of CSF on Lowenstein–Jensen medium or by guinea-pig inoculation has a higher diagnostic yield than direct CSF examination but takes 3–6 weeks and therefore seldom affects initial management. Newer methods such as radiometric technology using liquid media (Bactec, Becton Dickinson) provide more rapid results but still take between 2 and 3 weeks [2,7]. An enzyme-linked immunosorbent assay (ELISA) that detects CSF mycobacterial antigens has proved both sensitive and specific [23] as has detection of tuberculostearic acid in CSF [24], although these techniques are not widely available. The polymerase chain reaction has recently been used to validate traditional methods of diagnosis and has been found to be positive in 86% and 75% of patients with highly probable and probable tuberculous meningitis respectively. These results were found to correspond to the clinical response to chemotherapy [25].

The tuberculin test is difficult to interpret in CNS tuberculosis in adults, particularly in the immunosuppressed population, who may be anergic, and in endemic areas where the majority of adults can be expected to have had prior exposure to tuberculosis. However, in infants a positive tuberculin test may be helpful. Clinical features of extrameningeal tuberculosis are usual in both HIV-infected [13,17] and non-infected patients [26]. Hyponatraemia is frequently found [27] and may result from inappropriate antidiuretic hormone secretion [28], as in other organic brain syndromes, rather than as a result of adrenal insufficiency, which appears to be uncommon in tuberculosis [29].

Neuroradiological scanning has contributed greatly to the diagnosis and management of CNS tuberculosis, particularly in detecting hydrocephalus, which has been demonstrated in 87% of children and 12% of adults with tuberculous meningitis [30]. Tuberculomas appear on cerebral CT as isodense, hypodense or hyperdense rounded lesions, 1.5–7 cm in diameter with peripheral enhancement and perifocal oedema after the injection of contrast [31]. Lesions are calcified in 38% of patients with meningitis and in 1–6% of those with tuberculomas [32]. Magnetic resonance imaging (MRI) may also be useful [33] but probably does not add to information gained by CT. In India, ring- or disc-enhancing lesions on CT in

patients with epilepsy were found to be most commonly due to cysticercosis, although tuberculomas accounted for 14% of all biopsied lesions [21]. In HIV-infected patients with tuberculous meningitis, CT has been found to be abnormal in 69% and appearances are similar to those in non-HIV-infected patients [13].

### Treatment and prognosis

The treated mortality in CNS tuberculosis is 20–50% [34] including those infected with HIV [13]. In survivors the sequelae can be devastating; in India 53% of survivors had permanent sequelae, 41% of whom had moderate to severe disability, such as hemiparesis, involuntary movements, substantial mental impairment, inability to function independently or a persistent vegetative state [35]. With this background of treatment failure despite antituberculous chemotherapy, much attention has been focused on the use of adjuvant corticosteroids. It has been postulated that they could improve morbidity and mortality by reducing cerebral oedema, cerebral vasculitis and the formation of exudate, thereby preventing the development of hydrocephalus [34]. The development of cerebral tuberculomas during antituberculous chemotherapy, associated with neurological deterioration, has also been described in patients with meningitis as well as in those with extrameningeal disease [36,37], and corticosteroids are probably beneficial in this situation [36]. Some favour their use in all patients with tuberculous meningitis [38], although the risk of reduced CSF penetrance of antituberculous drugs (by restoring the blood–brain barrier) are an important consideration when treating patients with less severe disease [39]. A randomized controlled trial of 43 patients in India suggested that sequelae were reduced in dexamethasone-treated patients, although no significant statistical difference was noted and there was no difference in mortality [40]. An older but larger study had suggested that corticosteroids improved survival [41], although this has been criticized because of its high overall mortality (51%), the large number of patients lost to follow-up and its method of analysis [34]. Another study has suggested that steroids may improve mortality when used to reduce cerebral oedema in patients with severe disease but the numbers were small (23 patients) and the results not statistically different [42]. The British Medical Research Council has defined three stages of CNS tuberculosis [43]: stage I or mild cases, with no alteration in consciousness and without neurological signs; stage II or moderately advanced cases, with altered consciousness (but not comatose) and mild focal neurological deficits; and stage III or severe cases, who are comatose with multiple neurological deficits (including multiple cranial nerve palsies and bilateral neurological signs). Using these definitions a large Chinese study [44] has purported to show reduced mortality in stage II and III disease with no

difference in stage I disease. With no controlled studies yet showing increased mortality or morbidity with corticosteroid use in the later stages, the current consensus is to use these drugs in stage II and III disease at a dose equivalent to prednisolone 1 mg/kg daily for 30 days, followed by a gradual reduction in the dose over the next few weeks [34]. As yet, corticosteroid use in HIV-related CNS tuberculosis has not been evaluated.

There are few data to support the neurosurgical resection of all tuberculomas as they tend to respond to chemotherapy [32,33]. However, tuberculomas of the posterior fossa may require drainage, and the mechanical relief of hydrocephalus due to adhesions may also improve outcome [39]. In a series of 48 patients with tuberculous meningitis managed in a French intensive care unit, 15 patients underwent insertion of a CNS prosthetic device for the treatment of hydrocephalus. Despite this aggressive treatment 11 died, with neuroradiological signs of cerebral infarcts in nine, while one survivor had severe neurological sequelae. In two patients, death was attributed to nosocomial infection of the prosthetic device [45].

Prolonged adjunct therapy with interferon (IFN)- $\gamma$  and granulocyte colony-stimulating factor has been reported to cure an immunocompromised patient with refractory multidrug-resistant tuberculous meningitis [46]. In this case there was complete resolution of neurological and radiological signs following the introduction of this adjunct therapy. The proposed mechanism of action is via IFN- $\gamma$  activation of monocytes and macrophages against tuberculosis in the immunosuppressed patient.

### Superficial tuberculous lymphadenitis

This is the commonest form of extrapulmonary tuberculosis in both HIV-infected and non-infected patients [2,7]. Involvement of lymph nodes may result from direct extension of infection or from haematogenous spread. In developing countries, lymph node tuberculosis most commonly affects young adults [47,48]. In the UK, most cases are seen in patients of Indian subcontinent origin [49]. Non-Caucasian patients with lymphadenitis are usually aged 10–50 years, whereas Caucasians tend to be older than 50 [50–52].

#### Clinical features

The patient usually presents with slow painless swelling of cervical or submandibular nodes (Fig. 18.1). Other sites may also be involved, including supraclavicular, inguinal and axillary nodes (Fig. 18.2) and there may be multiple swellings. Occasionally the onset may be acute and painful with a perinodal reaction. Fever may occur but is more common in HIV-infected patients [53]. A cold abscess or sinus may form.

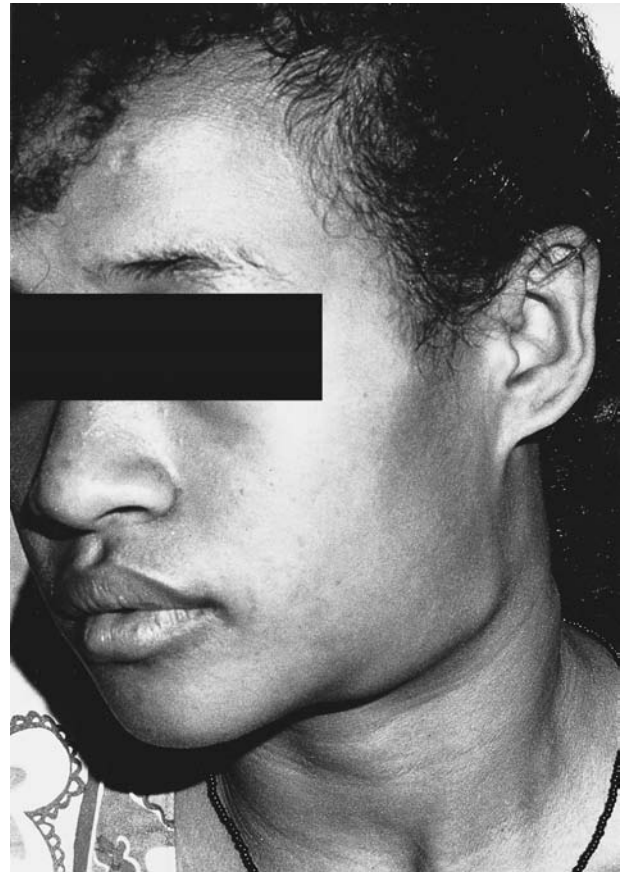


Fig. 18.1 Left-sided submandibular tuberculous lymphadenitis.

#### Investigations

The diagnosis is established by culture of material obtained via node biopsy, excision or fine-needle aspiration. Wide-needle aspiration of tuberculous lymph nodes under local anaesthesia has been successfully employed in Africa, with a sensitivity of 74.8% and specificity of 97.4% [54]. Pathological examination of tissue may show typical tuberculous histopathology. Mycobacterial lymphadenitis in children is most commonly due to non-tuberculous mycobacteria, whereas in adults *M. tuberculosis* is the usual infecting organism [48,55]. Patients with HIV infection have a poor cellular response and are less likely to demonstrate caseating granulomas [55]. Typically, in HIV-infected patients, smears of infected nodes demonstrate a greater burden of organisms than in HIV-negative patients, reflecting advanced immunosuppression [56]. Whereas HIV-infected patients usually have evidence of parenchymal lung disease, only 25–30% of HIV-negative patients have evidence of pulmonary involvement [53,57].

### Tuberculous pericarditis

Pericarditis is a serious and life-threatening manifestation of tuberculosis. Although it is rare in developed countries,





**Fig. 18.2** Left-sided axillary tuberculous lymphadenitis.

in some developing countries it is the commonest cause of pericardial disease and an important cause of heart failure [58]. Prior to the emergence of HIV infection, tuberculous pericarditis was seen most frequently in the Caucasian population in the third, fourth and fifth decades [59,60], and accounted for 11% of all pericarditis where a specific cause was documented [58]. In the UK, most cases occurred in patients of Asian origin of whom 88% were under the age of 45 [60]. In some developing countries pericardial disease is as common in children as it is in adults [58,61]. HIV infection is now known to be strongly associated with pericardial tuberculosis; 84% of African patients with tuberculous pericardial effusions are infected with HIV [3] and in the HIV-infected population tuberculosis is the commonest cause of a large pericardial effusion [62].

### Pathogenesis

The disease begins either by infiltration of the pericardium by a caseous node or by miliary spread. The heart becomes covered by a fibrinous, caseous material that with the exudate can result in pericardial effusion. If the process heals by fibrosis, then constrictive pericarditis ensues [58]. Tuberculous mediastinal lymphadenitis may lead to the formation of a fistula between a bronchus and the pericardium, resulting in pneumopericardium and occasionally cardiac tamponade [63].

### Clinical features

The commonest symptoms of pericardial disease are weight loss, cough, dyspnoea, orthopnoea, chest pain and ankle swelling. The most commonly elicited signs are fever, tachycardia, pericardial rub, paradoxical pulse,

hepatomegaly, oedema, neck vein distension, muffling of the heart sounds, abdominal distension, ascites and hepatomegaly. The clinical signs vary depending on the degree of effusion or constriction. Signs of constriction are most distinctive, with raised jugular venous pressure and a prominent 'Y' descent [58]. Friction rubs are usually absent but a diastolic knock with a third heart sound are typical. Inspiratory splitting of the second heart sound is usually found [58]. Symptoms and signs are similar in HIV-positive and HIV-negative patients, although HIV-positive patients are more frequently pyrexial and constriction is less frequently seen [63].

### Investigations

Chest radiography consistently shows cardiomegaly when pericardial effusions are present but the heart size may be normal when constriction predominates. Calcification of the pericardium is infrequently seen. Pleural effusions are seen in 40–77% of patients and other radiographic abnormalities, particularly pneumonia and mediastinal lymphadenopathy, are also common [58,62]. Electrocardiographic abnormalities occur in most, notably low-voltage complexes and T-wave inversion or flattening [58]. Echocardiography reveals pericardial effusion with or without pericardial thickening and fibrinous or caseous debris. Diastolic collapse of the right atrium is characteristically seen in patients with significant effusions and M-mode studies may demonstrate impaired left ventricular function [61]. Pericardial aspiration usually reveals blood-stained fluid, although it may be straw-coloured [58,61]. Microscopy may show a lymphocytic exudate but smears for acid-fast bacilli are negative in most cases [61]. *M. tuberculosis* can be isolated by culture in up to 50% of patients [59]. In HIV-positive patients in developing coun-

tries, a presumptive diagnosis of tuberculosis can be made on the basis of a pericardial effusion alone [62], although cardiomegaly and heart failure must be differentiated from primary HIV cardiomyopathy in patients with more advanced HIV disease. A high index of suspicion must be maintained in other patients, in whom the differential diagnosis includes pyogenic, malignant and autoimmune-related pericardial disease. In developing countries and in patients of African or Asian origin, amoebic pericardial effusions should be considered, particularly if symptoms are acute. Serodiagnosis, using a solid-phase antibody competition sandwich ELISA, has recently been evaluated and has a sensitivity of 61% and specificity of 96% [64]. This technique may prove useful in patients in whom it is not possible to culture pericardial fluid.

### Treatment

The response to chemotherapy is variable and most authorities advocate adjuvant corticosteroid treatment [38], with or without pericardiocentesis and/or pericardectomy. Complete open drainage of pericardial fluid on admission has been shown to reduce significantly the need for subsequent pericardiocentesis but does not appear to influence the need for pericardectomy for subsequent constriction or the risk of death [65]. Adjuvant prednisolone during the first 11 weeks of chemotherapy significantly reduces the risk of death due to pericarditis and also reduces the need for repeated pericardiocentesis [66]. The dose of prednisolone in adults is 60 mg daily for the first month, 30 mg daily for the second month, 15 mg daily for 2 weeks and 5 mg daily for the final week. In patients presenting with constriction, prednisolone significantly reduces pulse rate and jugular venous pressure [66]. However, both parameters are comparable to those of patients receiving chemotherapy alone following discontinuation of prednisolone after 11 weeks [66]. Long-term follow-up of patients with constriction treated with prednisolone shows a more rapid return to unrestricted activity and a reduction in mortality related to pericarditis. However, the need for subsequent pericardectomy is not reduced and is necessary in 21–30% of patients. Pericardectomy is indicated for those not responding to chemotherapy and corticosteroids, particularly in refractory heart failure where operative intervention may be life-saving.

### Bone and joint tuberculosis

Bone and joint tuberculosis is a common manifestation in developing countries, occurring in up to 20% of all patients with diagnosed active tuberculosis [67]. In the UK, bone and joint disease is less common, occurring in about 5% of all tuberculosis notifications [68], with about half of these cases occurring in patients of Asian origin.

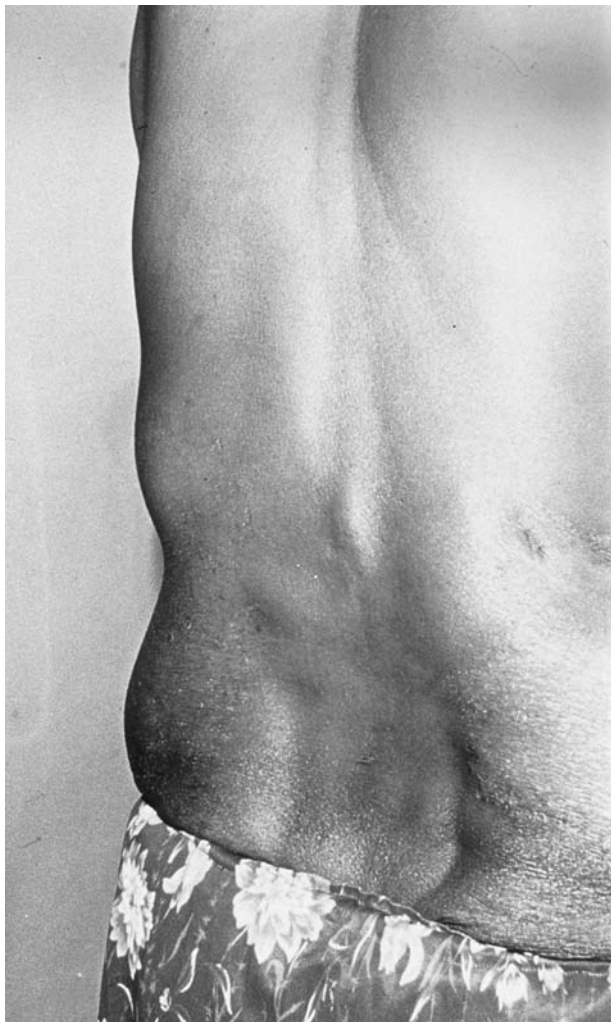
Disease is most common in children and young adults in developing countries [69]. Tuberculosis of the skeleton usually arises as a result of haematogenous spread and is said to occur 1–5 years after primary infection [70].

### Clinical features

Half of all bone and joint infections involve the spine, with the weight-bearing joints involved next most commonly [7,67]. Other sites can be involved, including the elbow and shoulder [71,72], the wrist [73], hands and fingers [67], and the non-articular skeleton including the ribs, scapula and skull [74,75]. The risk of bone and joint tuberculosis may be increased in patients with underlying inflammatory joint disease, particularly those receiving corticosteroid therapy [71], and may postdate pulmonary tuberculosis by years [73,76].

Spinal tuberculosis or Pott's disease is commonest in the lower thoracic and lumbar regions [69,77] but may also affect the cervical spine [67,73,78]. The vertebral bodies and intervertebral discs are most commonly affected. The usual presentation is with local pain, stiffness and limitation of movement. Diagnosis is often delayed and symptoms may have been present for months or years before presentation. Often a recent fall or apparent back trauma precipitates admission to hospital, resulting in the fortuitous discovery of spinal tuberculosis. Between 14 and 23% of patients present with clinically detectable abscess or sinus formation [77,79] (Fig. 18.3) and rarely with isolated abdominal symptoms due to an associated psoas abscess [80]. Neurological signs are present in 6–12% of patients [67,69,77,79] and vary depending on the spinal level involved. At worst the patient may present with complete motor and sensory loss in the lower limbs with loss of sphincter control [81]. Cervical spine involvement may present with quadriplegia, while lumbosacral tuberculosis is usually not associated with a neurological deficit [82]. Neurological signs may sometimes develop or worsen during chemotherapy, but in the majority of patients these neurological deficits improve [81]. Neurological involvement is caused by direct pressure on the cord from sequestered bone and disc, granulation tissue and pus, or spinal cord instability [78]. Less frequently, tuberculous inflammation crosses the dura to involve the meninges and spinal cord. Late-onset paraplegia is also well described and may occur years after the development of spinal deformity [78,83]. This may arise as a result of vascular insufficiency, prolonged angulation of the cord over an internal gibbus or reactivation of the tuberculous process [78]. Gibbous deformity, kyphosis and other spinal deformities occur in patients with more advanced disease due to collapse of vertebrae.

Systemic symptoms are variably present in spinal tuberculosis, but about 40% of patients experience weight loss [84]. Radiological evidence of past or present pulmonary



**Fig. 18.3** Lumbar hump due to Pott's disease complicated by a cold abscess to the right.

tuberculosis is present in 42% [77,84], although other forms of extrapulmonary tuberculosis are rarely encountered [67].

Tuberculosis of other peripheral bones and joints presents with chronic progressive pain, stiffness and swelling (Fig. 18.4), and a history of previous trauma is often elicited [72]. Systemic symptoms are present in about half of patients and soft tissue abscesses and sinuses may also be associated. Pulmonary tuberculosis is detected in approximately half of these patients [72].

### Radiological features

In early spinal disease, diminution of the disc space with erosion of end-plates is seen, with subsequent destruction and collapse of vertebral bodies (Figs 18.5 & 18.6). In about 60% of patients at least three or more vertebrae are



**Fig. 18.4** Tuberculosis of the second metacarpal with cold abscess formation in an Asian patient.

involved [69,79] and in 5% lesions extend from the thoracic spine to the sacrum [69]. Of patients with spinal disease, 57% have plain-film evidence of psoas or paraspinal abscess [77], although when CT is employed abscesses are detected in 91% [84]. In Bombay the clinical diagnosis of spinal tuberculosis was confirmed when MRI was used in 23 of 24 symptomatic patients with normal spinal radiographs [85].

In peripheral joint tuberculosis the commonest radiographic abnormalities are bony erosions and destructive changes, joint space narrowing, asymmetry of condyles (knee joints), osteopenia, cortical cysts and pathological fractures [72].

### Diagnosis

For the most part diagnosis is based on clinical and radiological evidence, particularly in spinal disease where histological or microbiological diagnosis may not be feasible. A high index of suspicion should be maintained in all age groups in developing countries. In developed countries the immigrant population and patients with previously documented or suspected tuberculosis are also at greater risk. Spinal disease should be differentiated from metastatic disease, particularly in developed countries where



**Fig. 18.5** Pott's disease of the spine affecting the T12/L1 disc space and adjacent vertebrae.

Pott's disease is rare. Rapid diagnosis of early lesions may be made if MRI is available. Peripheral joint disease may be more difficult to diagnose and depends on the exclusion of other infective and non-infective arthritides, including gout, rheumatoid arthritis, connective tissue disease and sarcoidosis. Culture of synovial fluid may be positive in 64% and typical caseating granulomas are seen in about half the patients who undergo synovial tissue biopsy [71,72]. Stains for acid-fast bacilli in synovial fluid are infrequently positive [71,72].

### Treatment

The majority of patients with spinal tuberculosis respond to short-course chemotherapy alone, including those with sinuses or abscesses on admission [69]. Results are less favourable on regimens that do not include rifampicin. Immobilization of the spine with a plaster-of-Paris cast is no longer advocated [79]. In specialist units with vast experience, the 'Hong Kong' operation, which involves resection of lesions and anterior spinal fusion with autologous bone grafts, has proved successful but is not a substitute for chemotherapy [77]. In a large series of paraplegic patients treated with chemotherapy alone, 72% were func-

**Fig. 18.6** (a) Early tuberculous changes in the lumbar spine showing disc narrowing at L1/2, destruction of the body of L2 and demineralization of the adjacent end-plate. (b) The same patient 17 months later showing mild gibbous deformity resulting from extensive collapse of L2.



(a)



(b)

tionally and neurologically normal between 1 and 6 years of follow-up and 84% were sufficiently recovered to walk unaided. Only 6% of patients were left paralysed and unable to walk [81]. The role of surgery is yet to be clearly defined but is probably applicable to only a small percentage of patients with severe, deforming disease and then only in specialized centres. As the majority of spinal disease occurs in the developing world where such surgical expertise may be lacking, it is encouraging to see the success of new short-course chemotherapy regimens. In peripheral joint tuberculosis chemotherapy is also the mainstay of treatment [71].

### Gastrointestinal tract and peritoneal tuberculosis

Abdominal tuberculosis occurs infrequently in the indigenous population of the UK but is an important disease in migrants from Asia, in whom the incidence is highest in those under the age of 50 [86]. In the USA, two distinct groups are recognized as being at increased risk of abdominal tuberculosis: migrants from developing countries and patients infected with HIV [87]. In developing countries, peritoneal tuberculosis is a relatively common cause of ascites, and other forms of abdominal tuberculosis occur frequently enough to merit inclusion in any differential diagnosis of abdominal pain, organomegaly or abdominal mass, particularly in young adults with constitutional symptoms.

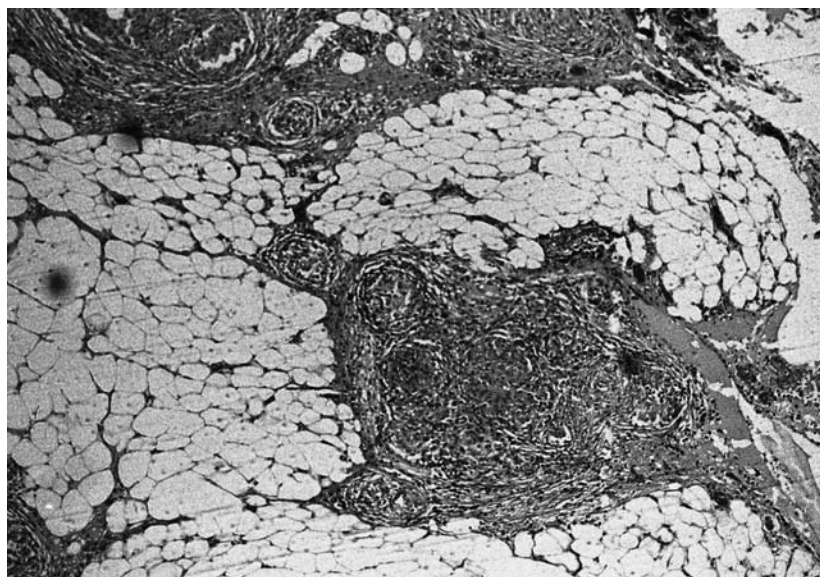
#### Pathogenesis

The peritoneum and viscera (liver, spleen and pancreas) may be involved via the bloodstream, usually following reactivation of foci from a primary lung focus, although

haematogenous spread may complicate active pulmonary tuberculosis or miliary tuberculosis (Fig. 18.7). Contiguous spread from mesenteric lymph nodes, intestine or fallopian tubes may also occur. The majority of patients with peritoneal tuberculosis have ascites at the time of presentation but a small proportion may have a 'dry' fibroadhesive form of the disease [88]. The gastrointestinal tract may be involved via four mechanisms: (i) swallowing infected sputum; (ii) ingestion of contaminated milk (rare in developed countries); (iii) haematogenous spread; and (iv), rarely, direct extension from adjacent organs. The ileocaecal area and jejunum are the commonest sites of tuberculous involvement but any level, from the oesophagus to the anus, may be involved. Pathologically most inflammation takes place in the submucosa and serosa, leading to bowel wall thickening and later fibrosis. Ulceration occurs in some as a result of endarteritis of submucosal vessels [88]. Intestinal narrowing may occur as a result of stricture formation or by extrinsic compression from enlarged mesenteric lymph nodes.

#### Clinical features

One-quarter to half of all patients with abdominal tuberculosis present with peritoneal tuberculosis [86,88–90]. Symptoms develop insidiously over weeks or months, with abdominal swelling due to ascites; most have fever, weight loss, abdominal pain and tenderness. In patients with ascites, particular attention must be paid to their cardiovascular status as pericardial disease may present similarly. About 16% of patients with peritoneal disease also present with diarrhoea [89]. Evidence of active pulmonary tuberculosis is present in up to half and 48–62% have abnormal chest radiographs suggestive of active or healed pulmonary tuberculosis [88,89]. Peritoneal tuberculosis



**Fig. 18.7** Biopsy of peritoneal lesion showing tuberculous granuloma.

also accounts for about one-fifth to half of all cases of abdominal tuberculosis in patients with HIV infection [87,91], although absence of pain and abdominal findings are not uncommon.

Tuberculosis of the small bowel and colon also presents insidiously with non-specific symptoms. Abdominal pain is present in most, diarrhoea in one-fifth, weight loss in two-thirds and fever in 35–50% [88]. Nausea, vomiting, melaena and rectal bleeding may also be presenting features. Abdominal tenderness is elicited in most patients, and up to 50% have a palpable mass in the right iliac fossa [88]. A 'doughy abdomen' due to extensive intra-abdominal inflammation may also be detected.

The commonest complication of small bowel disease is obstruction, which occurs in about 20% of patients [88]. This may arise because of inflammatory thickening of the bowel, stricture formation, adhesions, or extrinsic obstruction due to mesenteric lymphadenitis. Perforation and fistula formation, massive bleeding and malabsorption may also occur.

Disease of the large bowel may mimic inflammatory bowel disease, with segmental ulcers, colitis, strictures and polyps. Patients present with palpable masses, bleeding, obstruction, perforation and sinus formation. Isolated anorectal disease mimicking Crohn's disease may be present.

Oesophageal disease is less common than small and large bowel disease. It usually arises as a result of direct extension from mediastinal lymph nodes or from a pulmonary focus [88,92]. Less commonly, oesophageal tuberculosis may arise in the absence of tuberculosis elsewhere. Patients typically present with dysphagia, odonophagia, aspiration due to tracheo-oesophageal fistulae and minor haematemesis. Although an uncommon manifestation of tuberculosis in the non-HIV-infected population, this manifestation may be more common in HIV-infected patients [93].

Gastric tuberculosis is also rare and the clinical presentation is likely to be confused with peptic ulcer disease. Duodenal disease is most commonly confused with neoplasm, peptic ulcer and Crohn's disease. In the HIV-infected population, the duodenum is the commonest gastrointestinal site for *M. avium-intracellulare* infection [94].

Patients with tuberculosis may present with hepatomegaly in conjunction with gastrointestinal tract or peritoneal disease [87,95,96] or in isolation as a hepatic abscess. Splenomegaly has been found to be present in one-third of patients with abdominal tuberculosis in Egypt [90]. Splenic involvement in patients with HIV infection is also described, usually in association with constitutional symptoms, with or without evidence of pulmonary disease [97,98]. Tuberculosis of the pancreas is rare but may present with all the features of acute pancreatitis [99].

Abscesses, particularly of the psoas muscle and mesenteric lymph nodes, occur frequently in abdominal tuberculosis and may lead to abdominal masses with or without sinus formation and occasionally to intestinal obstruction. Formation of abscesses, particularly in abdominal tuberculosis, appears to be a common complication in AIDS-related tuberculosis [100].

## Diagnosis

The diagnosis of abdominal tuberculosis is easily missed and is frequently made only following exploratory laparotomy in developed countries [89]. A high index of suspicion is required in developing countries where resources may be poor and treatment empirical. The diagnosis should be considered particularly in migrants to developed countries and in the HIV-infected population.

Plain film radiography may reveal a psoas abscess or evidence of past or present pulmonary tuberculosis. Ultrasound scans may show thickened, conglomerated loops of bowel, mesenteric lymph node enlargement or hypoechoic regions in the liver and spleen [97]. CT may be similarly useful.

Peritoneal tuberculosis may be diagnosed by paracentesis of ascites, although acid-fast bacilli are usually absent or scanty. Culture of peritoneal fluid increases the yield to 66–83% but is time-consuming and for the best results requires the centrifugation of 1 L of fluid [88]. Peritoneal biopsy is best performed laparoscopically or by mini-laparotomy. Characteristically, small (<5 mm) white 'miliary' deposits are seen and adhesions between the peritoneum and organs are common. Blind peritoneal biopsy is also frequently used, particularly in developing countries, but has a lower yield than more invasive procedures. Ascitic fluid protein greater than 25 g/L, a serum-ascites albumin gradient of less than 11 g/L and ascitic lactate dehydrogenase greater than 90 iu/L are sensitive in differentiating tuberculous peritonitis from ascites due to chronic liver disease [101]. The concentration of adenosine deaminase in peritoneal fluid is the most useful non-invasive method of diagnosis, levels greater than 33 u/L having a sensitivity and specificity of 100% and 95% respectively [88]. Its usefulness in HIV infection has yet to be determined. Ascitic IFN- $\gamma$  has been shown to have a sensitivity and specificity of 100% at a cut-off of 3 and 9 u/mL and in one study was shown to reduce false positives detected by raised adenosine deaminase [102]. The cost of this test makes it infeasible for use in developing countries.

Diagnosis of tuberculosis of the gastrointestinal tract requires a high index of suspicion. The clinical, radiological and endoscopic picture is most commonly confused with Crohn's disease, although the differential diagnosis includes yersiniosis, amoebiasis, neoplasm and gastrointestinal histoplasmosis. Gross endoscopic findings are

non-specific but biopsies (most usefully from ulcer margins) identify caseating granulomas or acid-fast bacilli in 35–60% of cases [88]. Again, culture of crushed tissue increases the yield but is time-consuming. Exploratory laparotomy may be required in difficult cases. Splenic aspiration and liver biopsy under ultrasound control have proved useful in HIV-infected patients [97]. Otherwise a therapeutic trial of antituberculous chemotherapy is justified in the presence of suggestive clinical findings.

### Management

Most patients respond well to chemotherapy, including 6- and 9-month regimens. Surgery is indicated for massive bleeding, obstruction, free perforation and confined perforation with abscess or sinus formation. Although widely used, there is no evidence that corticosteroids have a role in any form of abdominal tuberculosis.

### Genitourinary tract tuberculosis

Genitourinary tract tuberculosis is a common form of extrapulmonary tuberculosis, accounting for 18–22% of cases in the USA [95,96] and up to 41% of cases in Spain [103]. In Scotland about 20 new cases are seen annually per 1 million population [104] and in Europe it is estimated that 1% of renal replacement therapy results from tuberculosis [105]. Unlike other forms of extrapulmonary tuberculosis in the UK, genitourinary tuberculosis appears to occur relatively more frequently in Caucasians than in the Asian population [106]. However, this difference seems to be related to the older age of Asian patients with genitourinary tract tuberculosis and also to the higher incidence of other forms of extrapulmonary tuberculosis in the Asian population. Thus in the UK the occurrence is very similar in the two ethnic groups [107]. In developing countries, genital tract tuberculosis occurs most frequently in women of child-bearing age [108], whereas in developed countries the disease occurs most frequently in postmenopausal women [109]. Localized genitourinary tract tuberculosis is rarely diagnosed in HIV infection, although urine cultures are frequently positive in patients with disseminated tuberculosis [2].

### Pathogenesis

Genitourinary tract tuberculosis results from haematogenous spread to the kidney, with subsequent spread to the ureters, bladder, prostate, seminal vesicles, epididymis and female genital tract. It usually arises secondary to a previous primary focus and the time interval from primary infection has been estimated to be between 1 and 46 years [104]. About one-quarter of patients with urinary tract tuberculosis have a history of previous tuberculosis

and about 38–80% of women with genital tract tuberculosis have evidence of extragenital tuberculosis [103,110]. Prior to chemotherapy, the majority of patients dying from pulmonary tuberculosis had bilateral renal involvement [111]. However, nowadays unilateral involvement is more common. Rarely, isolated tuberculous interstitial nephritis may occur in the absence of other renal tract abnormalities [105].

### Clinical features

Commonly, patients present with frequency, dysuria, loin pain, nocturia and haematuria. Scrotal swelling due to epididymo-orchitis may occur and may be complicated by sinus or abscess formation [112]. Less commonly, clot colic or haematospermia may be the presenting symptoms. Constitutional symptoms such as weight loss and asthenia occur in up to 60% of patients [104]. Interstitial nephritis presents with progressive renal impairment and other symptoms and signs may be absent [105]. Female genital tract tuberculosis presents with infertility, menorrhagia, amenorrhoea or pelvic inflammatory disease, and in about 50% of cases adnexal masses are palpable on pelvic examination [109,110].

### Diagnosis

A history of recurrent urinary tract infection or pyuria with negative bacterial cultures should lead to the suspicion of renal tract tuberculosis, particularly if unexplained fever, perineal sinuses, a beaded vas deferens, scrotal sinus or induration of the prostate or seminal vesicles are noted on examination. Early morning urine specimens should be sent for microscopy and culture for acid-fast bacilli. About 48% will have positive Ziehl–Nielsen stains and the remainder will be culture positive after about 3 weeks [103]. An intravenous pyelogram is abnormal in most cases and may show calcification, dilatation of the calyces or loss of definition of minor calyces, hydronephrosis, hydroureter or a non-functioning kidney. Renal cavitation, multiple ureteric strictures or a shortened refluxing ureter may also be seen [95,96]. Radiological evidence of involvement of both the upper and lower renal tract is highly suggestive of tuberculosis [103]. Tuberculous interstitial nephritis can only be confidently diagnosed following renal biopsy, which demonstrates diffuse interstitial nephritis and caseating granulomas. In these patients, microscopy and culture of urine is frequently negative for mycobacteria [105]. Female genital tract tuberculosis is usually diagnosed following the histological or microbiological examination of endometrial curetting [109]. Histological examination of the fallopian tubes in such patients invariably shows tuberculous involvement and in 20–40% of cases the ovaries are also involved [110].



## Management

The surgical management of genitourinary tuberculosis is largely reserved for severe or life-threatening complications such as haemorrhage, severe hypertension or suspicion of malignancy [103]. Nephrectomy for a single non-functioning kidney is no longer recommended. Corticosteroids have been advocated to relieve symptoms of cystitis or in speeding the resolution of ureteric obstruction [38] and also appear to be obligatory in the treatment of tuberculous interstitial nephritis [105].

## Cutaneous tuberculosis

Cutaneous tuberculosis [113–115] is very uncommon but may present in one of six ways.

**1** A primary complex, usually on the face or a mucous membrane, may arise due to direct inoculation of *M. tuberculosis*. A well-demarcated, ulcerating papule (tuberculous chancre) is present, which is often painless, and the local lymph nodes are infected (Fig. 18.8).

**2** Miliary tuberculosis (tuberculosis cutis miliaris acuta generalisata) classically occurs in immunocompromised children and results in symmetrical crops of papules, vesicles and necrotic lesions. It occurs only rarely in the immunocompetent adult [116], but recently has been noticed in increasing frequency in patients with advanced HIV infection [117,118]. Miliary disease in the HIV-infected patient may also present with a localized painful fluctuant swelling [118].

**3** Verrucous tuberculosis is an occupational hazard of pathologists and others working with infected material and usually presents as a painless papule or papulopustule that evolves into a warty hyperkeratotic plaque,

often on the back of the hand. The lesion may resolve spontaneously after several years.

**4** Orificial tuberculosis, consisting of painful ulcers around the mouth, nose or anus, may be the presenting sign of pulmonary or gastrointestinal tract tuberculosis.

**5** Colliquative tuberculosis or scrofuloderma results from direct infection and breakdown of skin overlying a tuberculous focus, such as a lymph node, bone, joint or epididymis.

**6** Lupus vulgaris begins with brownish-red discoloration. It gradually expands to form a soft brownish-red serpiginous plaque with apple-jelly nodules. It may occur anywhere on the body but is most common on the face. It is chronic, resulting in scarring and occasionally the formation of deep erosive ulcers.

The diagnosis of tuberculosis of the skin is made by a pathological and bacteriological examination of a representative biopsy. Smear-positive lesions occurring in the absence of other clinical manifestations of tuberculosis must be differentiated from infection with other mycobacterial species, particularly the *M. avium-intracellulare* complex in patients with advanced HIV infection [118].

## Tuberculosis of the breast

Tuberculosis of the breast (Fig. 18.9) is a rare manifestation of tuberculosis. It is a disease of younger women in developing countries and is usually unilateral. In the UK it occurs most commonly in women of Asian origin [119]. The breast probably becomes involved by retrograde lymphatic extension from primary foci of the disease in the lymph nodes of the mediastinum, axilla, parasternal and cervical regions. It could also result from haematogenous invasion or by spread of infection from adjacent tissues.

**Fig. 18.8** Tuberculous ulcer at base of anterior triangle of neck, with associated regional lymphadenopathy (circled).





**Fig. 18.9** Gross enlargement of the breast due to tuberculosis.

Patients invariably have previous or coexistent evidence of tuberculosis elsewhere [119] but the diagnosis must be confirmed by the demonstration of acid-fast bacilli in needle aspirates. Histological findings typical of tuberculosis must be differentiated from a granulomatous reaction to a breast cancer as well as other infectious granulomatous reactions [120].

### Ocular manifestations of tuberculosis

Ocular manifestations of tuberculosis are rare, occurring in only 1.4% of patients [114,121]. Phlyctenular conjunctivitis is characterized by a single vesicular lesion near the limbus surrounded by an area of erythema. It rapidly becomes a small yellowish ulcer and heals within a few weeks. Direct bacillary involvement of the conjunctiva has been recognized. Tuberculous keratitis and scleritis usually result from the spread of infection and granulomatous reaction from within the eye. The orbit is most frequently involved following contiguous spread from orbital periostitis.

Granulomatous lesions have been described from all parts of the uveal tract but the posterior choroid is the commonest site. Retinal oedema is seen in the earliest stages but, untreated, choroidal nodules usually appear. Larger lesions heal with choroidal and retinal scarring and this process may be complicated by retinal detachment and neovascularization. Panuveitis always accompanies choroidal disease. Choroidal tubercles may be seen in about half of patients with miliary tuberculosis. Tuberculous meningitis may also result in optochiasmal chorioiditis.

Specific antituberculous treatment leads to rapid resolution of the eye lesions. Local treatment with corticosteroids and mydriatics can also be given and severe disease may be managed with adjuvant corticosteroids.

teroids and mydriatics can also be given and severe disease may be managed with adjuvant corticosteroids.

### Tuberculosis of the upper respiratory tract

Tuberculosis of the upper respiratory tract (Fig. 18.10) occurs in about 1.8% of tuberculosis admissions [122] and is normally accompanied by pulmonary disease. The larynx is most commonly involved and this form of tuberculosis is highly infectious. As well as the systemic features of tuberculosis, hoarseness, cough and odynophagia are prominent symptoms. The laryngoscopic appearance varies from beefy-red erythema to oedema and frank ulceration. Tuberculosis of the larynx must be differentiated from laryngeal carcinoma by smears or biopsy of the involved tissue [123]. Lateral soft tissue radiography of the neck, tomography of the larynx and contrast laryngography are the radiological techniques commonly used to assess laryngeal involvement [123].

Tuberculosis of the nasal mucous membranes is extremely rare and can mimic Wegener's granulomatosis [124]. Diagnosis is confirmed by biopsy or smears.

Tuberculous otitis media usually presents with deafness, facial palsy, multiple perforations and painless otorrhoea [125]. Otagia may also occur [122,126] and the presentation may be complicated by secondary infection. Smear and/or culture of material is diagnostic in about half of patients and the diagnosis relies on histological examination in the remainder [125]. The results of antituberculous therapy are good, although tympanoplastic surgery may be required in those in whom there is extensive destruction of the tympanic membrane.



Fig. 18.10 Tuberculosis of pharynx and soft palate.

### Tuberculous bacteraemia

Tuberculous bacteraemia [127] is detected in 20–50% of patients with HIV-associated tuberculosis [2] but is rare in HIV-negative patients with tuberculosis [128]. In AIDS, 83% of patients with disseminated tuberculosis [128] and 71% with pulmonary involvement [129] have positive blood cultures. In some HIV-positive patients with advanced immunodeficiency, blood may be the only site from which *M. tuberculosis* is isolated. In developed countries where tuberculosis is not endemic, a positive mycobacterial blood culture in the HIV-infected individual is considerably more likely to be due to infection with

the *Mycobacterium avium* complex [130]. Thus initial therapy, pending speciation, should be targeted against this complex unless there is also clinical evidence of tuberculous infection.

### Acknowledgement

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# MANAGEMENT OF TUBERCULOSIS

A. GORDON LEITCH

The history of tuberculosis treatment has been fully documented by Keers [1]. Prior to the 1950s the mainstay of management was bedrest, fresh air, sunshine (where available) (Fig. 19.1) and, in suitable cases, surgical intervention. Resection of tuberculous lesions was performed, but much more commonly the active management of tuberculous lesions depended on 'collapse therapy'. Collapse therapy 'rested' diseased lung and might take the form of artificial pneumothorax (Fig. 19.2), induction and maintenance of a pneumoperitoneum (Fig. 19.3), phrenic nerve crush or the performance of a thoracoplasty. Thoracoplasty involved the resection of five, seven or, exceptionally, 11 ribs on the affected side to cause collapse of the underlying lung [2] (Fig. 19.4). An additional surgical development was collapse of the lung induced by pleural plombage, in which the pleura, and hence the underlying lung, were compressed by implanted material, most commonly lucite balls and less commonly mineral oil [3].

The discovery of streptomycin and of its activity against mycobacteria by Schatz and Waksman in 1944 [4] heralded a new era of tuberculosis chemotherapeutics. The antimycobacterial effect of para-aminosalicylic acid (PAS) was first described by Lehmann [5] and this was followed by isoniazid in 1952 [6]. The British Medical Research Council were quick to investigate streptomycin treatment of tuberculosis in one of the world's first controlled trials [7]; 21% of the controls died and only 8% showed radiographic improvement, whereas in the treated group 51% showed radiographic improvement and only 7% died. In this study, many patients who had initially improved with streptomycin treatment deteriorated after 3 months and it became apparent that in most cases treated with streptomycin alone, mycobacterial resistance to this drug emerged after 3 months of treatment. With the development of PAS and isoniazid, subsequent Medical Research Council studies confirmed that monotherapy led to the emergence of drug-resistant bacteria (e.g. to isoniazid alone [8]), whereas combinations of drugs (streptomycin and PAS, streptomycin and isoniazid, PAS and isoniazid)

were shown to be more effective and to prevent the emergence of drug-resistant organisms [8–10]. These early observations were further developed in Edinburgh, where it became apparent and was subsequently reported in 1958 that if tuberculous disease was caused by fully drug-sensitive organisms it was possible, employing suitable combination therapy with streptomycin, PAS and isoniazid, to prevent the emergence of drug-resistant organisms and to effect a 100% cure [11,12].

With these early regimens it was necessary to continue therapy for 18 months or 2 years. With the passage of time and the introduction of new drugs the emphasis has been placed on devising courses of chemotherapy that are as effective and which sterilize tuberculous lesions in the shortest possible period [13–17]. The rationale of such short-course chemotherapy is outlined below.

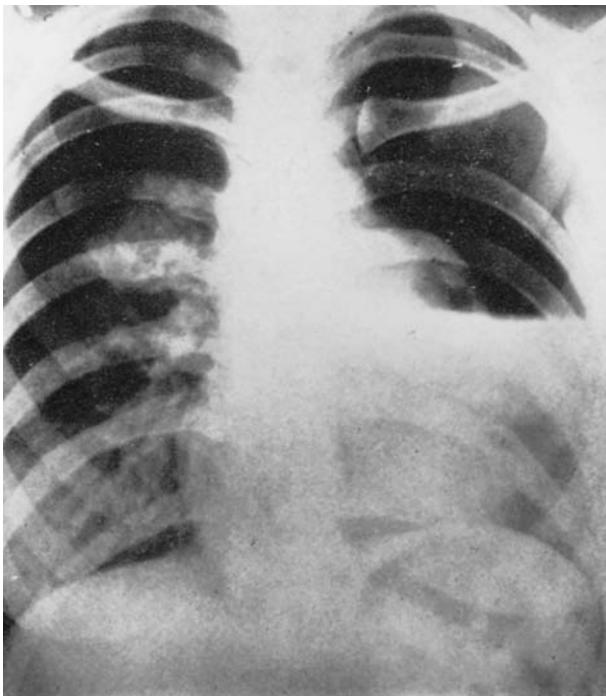
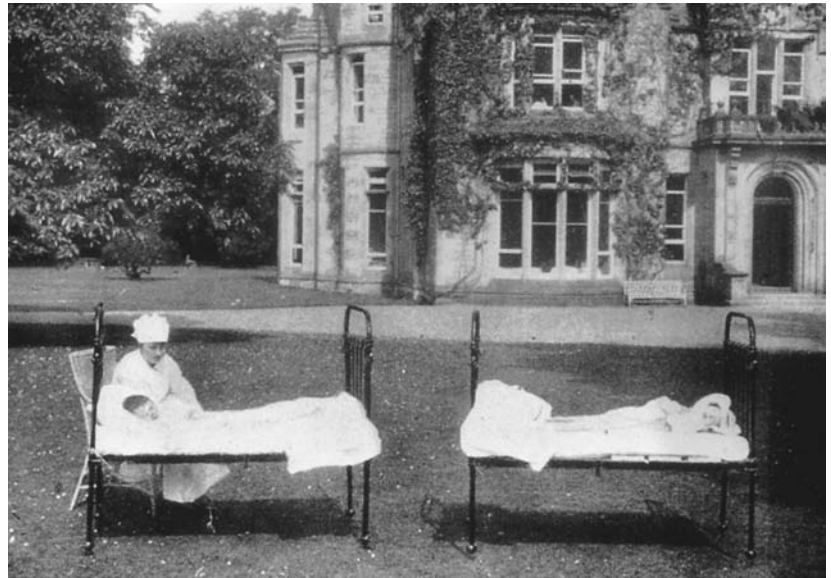
## Rationale of short-course chemotherapy

### Bacterial populations in tuberculous lesions

Following ingestion by macrophages, tubercle bacilli are released with the development of caseation (Fig. 19.5). The low oxygen tensions prevailing in caseous tissue do not favour rapid multiplication of bacilli. Following liquefaction of caseous tissue and cavity formation, the prevailing oxygen tension is much higher, favouring extracellular bacillary multiplication. Continuing ingestion of bacilli by macrophages with further caseation and cavity formation extends the process. It has been estimated that the population of slowly growing organisms in macrophages and caseous lesions/tissue is less than  $10^5$ , whereas in cavities the rapidly growing population numbers  $10^7$ – $10^9$  organisms [14]. Since mutants resistant to streptomycin, isoniazid and ethambutol in wild strains of tubercle bacilli number 1 per  $10^5$ – $10^6$  organisms and those resistant to rifampicin 1 per  $10^7$  [14], such strains could easily be selected by therapy with one drug. Such selection is

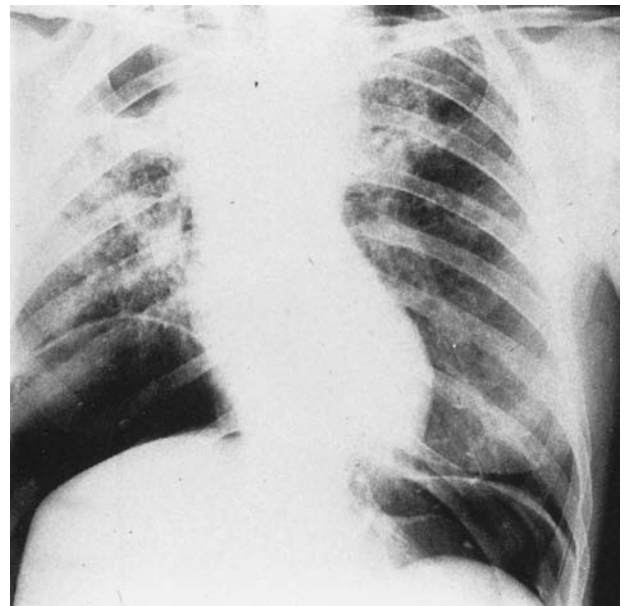


**Fig. 19.1** Open air treatment of pulmonary tuberculosis by rest and fresh air in the grounds of the Royal Victoria Hospital, Edinburgh, c. 1920.



**Fig. 19.2** Chest radiograph showing an induced artificial pneumothorax for treatment of disease in the left lung. Adhesions have prevented complete collapse.

avoided by multiple drug therapy. The aims of therapy are the speedy elimination of the large population of rapidly dividing organisms in cavities (bactericidal action) and the sterilization of the slowly dividing organisms (the persisters) in cells and caseous tissue. The available antituberculosis drugs make different contributions to these bactericidal and sterilizing actions.

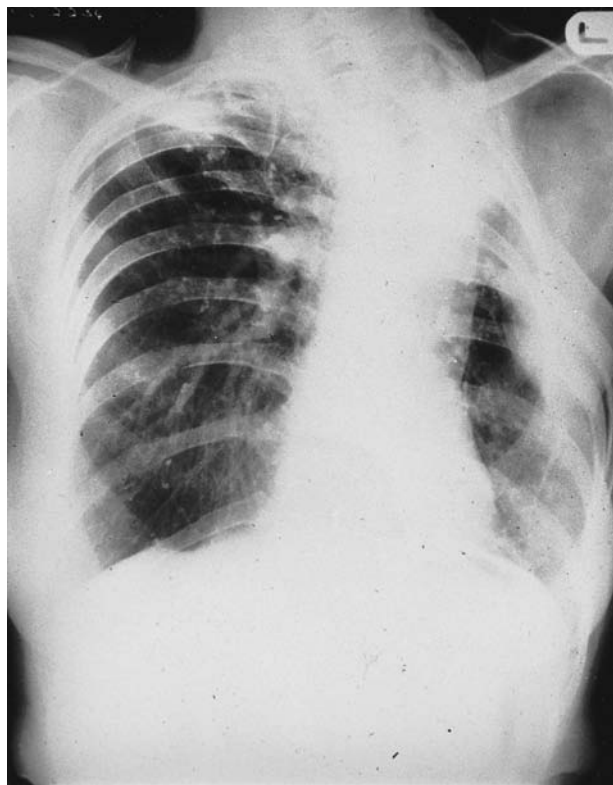


**Fig. 19.3** Chest radiograph showing artificial pneumoperitoneum.

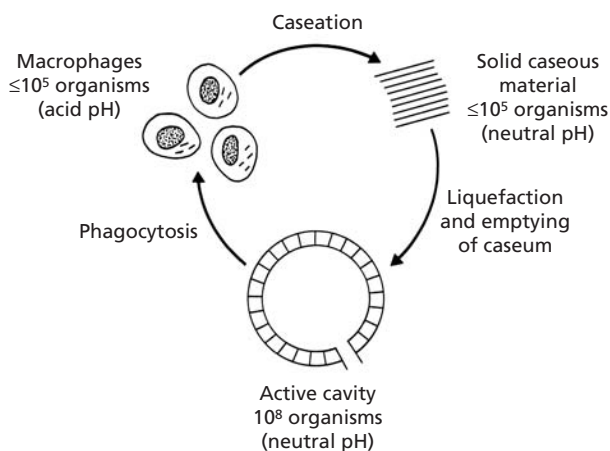
### Activity of the principal antituberculosis drugs

From studies of the fall in sputum bacterial counts in the early days of treatment with single drugs, it has been established that isoniazid is the most potent bactericidal agent, rifampicin is less bactericidal and streptomycin and pyrazinamide have only low bactericidal activity [18]. The sterilizing activity of drugs has been particularly studied in the experimentally infected mouse, where rifampicin and pyrazinamide are very potent sterilizing drugs [19]. Isoniazid plus either rifampicin or pyrazinamide are the





**Fig. 19.4** Chest radiograph showing a five-rib thoracoplasty on the left side with underlying treated pulmonary tuberculosis (50 years on).



**Fig. 19.5** Bacterial populations in the lesions of human tuberculosis. (From Grosset [14].)

most potent combinations and the addition of streptomycin or ethambutol to these combinations adds little to their sterilizing capacity.

It is thought that different populations of bacteria exist within tuberculous lesions and each is particularly accessible to the action of a different antituberculosis drug [13]. One population of rapidly growing bacilli, e.g. in cavity

walls, is particularly vulnerable to the action of isoniazid. Two separate slowly growing populations are selectively affected by pyrazinamide and rifampicin. Pyrazinamide is believed to be particularly effective against bacilli in an acid (presumably intracellular) environment, since it is only an efficient antibacterial agent *in vitro* at a pH of 5.6 or less. Rifampicin has been shown to be a particularly effective bactericidal agent for dormant bacilli which have short bursts of metabolic activity [20]. Finally, a fourth population of totally dormant bacilli not killed by any drug is believed to exist.

The principles of current short-course chemotherapy are outlined in Fig. 19.6. Rapidly multiplying extracellular bacilli are killed by isoniazid and, to a lesser extent, rifampicin and streptomycin. Slowly growing bacilli in cells and caseous lesions, the persisters, are sterilized by the action of isoniazid, rifampicin and pyrazinamide. Failure to achieve adequate sterilization leads to relapse and it has now been established that the shortest course of chemotherapy required for adequate sterilization with currently available drugs is 6 months [21]. Suitable regimens are reviewed later in this chapter.

## Antituberculosis drugs

Modern drug treatment regimens consist of an initial or introductory phase of therapy followed by a maintenance or continuation phase of therapy.

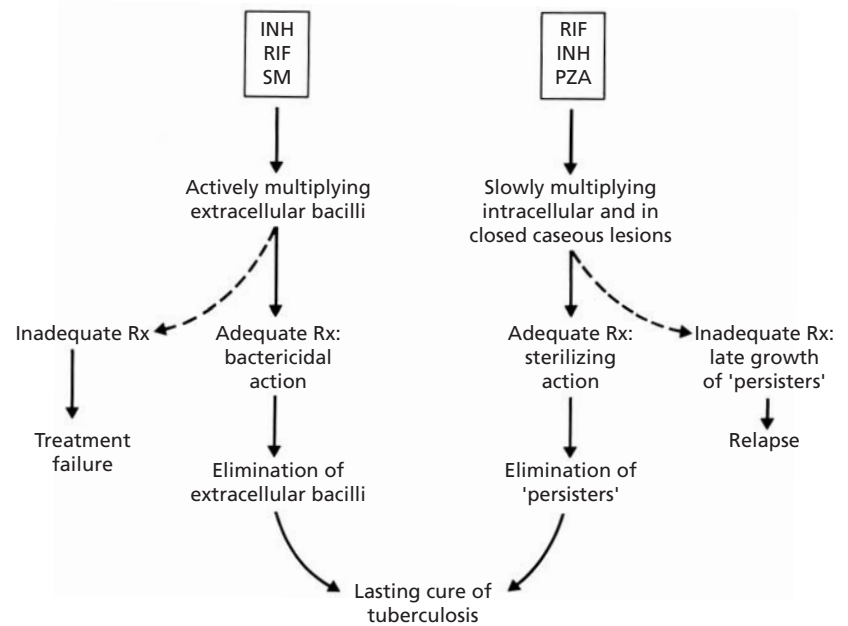
### First-line drugs

First-line drugs are those used in initial and maintenance chemotherapy unless drug resistance is known. The standard dosages for daily and intermittent therapy in children and adults and the commoner side-effects of these drugs are shown in Table 19.1.

### Rifampicin

Rifampicin is a semisynthetic broad-spectrum bactericidal antibiotic derived from *Streptomyces mediterranei*. It was the introduction of this antibiotic that permitted the development of the first effective short course of 9-month chemotherapy for tuberculosis [22,23]. In addition to its antituberculosis activity, it has a wide range of activity against other bacteria, including *Staphylococcus*, *Streptococcus*, *Clostridium*, coliforms, *Pseudomonas*, *Proteus*, *Salmonella*, *Shigella*, *Bacterioides* and *Legionella*.

Rifampicin is almost completely absorbed from the gastrointestinal tract after an oral dose and is partly deacetylated in the liver by an enzyme induced in the first few days of treatment. When taken on an empty stomach, peak plasma levels of 6–7  $\mu\text{g/mL}$  are reached at 3 h and the drug has a half-life of about 5 h [24]. Most strains of *Mycobacterium tuberculosis* are inhibited *in vitro* by concen-



**Fig. 19.6** Principles of modern chemotherapy of tuberculosis. INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; SM, streptomycin. (From Stead & Dutt (*Am Rev Respir Dis* 1982; 125: 94).)

**Table 19.1** Dosage and adverse effects of first-line antituberculosis drugs.

Drug	Dosage			Common adverse effects*
	Adult	Child	Intermittent	
Isoniazid	300 mg standard 5 mg/kg in chemotherapy 12 mg/kg in miliary	10 mg/kg	15 mg/kg	Hypersensitivity, hepatitis
Rifampicin	>50 kg, 450 mg >50 kg, 600 mg	10–20 mg/kg	600–900 mg 600–900 mg	Gastrointestinal, hypersensitivity, hepatitis Induction of liver enzymes Toxicity of intermittent therapy
Ethambutol	25 mg/kg for 2 months; then 15 mg/kg		Thrice weekly, 30 mg/kg Twice weekly, 45 mg/kg	Retrobulbar neuritis
Pyrazinamide	<50 kg, 1.5 g 50–74 kg, 2.0 g >75 kg, 2.5 g	40 mg/kg (max. 2 g)	Thrice weekly, 2.0 g Twice weekly, 3.0 g Thrice weekly, 2.5 g Twice weekly, 3.5 g	Arthralgia, hepatitis
Streptomycin	>30 kg, 750 mg >30 kg, 1 g (750 g if >40 years)	20 mg/kg (max. 1 g)	1 g	Ototoxicity (vestibular disturbance)

\*See text for detailed discussion of side-effects.

trations of 0.5 µg/mL. Although about 75% of the drug is protein bound, it penetrates well into tissues and cells. Therapeutic concentrations are reached in cerebrospinal fluid (CSF) when the meninges are inflamed. It is excreted almost entirely in the bile but there is enterohepatic circulation and some does appear in urine [25].

Rifampicin may be detected in urine following extraction of 10 mL urine by analytical-grade chloroform in a screw-capped tube by gentle tilting [26]. The test is negative if no colour develops, a yellow to orange colour in the

chloroform layer indicating the presence of rifampicin. The test is valid up to at least 6 h and, in some patients, up to 12 h after ingestion of rifampicin. Tetracyclines, nitrofurantoin and phenothiazine derivatives also give a yellow colour.

Rifampicin is available as capsules or tablets of 150 and 300 mg and as a syrup (100 mg/5 mL). Combined preparations with isoniazid and with isoniazid plus pyrazinamide are also available. An intravenous preparation may also be useful in certain clinical situations; 300 mg of red

lyophilized powdered rifampicin is reconstituted in 5 mL of solvent solution, diluted in 250 mL of infusion solution and infused over 2–3 h.

### Adverse effects

Serious adverse reactions to rifampicin are not common. The drug is excreted in body fluids and, as a consequence, all patients should be warned that their urine and also sweat and tears may be coloured orange-pink.

Of the gastrointestinal reactions, nausea, anorexia and mild abdominal pain are most common, with vomiting and diarrhoea occurring less frequently. These occur in less than 5% of patients and are more common in the elderly. They may be resolved by giving the drug at night or, if this fails, during a meal. Transient elevation in aspartate aminotransferase levels are common (14–40% of patients) and of no clinical significance. Major elevations of aspartate aminotransferase to greater than 150 iu/L occur in 4% and hepatitis with jaundice in about 1%. Risk groups for jaundice include elderly women, alcoholics and those with a previous history of liver or biliary disease [27]. Rifampicin should be administered with care to these groups. Concern about the rare development of acute hepatic necrosis in patients treated with rifampicin has led to the publication of management guidelines [28].

Cutaneous reactions are usually mild, consisting of flushing with or without itching or a rash, and commonly occur 2–3 h after taking the drug. Patients usually desensitize themselves to these reactions but occasionally an antihistamine may be required. Severe conjunctivitis and chronic papular acneform reactions of the head, neck and shoulders have also been described.

Cases of osteomalacia, pseudomembranous colitis, pseudoadrenal crisis, light-chain proteinuria with renal failure and cutaneous vasculitis have also been described [29–31].

Several other syndromes may occur with intermittent rifampicin regimens. The flu syndrome with flu-like symptoms lasting for up to 8 h after administration of the drug may occur a few months after treatment has been started and is attributed to the development of circulating rifampicin-dependent antibodies [32]. It may resolve spontaneously or necessitate a switch to a daily regimen. Thrombocytopenic purpura can occur and is an absolute indication for stopping therapy with rifampicin permanently. Asthmatic and hypotensive syndromes may occur separately or together and require corticosteroid therapy before conversion to a daily regimen. Acute haemolytic anaemia and acute tubular necrosis have also been reported. The incidence of side-effects in recent reports of intermittent therapy has been gratifyingly low [33,34].

Finally, rifampicin is a potent inducer of liver enzymes, resulting in increased metabolism of concurrently admin-

istered drugs. The contraceptive pill is unreliable during rifampicin therapy and alternative modes of contraception should be employed. Doses of corticosteroids [35], oral anticoagulants, oral diabetic agents, antiarrhythmic agents such as verapamil [36], theophyllines, digitalis, anticonvulsants, ketoconazole and cyclosporin [37] may need to be increased during therapy with rifampicin and be decreased thereafter.

### Isoniazid

Isoniazid is the most widely used antituberculosis agent. It is ideal in many respects, being bactericidal, relatively non-toxic, easily administered and inexpensive. It is readily absorbed from the gastrointestinal tract, with peak concentrations of approximately 5 µg/mL occurring about 2 h after administration [14]. Most strains of *M. tuberculosis* are inhibited *in vitro* by concentrations of 0.05–0.2 µg/mL. It penetrates well into all tissues including CSF. Some of the drug is excreted unchanged in urine but a proportion is acetylated by hepatic acetyltransferase to an inactive form.

An individual's rate of acetylation is genetically determined. Europeans and southern Indians are predominantly slow acetylators, with a mean serum half-life for isoniazid of about 3 h; the Japanese, Korean and Eskimo populations have a majority of rapid acetylators, with an isoniazid half-life of about 1.4 h. Differences in acetylator status do not influence the therapeutic efficacy of isoniazid nor are they related to the risk of isoniazid-induced hepatitis [38–41].

The drug is usually given orally and is supplied in 50 and 100 mg tablets or as an elixir containing 50 mg/5 mL. Combined preparations with rifampicin and rifampicin plus pyrazinamide are available. Isoniazid solution may also be given intravenously. Research into the development of a sustained-release isoniazid preparation, which would be of value in the treatment of poorly compliant patients, is ongoing [42,43].

### Adverse effects

Hepatitis is uncommon in the young but may approach a frequency of 2% when used chemoprophylactically in adults over 35 years of age [44]. Alcohol consumption is a definite risk factor. Peripheral neuropathy is the principal adverse effect and is more common in the malnourished, the elderly, patients with chronic liver disease, slow acetylators and in pregnancy [45]. It may be prevented by the simultaneous administration of 10 mg pyridoxine [46]. Larger doses (100–200 mg) of pyridoxine are needed to treat established neuropathy. Optic neuritis, psychosis and convulsions are less common side-effects [47]. Impaired concentration and excessive sleepiness may occur. Rarer adverse effects include pellagra in nicoti-

namide-deficient patients, haemolytic anaemia in glucose 6-phosphate dehydrogenase deficiency, agranulocytosis, lupoid reactions and arthralgia [38]. The interaction of isoniazid and phenytoin increases the serum concentration of both drugs; serum phenytoin levels should be monitored and the dosage decreased if necessary [16].

### Pyrazinamide

Pyrazinamide is bactericidal in an acid environment and has a sterilizing effect on intracellular mycobacteria [48,49]. *M. bovis* is resistant to the drug. It is well absorbed from the gastrointestinal tract, with peak concentrations of about 50 µg/mL occurring 1.5–2 h after ingestion. At a pH of 5.5 the minimal inhibitory concentration of pyrazinamide for *M. tuberculosis* is 20 µg/mL. It penetrates well into tissues including CSF.

The drug is available in 500mg tablets administered orally or in a combined preparation with rifampicin plus isoniazid. If intravenous therapy is required, lyophilized morphazinamide is available in 1-g vials for administration by drip infusion following reconstitution with solvent.

### Adverse effects

Hepatitis was commoner when higher doses of the drug were used than are now recommended (see Table 19.1). It occurs in about 1% of patients but milder subclinical derangement of liver function tests is common. The drug should be administered with caution to those with a history of liver or biliary tract disease. It should be noted that there is no significant increase in hepatotoxicity when pyrazinamide in standard dosage is added to a regimen of isoniazid and rifampicin during the initial 2 months of therapy [49]. Arthralgia is an uncommon adverse effect that appears in the first 2 months of treatment, more frequently in Chinese patients. It is due to inhibition of renal tubular secretion of uric acid by pyrazinoic acid, the main metabolite of pyrazinamide, and can be treated with non-steroidal anti-inflammatory agents [50]. High serum concentration of uric acid may uncommonly precipitate gout. Rarer adverse effects include anorexia, nausea and vomiting and sideroblastic anaemia [29].

### Streptomycin

Streptomycin is bactericidal in an alkaline environment. It is given parenterally by intramuscular injection and peak plasma levels in the range of 40 µg/mL are achieved 1 h after injection. Most strains of *M. tuberculosis* are inhibited *in vitro* at a concentration of 8 µg/mL. It diffuses readily into most body tissues, including CSF when meningitis is present. It crosses the placenta and fetal serum levels are about half those in maternal blood. The drug is excreted

almost entirely by glomerular filtration and dosage must be modified in renal failure to avoid toxicity.

Streptomycin sulphate for intramuscular injection is supplied as a powder in vials and should be reconstituted immediately before use. Between the ages of 40 and 60 years the dose should be reduced to 0.75 g; above 60 years it is wise to monitor serum levels, ensuring that trough plasma levels do not exceed 2 µg/mL [51].

### Adverse effects

Streptomycin is toxic to the eighth cranial nerve, with vestibular damage more common than auditory damage. The patient usually complains of progressive giddiness and unsteadiness of gait. Nystagmus may be present. The damage to the nerve is permanent but most patients eventually compensate via ocular and proprioceptive compensatory mechanisms. The risk increases with the dose of drug and with age [52,53]. Deafness occurs rarely. Streptomycin is ototoxic to the fetus. Other adverse effects include anaphylaxis, renal tubular damage and blood dyscrasias, including haemolytic and aplastic anaemia, agranulocytosis and thrombocytopenia [29]. Streptomycin potentiates the neuromuscular block produced by curare and is contraindicated in individuals suffering from myasthenia gravis.

### Ethambutol

Ethambutol is generally considered to be a bacteriostatic drug, although it is bactericidal *in vitro* [54]. It is well absorbed after ingestion, with peak plasma levels of 4 µg/mL occurring 2–4 h after a dose of 15 mg/kg [16]. Most strains of *M. tuberculosis* are inhibited *in vitro* by concentrations of the drug in the range 1–5 µg/mL. CSF concentrations of ethambutol are low (1–2 µg/mL with a dose of 25 mg/kg) even in the presence of meningitis. The drug is excreted in the urine and accumulates in patients with renal insufficiency. It is available in a combined preparation with isoniazid.

### Adverse effects

The principal adverse effect is retrobulbar neuritis [55–57], presenting with blurred vision, central scotomas and disturbance of red–green vision. Recovery is the rule if the drug is stopped at the first sign of visual problems but if these are ignored optic atrophy may result. This complication is uncommon at a dose of 15 mg/kg but increases with a daily dose of 25 mg/kg [56,58,59]. Patients should be warned to report visual symptoms immediately and to stop treatment if symptoms develop; pretreatment testing and recording of visual acuity is advised for patients taking this drug [57]. Particular care in dosage adjustment is necessary for those with renal impairment and the drug

**Table 19.2** Dosage and adverse effects of second-line antituberculosis drugs.

Drug	Dosage		Common adverse effects*
	Adult	Child	
Thiacetazone	150 mg	4 mg/kg	Gastrointestinal
Para-aminosalicylic acid (sodium salt)	10–20 g (in divided doses, twice daily)	300 mg/kg	Gastrointestinal, febrile cutaneous reactions
Ethionamide, prothionamide	<50 kg, 750 mg ≥50 kg, 1 g		Gastrointestinal, metallic taste in mouth
Cycloserine	500–100 mg (15–20 mg/kg)		Confusion, slurred speech, convulsions
Kanamycin, capreomycin, viomycin	As streptomycin (see Table 19.1); monitor serum urea and electrolyte concentrations		

\*See text for detailed discussion of side-effects.

is best avoided in young children. Serum levels should not exceed 5 µg/mL.

### Reserve drugs

Reserve drugs are used in the treatment or retreatment of patients with known or suspected mycobacterial drug resistance, usually to more than one drug as described later in this chapter. The usual dosage regimens and side-effects are shown in Table 19.2.

#### Para-aminosalicylic acid

PAS is a bacteriostatic drug, infrequently used in developed countries since the introduction of short-course chemotherapy regimens. It is bulky and unpleasant to take, the cachets being large in size and the tablets numerous. Twice-daily dosage may be needed. Combined preparations with isoniazid are available and should be used to avoid monotherapy. The drug may be detected in urine by Phenistix reagent strips, which turn reddish-brown in the presence of PAS.

#### Adverse effects

Gastrointestinal disturbance in the form of anorexia, nausea, vomiting and abdominal discomfort are common. Diarrhoea may be severe and result in a malabsorption syndrome [60]. Pulmonary eosinophilia may occur and be misinterpreted as deteriorating tuberculous disease. Haemolytic anaemia, thrombocytopenia and a glandular fever-like syndrome have been described. Prolonged administration of PAS may in rare cases produce hypothyroidism and goitre [61]. Hypersensitivity reactions may occur in 5–10% of patients.

#### Thiacetazone

Thiacetazone is a low-potency cheap drug given orally and is frequently used as a companion drug for isoniazid

in developing countries. It is poorly tolerated by Caucasians and the Chinese but better tolerated by Africans [62–65]. Natural resistance to thiacetazone occurs in varying proportions of mycobacterial strains [66] and there may be cross-resistance between thiacetazone and ethionamide. The drug is contraindicated in liver disease and in patients positive for human immunodeficiency virus (HIV).

#### Adverse effects

Generalized reactions (see later) are common. Nausea, abdominal discomfort and vomiting commonly occur. Other adverse effects include anaemia, agranulocytosis, thrombocytopenia, cerebral oedema, conjunctivitis, blurred vision and jaundice. Thiacetazone may enhance the ototoxicity of streptomycin.

Cutaneous hypersensitivity reactions progressing to toxic epidermal necrolysis have been reported in a significant percentage of patients with HIV-associated tuberculosis treated with thiacetazone-containing regimens in East Africa [67–69]. HIV-positive patients or those with clinical markers for AIDS should have ethambutol substituted for thiacetazone in their treatment regimen [69].

#### Cycloserine

Cycloserine given orally has weak bacteriostatic antimycobacterial action but may be valuable in preventing the development of resistance to companion drugs.

#### Adverse effects

The principal adverse effects are on the central nervous system [70]. Dizziness, slurred speech, headache, tremor, insomnia, confusion, depression and suicidal behaviour may result. Peripheral neuropathy may also occur and pyridoxine therapy should be given.

### Prothionamide and ethionamide

These two powerful drugs are similar in action, although prothionamide is considered to be the less unpleasant of the two [71–73]. It is taken in tablet form. Night-time dosage with an antiemetic taken 30 min before may be useful in maintaining treatment [16]. Thiacetazone-resistant organisms are often sensitive to prothionamide but the reverse does not apply.

#### Adverse effects

Anorexia, nausea or metallic taste in the mouth, salivation, vomiting and sulphurous eructations may occur. These may be alleviated by administration of prochlorperazine. Psychic disturbances, hypoglycaemia, hepatitis, gynaecomastia, menstrual disturbance and peripheral neuropathy may also occur. The drug should be avoided in pregnancy for it is teratogenic in animals, and care should be taken in the presence of diabetes, liver disease, alcoholism or mental illness.

### Capreomycin

Capreomycin is an aminoglycoside antibiotic administered by intramuscular injection. There is no cross-resistance between streptomycin and capreomycin.

#### Adverse effects

Capreomycin, like streptomycin, is ototoxic and causes high-frequency hearing loss *before* vestibular dysfunction occurs. Baseline and monthly audiometry as well as regular vestibular function assessment are recommended. The drug is also more nephrotoxic than streptomycin and care should be exercised in its use in the elderly and in those with renal impairment [74]. Hypokalaemia, hypocalcaemia and hypomagnesaemia have been reported [75]. Its use is contraindicated in pregnancy.

### Viomycin and kanamycin

These aminoglycosides are weak antituberculosis drugs, with essentially the same dose and adverse effects as capreomycin, although kanamycin is more likely to cause deafness than the vertigo seen with streptomycin. Audiometric assessment is therefore recommended.

### Recent additions to the list of effective drugs

#### Amikacin

Amikacin is an aminoglycoside that is highly bactericidal against *M. tuberculosis in vitro*. It is given as a single dose of 15 mg/kg by intramuscular injection five times weekly

**Table 19.3** Suggested dosages and adverse effects of newer antituberculosis drugs.

Drug	Adult dosage	Common adverse effects
Amikacin	15 mg/kg i.m. five times weekly	Nephrotoxic, eighth cranial nerve
Quinolones		
Ciprofloxacin	750–1500 mg once daily	Gastrointestinal symptoms
Ofloxacin	400–800 mg once daily	Gastrointestinal symptoms
Rifabutin	>50 kg, 150 mg >50 kg, 300 mg	Hepatotoxic Hepatotoxic

but can be given intravenously by slow injection over 30 min (Table 19.3).

#### Adverse effects

Amikacin is nephrotoxic and should be used with caution in patients with impaired renal function. The dose should be adjusted if necessary to ensure that peak serum levels 30 min after intravenous or 60 min after intramuscular administration remain in the range 35–45 µg/mL. Other side-effects include vestibular dysfunction and hearing loss, particularly in those aged over 60 years. Baseline audiometry is recommended.

### Quinolones

A number of fluoroquinolones show *in vitro* activity against *M. tuberculosis*. Both ciprofloxacin and ofloxacin have been used in treatment combinations for patients with multidrug-resistant tuberculosis and they appear to be effective. Ciprofloxacin in a single oral 750-mg dose produces a serum level of 2 mg/L, which compares favourably with the minimal inhibitory concentration against *M. tuberculosis* of 0.5–1 mg/L. Ciprofloxacin may have both bactericidal and sterilizing activities [76]. The doses recommended in Table 19.3 are sensible but the results of further clinical studies are needed before the full contribution of this class of drugs can be fully documented.

#### Adverse effects

The quinolones are remarkably free from serious side-effects. Gastrointestinal upsets, dizziness and hypersensitivity are the most common effects reported.

#### Rifabutin

Rifabutin is a member of the rifampicin family [77], with activity against *M. tuberculosis* and a side-effect profile resembling that of rifampicin [78]. In one *in vitro* study

rifabutin has been shown to have activity against 20% of rifampicin-resistant strains of tuberculosis [79] and it may therefore be of value in the management of drug-resistant disease provided that the results of sensitivity testing to both rifampicin and rifabutin are available prior to the initiation of treatment. The doses recommended in Table 19.3 are those employed in a study of HIV-associated tuberculosis in Uganda, where rifabutin compared favourably with rifampicin in combination chemotherapy and resulted in earlier sputum smear and culture conversion [80].

### Adverse effects

The side-effect profile resembles that of rifampicin, although it is a weaker inducer of microsomal enzymes [81].

### New drugs

There is an urgent need for new antituberculosis drugs [82]. Only a limited number of drugs are available and the readiness with which multidrug-resistant organisms may emerge even in the developed world is only too apparent (see below). Many developing countries already harbour a substantial minority of untreatable patients who survive to excrete and infect others with drug-resistant organisms. It would be foolish to presume that drug-resistant tuberculosis is destined to become less of a problem; at the very worst, in the not too distant future parts of the world may effectively return to the era before chemotherapy when, because of multidrug-resistant disease, there will be no effective therapeutic combination available for treatment.

Developing new antituberculosis drugs is an expensive exercise and tuberculosis is not a disease of rich nations: profits for the pharmaceutical industry are not in sight. Some development projects are underway [82] but more are needed. In the mean time, the report that clofazimine, an antileprotic agent, and some of its analogues have been shown to have activity against *M. tuberculosis* is to be welcomed [83]—tuberculosis doctors need all the help they can get.

## Generalized reactions to antituberculosis drugs

### Clinical manifestations

The principal adverse effects of individual drugs have been outlined above [22]. Any antituberculosis agent may produce a generalized hypersensitivity reaction, although this is less common with current short-course regimens than it was in the days of treatment with streptomycin, PAS and isoniazid. Occasionally, patients become sensitive to more than one drug. Such reactions are rare in the

first week of treatment and commonest in the second to fourth week, although they may also rarely occur late in therapy [84].

The usual manifestations are of fever and rash, the fever often preceding the rash by a few days. The rash is erythematous, macular or papular and usually itchy. It is most prominent on the face, neck and extremities. In severe cases, exfoliative dermatitis, Stevens–Johnson syndrome and anaphylaxis may occur, resulting rarely in death. In severe reactions, periorbital swelling, generalized lymphadenopathy, hepatosplenomegaly, encephalitis, rigors and high fever may occur. Acute myocarditis and pulmonary eosinophilia have been described.

## Management

### General management

Minor rashes, such as commonly seen with rifampicin, may be successfully treated with an antihistamine without having to stop chemotherapy. In the majority of cases treatment should be stopped until the rash has subsided to prevent progression of the reaction. If continued treatment for tuberculosis is deemed mandatory, then two drugs not previously employed to treat the patient should be introduced. Antihistamines and calamine lotion may be all that is required for subsequent amelioration of symptoms. Severe illness with hypotension or exfoliative dermatitis warrants systemic corticosteroid therapy, with intravenous hydrocortisone and prednisolone 40–60 mg orally per 24 h initially. The corticosteroid dosage can be titrated down subsequently according to the response.

### Identification of the offending drug(s)

When the reaction has subsided the patient should be challenged without delay with single drugs, beginning with those least likely to have caused the reaction. Once two drugs have been identified to which the patient is not hypersensitive, treatment may be restarted with these drugs while desensitization to the offending drug is carried out. It is vitally important that monotherapy should not be used since bacterial drug resistance has been known to develop during such carelessly conducted desensitization procedures. The sequence and doses of challenge regimens to be used to identify the responsible agent are shown in Table 19.4 [85], with the most likely offenders appearing at the foot of the table.

### Desensitization

If a hypersensitive reaction occurs to the challenge dose, then one-tenth of this dose should be used initially, doubling it every 12 h until full dosage is reached. Should a reaction occur during desensitization, the procedure



**Table 19.4** Challenge doses for detecting cutaneous or generalized hypersensitivity to antituberculosis drugs.

Drug	Challenge dose	
	Day 1	Day 2
Isoniazid	50 mg	300 mg
Rifampicin	75 mg	300 mg
Pyrazinamide	250 mg	1.0 g
Ethionamide, prothionamide	125 mg	375 mg
Cycloserine	125 mg	250 mg
Ethambutol	100 mg	500 mg
Para-aminosalicylic acid	1.0 g	5.0 g
Thiacetazone	25 mg	50 mg
Streptomycin or other aminoglycosides	125 mg	500 mg

If the reaction was severe, it is advisable to give smaller initial challenge doses, about one-tenth the doses shown for Day 1. If no reaction occurs to the challenge doses, then the drug may be resumed in full dosage *provided that another drug to which the patient is not hypersensitive is also prescribed in full dosage.*

should be resumed with a lower dose and conducted more slowly. In patients with severe reactions (except those who have had exfoliative dermatitis) and also if rapid desensitization is required, this may be done under cover of therapy with prednisolone 20 mg daily (40 mg in rifampicin-treated patients). The day after starting corticosteroid therapy one-quarter of the total dose is given in two divided doses, followed by one-half, three-quarters and full dosage on successive days. The dose of prednisolone can be gradually reduced thereafter, the rate depending on the severity of the initial reaction. Desensitization is infrequently required; the editors, with 100 years of chest medicine experience between them, have employed this procedure fewer than 10 times.

### Chemotherapy regimens for pulmonary tuberculosis

Most chemotherapeutic regimens that have been accepted as effective have been tested in patients with sputum smear-positive pulmonary tuberculosis. It is reasonable to presume that such regimens are also effective in smear-negative/culture-positive or culture-negative disease. In the developed world the same regimen is usually employed irrespective of the bacteriological status of disease. However, simpler (and cheaper) regimens have been developed in some countries for the treatment of smear-negative disease. These regimens and others are described after the account of standard short-course chemotherapy for compliant patients that follows. The relevance of compliance and the strategies that can be employed to guard against the emergence of drug-resistant organisms are dealt with fully in later sections; they assume major importance with the announcement of

**Table 19.5** Combined formulations of antituberculosis drugs that should be used in standard short-course chemotherapy.

#### *Initial phase of treatment*

Rifater tablets (containing rifampicin 120 mg, isoniazid 50 mg and pyrazinamide 300 mg)  
 <40 kg, 3 tablets  
 40–49 kg, 4 tablets  
 50–64 kg, 5 tablets  
 65 + kg, 6 tablets

#### *Continuation phase of treatment*

Rifinah or Rimactazid

<50 kg: Rifinah 150 or Rimactazid 150, 3 capsules (each containing rifampicin 150 mg and isoniazid 100 mg)  
 >50 kg: Rifinah 300 or Rimactazid 300, 2 capsules (each containing rifampicin 300 mg and isoniazid 150 mg)

Note: All medications to be taken fasting 30 min before breakfast.

the World Health Organization's worldwide commitment to the provision of DOTS (directly observed therapy, short course) in developing as well as developed countries.

### Compliant patients

#### Standard 6-month short-course chemotherapy

In Singapore, 6-month short-course chemotherapy, with an initial phase of 2 months of streptomycin, isoniazid, rifampicin and pyrazinamide followed by a 4-month continuation phase of rifampicin and isoniazid, was almost 100% successful in the treatment of pulmonary tuberculosis. If relapse occurred it was with fully sensitive organisms [86]. The British Thoracic Society have since confirmed these findings and demonstrated that streptomycin can be replaced by ethambutol 25 mg/kg in the initial 2-month phase without significant difference in therapeutic outcome [87,88]. With this regimen, 77% of patients had sputum conversion to culture negative at 2 months compared with only 64% on the standard 9-month regimen [88]. Wherever possible drugs should be given in combination formulations of proven bioavailability as an added protection against the emergence of drug resistance due to non-compliance (Table 19.5). The dosage regimen is illustrated in Table 19.6.

All drugs should be taken fasting 30 min before breakfast since concomitant food significantly decreases the bioavailability of rifampicin and isoniazid [89]. Because of the risk of ocular toxicity with ethambutol 25 mg/kg, the author has tended to use 15 mg/kg, which is safer and probably still perfectly adequate in fulfilling its role of preventing the emergence of resistant organisms in the few patients who may prove resistant to two of the other drugs. In any case, ethambutol can probably be omitted in patients with a low risk of isoniazid resistance [90,91].

**Table 19.6** Standard short-course chemotherapy: the 6-month regimen. (From British Thoracic Society [87,88].)

Isoniazid	300 mg orally	}	for 6 months
Rifampicin	600 mg (>50 kg) orally 450 mg (<50 kg) orally		
Pyrazinamide	1.5 g (<50 kg) orally 2.0 g (50–74 kg) orally 2.5 g (>75 kg) orally	}	for 2 months
Ethambutol	15–25 mg/kg orally, or		
Streptomycin	0.75 g i.m. 6 days out of 7		

Note: All orally administered drugs to be taken fasting 30 min before breakfast.

When the standard regimen is used it is important to remember to assess baseline visual acuity and baseline liver function and urate and to warn the patient of side-effects, particularly ethambutol on eyes and rifampicin on body fluids and other drugs (e.g. oral contraceptives).

### Assessing treatment response

In patients with positive bacteriology, sputum status should be assessed monthly; by 2 months more than 85% of positive sputum cultures should have converted to negative. Failure to convert should ring alarm bells about patient compliance and/or the emergence of drug-resistant disease. Drug sensitivity patterns should be rechecked and the need for supervised or directly observed therapy reviewed. It is helpful, if sputum is available, to document a negative sputum culture at the conclusion of therapy. Patients with fully sensitive organisms who have completed treatment need no regular follow-up but should be advised to report promptly should symptoms recur.

Clinically, after 1–4 weeks the patient should be feeling better, have gained weight and be free from fever, cough and sputum. Chest radiographic changes should have improved and may continue to improve over several months, eventually leaving residual fibrotic and/or cavitary change. Failure of the clinical or radiographic appearances to change after 2–3 months should lead to concerns about compliance and/or drug-resistant disease. If there is no bacteriological proof, the diagnosis should be reviewed.

### Infectivity following treatment

Most patients treated for tuberculosis are ambulatory or outpatient cases. Hospital admission is only necessary for severe disease, treatment or compliance problems. Patients are generally considered non-infectious after 2 weeks of chemotherapy and may return to work thereafter [92–94]. The decreased infectivity after 2 weeks is partly

due to the dramatic reduction in bacillary numbers in sputum and partly due to the reduction in cough. Clearly, however, live pathogenic bacteria are still present in sputum at this stage [95]. As a consequence, if the patient has been highly infectious, has persistent cough or is in regular contact with children or susceptible individuals such as hospital patients, the author prefers to keep the patient off work for at least 4 weeks.

### Monitoring for adverse reactions during standard short-course chemotherapy

Provided that baseline measurements of visual acuity and routine estimations of full blood count (including platelets), uric acid and liver function (bilirubin and hepatic enzymes) have been performed and patients know to report any new symptoms, routine monitoring of blood tests is not usually required. The patient should be seen at monthly intervals throughout therapy to allow clinical evaluation, including weighing and radiographic evaluation, at least initially. Further investigation is determined by clinical indications. A chest radiograph should be taken on completion of therapy.

### Other non-standard 6-month regimens

A number of studies from Singapore, Algeria, East Africa and Poland have described regimens based on an initial 1- or 2-month four-drug phase of therapy followed by a variety of 4-month intermittent or daily regimens that have had satisfactory success rates [86,96–100]. Since these regimens may be attractive for reasons of cost or the ability to supervise intermittent regimens in developing countries, they are listed in Table 19.7. However, it has been established by an American study that 6 months of rifampicin and isoniazid alone represents inadequate chemotherapy [101].

### Treatment of smear-negative pulmonary disease

In the developed world, standard short-course chemotherapy is employed. Two studies from North America have reported successful treatment of smear-negative disease with 6 months of dual therapy with rifampicin and isoniazid [102,103]. The success of different regimens in different geographical locations depends to a large extent on local disease factors (such as drug-resistance patterns) as well as social and cultural factors. National tuberculosis programmes in the developing world recommend the most appropriate regimens for smear-positive and smear-negative cases in their own countries where the luxury of routine mycobacterial culture and sensitivity pattern determination is usually not available [104,105].

**Table 19.7** Relapse rates with different 6-month chemotherapy regimens in patients with drug-sensitive bacilli.

Reference	Initial phase	Continuation phase	No. of subjects	Follow-up (months)	Relapse (%)
Singapore Tuberculosis Service/British Medical Research Council [86]	2SHRZ	4HRZ	84	6	0
	2SHRZ	4HR	80	6	1
Singapore Tuberculosis Service/British Medical Research Council [96]	2SHRZ	4H <sub>3</sub> R <sub>3</sub>	97	24	1
	1SHRZ	5H <sub>3</sub> R <sub>3</sub>	94	24	1
	2HRZ	4H <sub>3</sub> R <sub>3</sub>	109	24	1
Algerian Working Group/British Medical Research Council Co-operative Study [97]	2EHRZ	4HR	229	24	4
Third East African/British Medical Research Council Study [98]	2SHRZ	4TH	89	6	9
Tanzania/British Medical Research Council Study [99]	2SHRZ	4TH	105	24	3
Snider <i>et al.</i> [100]	2SHRZ	4H <sub>2</sub> R <sub>2</sub>	56	24	2
	2HRZ	4H <sub>2</sub> R <sub>2</sub>	116	24	3

E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; T, thiacetazone; Z, pyrazinamide.

Subscripts indicate degree of intermittency, e.g. H<sub>2</sub> represents isoniazid twice weekly; numbers preceding letters indicate duration in months, e.g. 4HR represent 4 months of therapy with daily isoniazid and rifampicin.

### Empirical treatment of smear-negative disease

Where tuberculosis is suspected on clinical and radiological grounds but bacteriological proof is lacking, it is proper to start standard short-course chemotherapy while awaiting the results of bacteriological cultures [106,107]. If cultures prove positive, treatment should be completed; if cultures are negative, treatment should usually also be completed, except in the unusual event of a clinical and radiological response to treatment that is inappropriate (i.e. usually too fast or too complete). In such cases a simple bacterial pneumonia may have responded to rifampicin treatment; nevertheless such cases should be kept under review for 6 months if treatment is to be stopped.

### Standard 9-month chemotherapy

Chemotherapy for 9 months with rifampicin and isoniazid, supplemented by either ethambutol or streptomycin for the first 2 months, has a negligible relapse rate [23,108]. The dosage regimens are shown in Table 19.8. Satisfactory results have also been reported for 9 months of rifampicin and isoniazid alone [109,110], but such a regimen would be likely to fail in the presence of isoniazid-resistant organisms. Low relapse rates have been reported with a 9-month regimen of daily rifampicin and isoniazid for 1 month followed by 8 months of rifampicin 600 mg and isoniazid 15 mg/kg twice weekly [111].

### Non-compliant patients

The responsibility of the supervising clinician for ensuring that not only are tuberculosis patients prescribed appro-

**Table 19.8** Short-course chemotherapy: the 9-month regimen. (From Third East African/British Medical Research Council Study [98] and Tanzania/British Medical Research Council Study [99].)

Rifampicin	600 mg (> 50 kg) orally	}	for 9 months
	450 mg (< 50 kg) orally		
Isoniazid	300 mg orally		
Rifampicin and isoniazid to be given in combined preparation			
Ethambutol	15–25 mg/kg orally, or	}	for 2 months
Streptomycin	0.75 g i.m.		
	6 days out of 7		

Note: All orally administered drugs to be taken fasting 30 min before breakfast.

priate medication but also receive the medication and take it as prescribed for the full duration of treatment was pointed out as long ago as 1960 by John Crofton [112]. He said, 'I find myself, faced with a new patient, assuming that I can be sure of arresting his disease, but tending to forget that I can be quite certain to do so only if I take an immense amount of trouble over his chemotherapy, his bacteriology and his social and personal problems!' The consequences of failure to ensure compliance made news when a resurgence of tuberculosis in New York City in association with HIV infection, homelessness and the decline of tuberculosis control programmes was reported by Brudney and Dobkin in 1991 [113]. Smear-positive patients admitted to hospital were treated appropriately but on discharge to the community were lost to follow-up and did not comply with therapy; many were subsequently readmitted with progressive untreated or

relapsed disease. Failure to ensure treatment compliance or adherence may result also in inadvertent monotherapy, with the emergence of single drug-resistant and eventually multidrug-resistant organisms, such as was recently well documented in New York City [114]. Combined drug preparations should always be prescribed to these patients.

The solution to problems of patient compliance/adherence is apparently simple; if necessary, administration of every dose of treatment should be supervised (DOT). Detailed analyses of the sociocultural factors associated with patient non-compliance have been published [115,116]; in addition to poverty, homelessness and alcoholism, drug addiction, HIV-related illness and linguistic/ethnic difficulties have been identified. If treatment is to be effective in these groups, and it can be [117–119], then expenditure on health services with a major emphasis on education, incentives and the development of community health services to ensure the success of DOT is necessary. Tuberculosis health visitors, experienced nurses trained to work in the community, are the obvious professionals to undertake the task of tracing and treating individuals in the community.

Nardell [120] has outlined a sensible stepwise approach to the management of patients with tuberculosis. The steps, moving from least to most restrictive and, inevitably, from lesser to greater resource implications, are as follows.

- 1 Self-administration of daily standard short-course chemotherapy with monthly clinic visits; compliance can be checked by urine testing for rifampicin [26] or isoniazid [121].
- 2 DOT: daily, twice or thrice weekly, fully supervised in clinic, home or alternative site.
- 3 Voluntary long-term hospitalization in a specialized tuberculosis treatment unit or medical ward.
- 4 Compulsory, court-ordered, long-term hospitalization in a secure tuberculosis treatment unit or similar facility.

Most patients where compliance is likely to be a problem may be treated with standard daily four-drug therapy during an initial intensive phase of treatment in the hospital or clinic, with continuation therapy (for disease due to fully sensitive organisms) with twice- or thrice-weekly rifampicin and isoniazid for a total of 9 months [111] (see Table 19.1 for doses). More old-fashioned, but equally effective, therapy is with streptomycin 1 g and isoniazid 15 mg/kg twice weekly for 1 year [122,123]. Where disease is due to drug-resistant organisms, therapy may need to be prolonged for up to 2 years with untested combinations of drugs (see later).

The problems of compliance in the developed world pale into insignificance when compared with the treatment of tuberculosis under programme conditions in the developing world [124]. In one study in Bombay, 100

private doctors prescribed 80 different regimens most of which were inappropriate and expensive and only four of which conformed with the six regimens recommended in India's national tuberculosis programme [125].

## **Chemotherapy regimens for extrapulmonary tuberculosis**

The largest mycobacterial populations are seen in cavitating pulmonary tuberculosis, where 100% cure is possible with current short-course chemotherapy. It seems reasonable therefore, since these drugs diffuse well into all tissues, that the same short-course chemotherapy should be effective in all forms of extrapulmonary tuberculosis, where the mycobacterial population is smaller [126]. Remarkably few trials of such therapy have been reported. One group has reported a 97% success rate with no relapses following short-course chemotherapy in all forms of extrapulmonary tuberculosis [127].

### **Lymph node tuberculosis**

Standard 9-month chemotherapy has been shown to be effective in lymph node tuberculosis [128]. Standard 6-month short-course chemotherapy is similarly effective even when given intermittently [129]. Following termination of treatment in both this study and an earlier one of 18-month chemotherapy, increase in lymphadenopathy and even sinus formation occurred in a small percentage of patients [128,130]. This phenomenon, which may be due to tuberculin hypersensitivity, may occasionally require surgical intervention or corticosteroid therapy [131].

### **Bone and joint tuberculosis**

Surgical intervention is not usually necessary in skeletal tuberculosis, except in spinal tuberculosis where spinal cord compression is present or threatened [132]. The outcome in spinal tuberculosis is as good with 18-month ambulatory chemotherapy with PAS and isoniazid as it is in those immobilized with bedrest or plaster of Paris [133]. Anterior spinal fusion and débridement give no significant benefit over chemotherapy alone [134]. The results of short-course chemotherapy trials are awaited but there is no *a priori* reason to question the effectiveness of standard short-course chemotherapy in this situation.

### **Genitourinary tuberculosis**

Although success has been reported with 4-month chemotherapy for genitourinary tuberculosis [135], most chest physicians would prefer to adhere to proven therapy with standard short-course chemotherapy [136]. It is the

author's practice to prescribe prednisolone 40mg daily for 6 weeks with a graduated reduction in dosage thereafter in an attempt to prevent ureteric stricture formation [137]. Nevertheless, a few patients eventually require either ablative or reconstructive surgery [137].

### Central nervous system tuberculosis

The sequelae of tuberculous meningitis are so severe that prompt initiation of chemotherapy and corticosteroid therapy is mandatory. Rifampicin-based regimens are better than those not containing this drug, and at least three drugs should be used [138–140]. Rifampicin (15 mg/kg daily up to 600mg), isoniazid (15mg/kg daily, supplemented by pyridoxine 100mg) plus pyrazinamide in full dosage with either or both of ethambutol (15mg/kg daily up to 1g) and streptomycin (20–25mg/kg daily up to 1g) are recommended. Corticosteroids are believed to reduce neurological morbidity in tuberculous meningitis and have been shown to reduce mortality [141]. The recommended dosage is prednisolone 1 mg/kg daily. There is no indication for intrathecal therapy.

Hydrocephalus, if present, is usually of the communicating variety and may respond to therapy with acetazolamide and repeated lumbar puncture [142]. Obstructive hydrocephalus requires ventriculoatrial shunting [143,144].

The mortality of tuberculous meningitis is high at 20–25% even with presently available treatment [143,145–149]. Outcome is best in those who have no neurological abnormalities at presentation and worst in those with positive neurological findings, including disturbance of consciousness [145]. Tuberculoma of the brain is encountered uncommonly in the developed world but a report from India of 108 such patients documents the effectiveness of 9-month chemotherapy with rifampicin, isoniazid and pyrazinamide [150].

### Miliary tuberculosis

Treatment of miliary tuberculosis is with short-course chemotherapy for both adults and children, the dose of isoniazid being increased to 10–15 mg/kg. If the patient is severely ill or has tuberculous meningitis, then corticosteroid therapy should be added. In an adult a dose of 40mg prednisolone daily for 4–6 weeks is sufficient, reducing thereafter by 5mg every 5–7 days. In children the same type of regimen can be followed, with an initial dose of 2mg/kg daily for those under 2 years of age, 1.5mg/kg daily for those aged 2–10 years and 1mg/kg daily for those over 10 years. Recovery should be the rule in all patients receiving appropriate chemotherapy. Unfortunately, particularly in the elderly with cryptic disease, delays in diagnosis or failure to make a diagnosis may result in death.

## Chemotherapy regimens for primary tuberculosis

The management of the child whose only manifestation of tuberculosis is a positive tuberculin test has been discussed in Chapter 17. In any patient with a radiographically visible lesion, the rate of complication by disseminated tuberculosis in the younger age group, or by progressive pulmonary tuberculosis in those who have passed puberty, is such that chemotherapy is mandatory in all cases [151,152].

Where there is no suspicion that the infection is with a drug-resistant organism the preferred treatment is with rifampicin 10–20mg/kg (maximum 600mg) plus isoniazid 5mg/kg (maximum 300mg), both given on an empty stomach in a single daily dose. If primary resistance may be a problem, a third drug, either pyrazinamide (40mg/kg, maximum 2.0g) or PAS (250mg/kg), should be added until the sensitivities are known. Ethambutol should be avoided if possible in young children, who may not be able to report ocular toxicity. Chemotherapy should be continued for 9 months for a two-drug rifampicin-based regimen and for 12–18 months for other regimens, the longer period being for more severe and extensive lesions. Although isoniazid alone has been used to treat primary tuberculosis, the success rate is less than the 100% achieved with adequate combination chemotherapy and its use is not advised [152,153]. Side-effects from antituberculosis drugs appear to be no more common in children than in adults [154].

Following the initiation of chemotherapy the lymph node enlargement gradually subsides over a few months, although the parenchymal component may resolve more rapidly. Calcification may be the only residuum. Mechanical lesions due to bronchial complications may occasionally occur during chemotherapy, leading to radiological and clinical deterioration necessitating treatment with steroids (see later).

## Treatment in other special situations

Situations in which antituberculosis chemotherapy needs careful management are in the presence of renal or hepatic disease, in pregnancy, in small children and in HIV infection [22].

### Renal disease

The severity of renal impairment can be expressed in terms of creatinine clearance or the serum creatinine, the latter being less accurate unless corrected for age (Table 19.9). In the presence of renal impairment rifampicin is the safest drug to use in standard dosage, since in complete renal failure it is excreted entirely in the bile. Isoniazid in standard dosage is safe except in the presence of severe

**Table 19.9** Grading of severity of renal impairment.

Grade	Creatinine clearance (mL/min)	Serum creatinine (μmol/L)
Mild	20–50	150–300
Moderate	10–20	300–700
Severe	<10	>700

**Table 19.10** Dosage schedules for ethambutol in patients undergoing dialysis.

Dialysis programme	Creatinine clearance (mL/min)	Dosage
Regular	50–100	25 mg/kg twice weekly
	30–50	25 mg/kg twice weekly
Three times weekly		25 mg/kg
Twice weekly		40 mg/kg
Once weekly		90 mg/kg

renal disease, when only 200mg daily should be given, supplemented by pyridoxine 100mg daily to prevent peripheral neuropathy. Pyrazinamide may also be safely administered in standard dosage to patients with renal failure [137].

The aminoglycosides streptomycin and capreomycin should be given in reduced dosage if the creatinine clearance is less than 50mL/min and serum levels monitored to ensure trough levels (at 24 h) of less than 2μg/mL. A dose of 0.25g for 3 days per week may be adequate to sustain an appropriate serum concentration. If the patient is receiving regular dialysis, streptomycin 0.75g should be given 4–6 h before dialysis.

Cycloserine, PAS and ethambutol should be avoided in renal disease. If ethambutol is absolutely necessary, careful daily monitoring of serum levels to ensure that they do not exceed 5μg/mL is essential if eye toxicity is to be avoided. The interval between doses may need to be increased to 48 h; alternatively, a reduced daily dosage of 8–10mg/kg may be employed. For patients undergoing dialysis an appropriate schedule for ethambutol is shown in Table 19.10.

### Hepatic disease

Isoniazid, pyrazinamide and rifampicin may all cause hepatotoxicity in patients with liver disease, and liver function tests should be monitored closely in these groups. Rifampicin hepatotoxicity may be dependent on the concurrent administration of isoniazid [155]. Acute liver failure is the ultimate price for paying inadequate attention to the hepatotoxic potential of antituberculous

drugs [156]. Suggested guidelines for monitoring liver function have been published [28]. If major hepatotoxicity ensues with conventional short-course chemotherapy regimens and it proves impossible to resume therapy with any or all of rifampicin, pyrazinamide and isoniazid, then it may be possible to complete chemotherapy utilizing alternative triple therapy. Streptomycin, PAS or isoniazid and ethambutol for 3 months should be followed by 15 months of the two oral agents.

### Pregnancy

Pharmacological intervention of any kind during pregnancy always gives rise to debate. Of the available drugs, streptomycin is ototoxic to the fetus and should not be used during pregnancy. There is no evidence that isoniazid, ethambutol or PAS cause any kind of congenital malformation or are toxic in other ways to the fetus. Although known to be teratogenic in animals, rifampicin is not known to be teratogenic in the human [157]. Snider *et al.* [158] recommend that isoniazid and ethambutol be used to treat minor tuberculous disease in pregnancy and that rifampicin should be added if a third drug is warranted. It is the author's practice to employ the standard 9-month regimen with rifampicin, isoniazid and ethambutol in the initial 2-month phase followed by 7 months of rifampicin and isoniazid [22].

### Childhood

The basic principles of treatment of tuberculosis in childhood are essentially the same as for adults [159]; 9-month regimens containing at least isoniazid and rifampicin have been demonstrated to have a high rate of success in children. Because of difficulties in monitoring for ocular toxicity in young children, ethambutol is best avoided. Streptomycin or pyrazinamide are alternatives. The doses of standard antituberculosis drugs for children are shown in Table 19.1.

### HIV infection

Isolated case reports of failure of standard chemotherapy for tuberculosis in apparently, but not definitely, compliant patients with AIDS [160,161] have led to the inevitable questioning of the adequacy of such therapy for such patients [162]. Relapse is certainly commoner among HIV-positive than HIV-negative tuberculosis patients prescribed less-potent drug regimens in Africa [163,164]. With standard short-course chemotherapy, relapse rates are no more common in HIV-positive than in HIV-negative patients if the continuation phase of treatment is prolonged to give a total duration of chemotherapy of 9 months [165,166]. The rate of sputum culture conversion is similar in both groups. Antituberculosis chemotherapy

combined with zidovudine therapy is safe and well tolerated [167].

### Drug resistance and the management of disease due to drug-resistant organisms

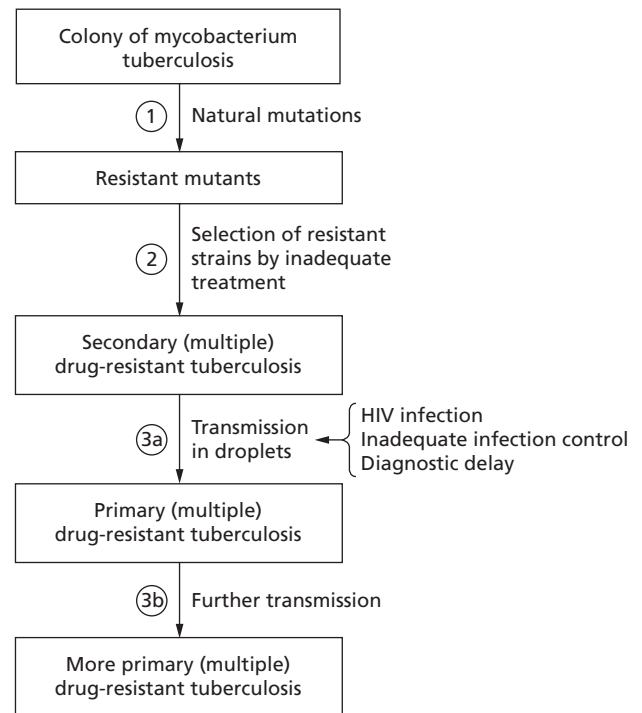
It took the emergence of multidrug-resistant tuberculosis in New York City [114] to fully focus the professional mind on the problems of preventing drug-resistant tuberculosis. The problem is not new to the world—reports from some countries indicate resistance rates of 37% to rifampicin and 55% to isoniazid [168]—but is relatively new as a major problem in the developed world. Rieder [169] and others [170] have emphasized that the present problems with drug-resistant tuberculosis are due to complacency over previously well established principles.

The simple observation that it is not enough to prescribe the microbiologically appropriate drugs but that it is also necessary to ensure that the drugs are taken for the prescribed duration [112], however difficult that may be, has been forgotten. If therapy composed of single drug formulations is left unsupervised in the hands of the poor, the homeless, the addicted and the HIV infected, monotherapy may result. Monotherapy may lead to acquired resistance and inadequately treated disease will result in the transmission of primarily resistant disease to others. The cycle may repeat and multidrug resistance, as reported from New York City, emerges.

If it can happen in New York City, there can be little wonder that drug resistance is a problem worldwide. Of increasing concern are the possible worldwide consequences of introducing short-course chemotherapy with the primary antituberculosis drugs, i.e. the World Health Organization's DOTS programme [171]. Reassuringly, in Tanzania the programme, which *must* incorporate rifampicin in combination with isoniazid, has not led to any increase in rifampicin resistance [172]. The worst possible scenario [172], one in which tubercle bacilli become increasingly resistant to multiple drugs resulting effectively in a return to the prechemotherapy era of tuberculosis with 50–80% mortality rates, will only be avoided if the long-established principles of treating tuberculosis are rigidly observed. At present, this means considering the need for DOT for every patient [120].

### Development and spread of drug-resistant tuberculosis

The pathways involved in the development and spread of multidrug-resistant tuberculosis are shown in Fig. 19.7 [173]. Mutant bacilli resistant to single drugs exist in nature (as described earlier) and are selected by inadequate treatment. Inadequate treatment may involve ingestion of only one drug (direct monotherapy) or ingestion of



**Fig. 19.7** The three stages in the development and spread of multidrug-resistant tuberculosis. A fourth contribution to the problem comes from migration of patients with primary and secondary resistance into the control area. (From Lambregts-van Weezenbeek & Veen [173] with permission.)

a combination of drugs only one of which the strain is sensitive to (indirect monotherapy). Secondary (or acquired) resistance to one drug results. New mutations in this growing bacillary population eventually lead to multidrug resistance if inadequate treatment is continued.

Tuberculosis patients with secondary drug-resistant tuberculosis may infect others who are then said to have tuberculosis that demonstrates primary resistance. Such transmission is facilitated by HIV infection, where disease development and progression seem more rapid [174], by inadequate infection control procedures (particularly in healthcare settings) and by diagnostic delays. Primary or secondary drug-resistant tuberculosis may also be imported, particularly from countries with a high prevalence of disease where control programmes may be inadequate. Primary drug resistance, like secondary drug resistance, may be transmitted to others thus spreading drug-resistant disease within the community.

The extent of drug-resistant tuberculosis can only be determined by laboratory surveillance of isolated strains. In the developed world all isolated strains should have their drug sensitivity patterns determined [174]. In the developing world, with fewer resources, periodic surveys may serve as a marker for developments in the community [175].



### Interventions of value in preventing the emergence of drug resistance

In most developed countries standard short-course chemotherapy with four drugs is continued until drug sensitivity patterns are known. Since drug resistance, even to one drug, is uncommon (<2% in the UK), indirect monotherapy is unlikely to occur in the initial phase and the continuation phase can be planned with knowledge of any detected drug resistance, ensuring that the disease is treated with at least two drugs to which the organism is sensitive. Where the possibility of multidrug resistance is high, e.g. a relapsed patient with previous suspect chemotherapy, an immigrant from a country where drug resistance is common or a contact of a known case of multidrug-resistant tuberculosis, then treatment should be initiated with *at least three drugs* to which the bacillus is known or likely to be sensitive. If the patient's clinical condition permits, it is sometimes wise to withhold therapy until full drug sensitivity details are available in order to allow informed treatment planning. All therapy should be supervised and should continue until sputum cultures have been negative for at least 6 and preferably 12 months. In any country the standard treatment guidelines should be based on an awareness of the drug-resistance pattern of disease in the community.

Education of the medical and paramedical professions in all aspects of the diagnosis and management of tuberculosis needs to be maintained or re-emphasized. In countries where disease incidence is low, advice from tuberculosis specialists should be sought as soon as the diagnosis is made and if any doubt about appropriate management exists.

A strong case can be made for restricting the use of rifampicin to tuberculosis alone and then only when supervised. Where at all possible, rifampicin should only be prescribed in the form of combination tablets (plus isoniazid with or without pyrazinamide) but these tablets must be of proven bioavailability [176].

Finally, efforts to improve patient compliance/adherence must be pursued as described above. Such measures may include education, free treatment, treatment incentives and DOT, which in itself has been shown to decrease

the frequency of drug-resistant disease in the community [177].

### Treatment of drug-resistant disease

The essentials of treatment have been outlined above. Detailed practical advice has been published [178,179]. The essence of success is to treat with at least two and preferably three drugs to which the organism is known or believed to be sensitive until sputum cultures have been negative for at least 6 and possibly 12 months. Where disease is intractable, surgical resection may be of value [180]. In hospitalised patients precautions to prevent spread of disease have been discussed in Chapter 16 (pp. 478–9).

### Corticosteroid therapy in tuberculosis

The use of corticosteroids in the management of patients has recently been extensively reviewed [181,182]. It must be emphasized that corticosteroids should never be given to patients with tuberculosis unless they are receiving adequate antituberculosis therapy. The main indications for corticosteroid therapy in tuberculosis are as follows:

- 1 in very seriously ill patients to buy time for chemotherapy to become effective [183];
  - 2 to control drug hypersensitivity reactions [184];
  - 3 in tuberculosis of the serous sacs, i.e. pericarditis [185], peritonitis and pleural effusion to prevent fibrosis and adhesions and to hasten absorption of fluid;
  - 4 in tuberculous meningitis to prevent morbidity and mortality due to adhesions, particularly in stage II and III disease [186];
  - 5 in genitourinary tuberculosis to prevent the development of ureteric strictures [137];
  - 6 occasionally for the suppression of lymph node enlargement during chemotherapy, e.g. where mediastinal lymph nodes are causing bronchial obstruction or, occasionally, for the management of tuberculous endobronchitis [187].
- The usual dose of prednisolone is 40 mg daily in adults if rifampicin is being used since it reduces the bioavailability of prednisolone [35]. Prednisolone is usually given for 6 weeks reducing gradually thereafter, e.g. over 4 weeks. Prednisolone should never be prescribed for tuberculosis in the absence of adequate chemotherapy.

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# OPPORTUNISTIC MYCOBACTERIAL DISEASE

A. GORDON LEITCH

Pulmonary disease resulting from *Mycobacterium tuberculosis* complex infection is often called classical pulmonary tuberculosis. *M. tuberculosis* is an obligatory parasite, being unable to exist for long outside the body of the host. In contrast, other species of mycobacteria exist free in nature and are well-recognized causes of disease in humans and animals [1–3]. Pulmonary disease is most often due to infection with the *M. avium-intracellulare* complex (i.e. *M. avium*, *M. intracellulare* or *M. scrofulaceum*), *M. kansasii*, *M. malmoense* or *M. xenopi*. However, at least 20 other mycobacteria may cause pulmonary disease (Table 20.1) and, as techniques for isolating and characterizing these mycobacteria improve, the numbers are likely to increase [4].

An assortment of names has been employed to describe the mycobacteria that cause lung disease other than classical pulmonary tuberculosis. These include atypical, anonymous, tuberculoid and non-tuberculosis mycobacteria, as well as mycobacteria other than tuberculosis. The designation 'opportunistic' mycobacteria has been employed since disease occurs sporadically and often in patients with pre-existing lung disease or suppressed immunity [5].

This chapter describes the epidemiology, bacteriology, clinical and radiological features and management of pulmonary disease caused by the most frequently encountered opportunistic mycobacteria, and lays down guidelines for the management of disease due to those species less frequently encountered.

## Epidemiology

### Distribution and extent of disease

Pulmonary disease caused by opportunistic mycobacteria (designated 'atypical') was first described in several large series of patients from the southern USA in the 1950s [6–8]. The patients affected were epidemiologically quite distinct from patients with pulmonary tuberculosis. Even at this early stage it was appreciated that they were older and

frequently afflicted with other chronic lung diseases, such as bronchiectasis, pneumoconiosis and healed tuberculosis. Positive Mantoux tests were less common in this group of patients and close contacts did not appear to have been infected.

Although then, as now, opportunistic mycobacterial disease was not a notifiable condition, it soon became apparent in the USA that disease due to *M. avium* complex was most common in the rural south-eastern states, whereas *M. kansasii* was a more common cause of disease in the central states [9]. This clinical observation was borne out by skin-test surveys utilizing tuberculin and opportunistic mycobacterial antigen: infection by opportunistic mycobacteria appeared to be particularly common in the rural areas of the south-eastern USA [10,11].

Subsequent reports based on laboratory isolates of opportunistic mycobacteria in the USA have indicated that they comprise 30% of all mycobacterial isolates in the USA and that *M. avium* complex is the most frequently detected [12]. A more recent survey in the USA estimates the prevalence of opportunistic mycobacterial disease at 1.8 per 100 000 population of which 1.1 per 100 000 is due to *M. avium* complex infection [13]. In western Europe, in contrast, *M. kansasii* is the commonest species encountered in general [14], although specific regional and national variations occur; in Scotland, for example, *M. avium* complex and *M. malmoense* predominate [15].

The advent of human immunodeficiency virus (HIV) infection has dramatically altered the epidemiology of opportunistic mycobacterial infection. *M. avium* is now recognized as one of the more common opportunistic infections in patients with AIDS in the USA [16,17], with up to 50% of patients having disseminated *M. avium* complex disease at the time of death [18]. More than 95% of these infections are due to *M. avium* rather than *M. intracellulare* serotypes [19]. Opportunistic mycobacteria other than *M. avium* may cause disease in the HIV setting; in south-east England, for example, although *M. avium* infections predominate in this population, a

Species	Growth rate	Runyan group	Usual disease
<i>M. tuberculosis</i> *	Slow	TB complex	Classical tuberculosis
<i>M. bovis</i>	Slow	TB complex	Classical tuberculosis
<i>M. africanum</i>	Slow	TB complex	Classical tuberculosis
<i>M. asiaticum</i>	Slow	I	Lung
<i>M. avium</i> *	Slow	III	Lung, nodes
<i>M. chelonae</i> *	Rapid	IV	Soft tissue, bone
<i>M. fortuitum</i> *	Rapid	IV	Soft tissue, skin
<i>M. gordonae</i>	Slow	II	Lung
<i>M. haemophilum</i>	Slow	III	Skin
<i>M. intracellulare</i> *	Slow	III	Lung, nodes
<i>M. kansasii</i> *	Slow	I	Lung
<i>M. leprae</i> *	Unculturable	-	Leprosy
<i>M. malmoense</i> *	Slow	III	lung
<i>M. marinum</i>	Slow	I	Skin
<i>M. scrofulaceum</i> *	Slow	I/II†	Lung, nodes
<i>M. simiae</i>	Slow	I	Lung
<i>M. szulgae</i>	Slow	I/II†	Lung, nodes
<i>M. terrae</i>	Slow	III	Lung
<i>M. thermoresistibile</i>	Slow	III	Lung
<i>M. ulcerans</i>	Slow	III	Skin
<i>M. xenopi</i> *	Slow	III	Lung

\* Important human pathogen.  
† Depending on culture conditions.

substantial minority of disease is caused by other opportunistic mycobacteria, of which *M. xenopi*, *M. kansasii* and *M. gordonae* are the most common [20].

Sources of infection

Most opportunistic mycobacteria may be isolated from water and soil [21,22]. In the USA, *M. avium* complex flourishes in natural waters, particularly in the south-east [23]. *M. kansasii* and *M. xenopi* have been isolated from tap water [24], even in hospitals, where cases of pulmonary disease have resulted [25]. *M. malmoense* has yet to be isolated from environmental sources, the difficulty in doing so perhaps reflecting its fastidious cultural characteristics.

The presumption must be that opportunistic mycobacterial pulmonary infection and disease result from the inhalation of, presumably aerosolized, organisms from the environment. Although similar mycobacteria-bearing aerosols are likely generated as a result of coughing in patients with disease, to all intents and purposes transmission of disease from humans or animals to other humans does not occur. Opportunistic mycobacterial pulmonary disease is *not infectious* and, unlike *M. tuberculosis* disease, has no important public health consequences; in particular, contact tracing, chemoprophylaxis, etc. are not required.

Ingestion of opportunistic mycobacteria is considered to be the likely cause of cervical lymphadenopathy in children. Direct inoculation of opportunistic mycobacteria, e.g. *M. marinum*, in water or from other material

Table 20.1 Mycobacteria causing human lung disease.

is likely to be the source of infection for patients with superficial cutaneous or soft-tissue infection.

Bacteriology

Classification

A relatively simple classification was introduced by Runyan in 1959 [26]. This depended on the cultural characteristics of the mycobacterium as shown in Table 20.2. Organisms were either slow growers (groups I–III) or fast growers (group IV); the slow growers were pigmented on exposure to light (I), pigmented in light and dark (II), or only weakly pigmented or non-pigmented (III). While still serving as a useful guide to the likely clinical relevance of an isolate, subsequent taxonomic advances, utilizing a wide range of techniques of characterization, have led to this scheme no longer being widely used. Classification of species can usually be obtained by applying a range of simple biochemical and cultural tests, such as temperature range, pigment production, oxygen preference and Tween-80 hydrolysis. More rapid methods for species identification are currently being developed and/or applied, including thin-layer chromatography, gas–liquid chromatography and high-pressure liquid chromatography, and the use of specific DNA probes, currently available for *M. avium* complex, *M. kansasii* and *M. gordonae*. The number of opportunistic mycobacterial species identified is continually growing [4,27]; most of those relevant to human pulmonary disease are shown in Table 20.1.



**Table 20.2.** Runyan classification of mycobacteria.

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Group I (photochromogens): slow-growing, pigmented on exposure to light
Group II (scotochromogens): slow-growing, pigmented in light and dark
Group III (non-photochromogens): slow-growing, weak or no pigmentation
Group IV (rapid growers): colonies within 7 days at 24°C and 37°C

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### Isolation and culture methods

The culture and identification of opportunistic mycobacteria is a procedure that should be reserved for the highest level laboratories. The simple digestion, decontamination and staining procedures used for *M. tuberculosis* have also proved useful for the other mycobacteria. Both the Ziehl–Nielsen stain and the fluorochrome procedure identify the presence of opportunistic mycobacteria in clinical material. Microscopy does not differentiate them from tuberculous mycobacteria with the exception of *M. kansasii* organisms, which are often larger with a more beaded appearance.

Almost all opportunistic mycobacteria with the exception of *M. haemophilum* can be cultured on conventional *M. tuberculosis* media, including the radiometric Bactec system (see Chapter 17). Growth is usually detected within 2–4 weeks on solid media and in 1 week with the Bactec system. It may be helpful to extend the duration of incubation to detect growth of some opportunistic mycobacteria, e.g. *M. malmoense* grows very slowly (mean 54 days, range 31–87 days) compared with all other mycobacteria (mean 30 days, range 10–84 days) [28].

### Antimycobacterial drug susceptibility testing

It is generally recognized that the application of the techniques of *in vitro* drug susceptibility testing relevant to the management of pulmonary tuberculosis is frequently, if not always, inappropriate in the context of opportunistic mycobacterial infection. Many of these mycobacteria may be drug resistant *in vitro* but, judged by clinical response, drug sensitive *in vivo* [29–31]. Most clinicians have experience of patients with pulmonary disease whose clinical condition is improving on standard antituberculous chemotherapy (rifampicin, isoniazid, ethambutol, pyrazinamide) but which deteriorates when chemotherapy is modified, apparently appropriately, when the results of drug susceptibility testing become available, only to improve again when the apparently ineffective initial therapy is reinstated.

A move towards recognizing the potentially confusing nature of drug susceptibility test results has been made by the American Thoracic Society [32]. They recommend that

routine susceptibility testing does not provide useful clinical information and should not be performed for *M. avium* complex or for the rapid growers *M. marinum*, *M. fortuitum* and *M. chelonae*. Drug susceptibility testing should be retained for *M. kansasii*, *M. xenopi*, *M. malmoense* and other less common mycobacteria. It is important to stress that there is no evidence to justify a conclusion that chemotherapy for such infections should necessarily be based on, or altered by, the results of *in vitro* susceptibility testing. It remains the case that with such infections the patient is the site of the susceptibility test, and current best practice is based more on clinical experience than laboratory-derived evidence. Fortunately most disease due to *M. kansasii*, *M. xenopi* and *M. malmoense* appears to respond to treatment with rifampicin and ethambutol with or without other drugs (see below).

A healthy degree of scepticism about *in vitro* susceptibility test results for opportunistic mycobacteria is warranted by the poor correlation of such results with response to treatment. The limitations of applying *M. tuberculosis* susceptibility testing to these mycobacteria may well be responsible. Some sense may have been generated by the observation that strains of *M. avium* complex, *M. xenopi* and *M. malmoense* which were resistant to both ethambutol and rifampicin when tested separately to each drug were sensitive in a minority, a majority and *in toto*, respectively, when susceptibility was tested to the two drugs combined [33].

In like fashion the full meaning of susceptibility test results with the newer drugs, such as the fluoroquinolones (e.g. ciprofloxacin), the macrolides (e.g. clarithromycin) and the rifamycins (e.g. rifabutin), and their relation to clinical effects remains to be determined.

### Diagnostic criteria

Since opportunistic mycobacteria are capable of colonizing the bronchial tree without causing disease, their isolated culture from sputum is not necessarily of pathological significance. Conventional criteria for the diagnosis of disease therefore require the presence of infiltrative lung disease (for which other causes have been effectively excluded) and isolation of the mycobacteria repeatedly from sputum. Culture of the organism from lung biopsy, bronchoalveolar lavage or pleural fluids or blood culture is of greater diagnostic significance than an isolated sputum culture. The American Thoracic Society [32] has agreed the following criteria for the diagnosis of opportunistic mycobacterial pulmonary disease.

1 For patients with a cavitary infiltrate on the chest radiograph when:

- (a) two or more sputa (or sputum and a bronchial washing) are positive for acid-fast bacilli and/or result in moderate to heavy growth of opportunistic mycobacteria on culture;

(b) other reasonable causes for the disease process, e.g. fungal disease, malignancy, tuberculosis, have been excluded.

Approximately 90% of patients with *M. kansasii* disease and 75% of patients with *M. avium* disease will have cavitary infiltrates and disease will be diagnosed by these criteria [34].

2 In the presence of a non-cavitary infiltrate not known to be due to another disease, opportunistic mycobacterial pulmonary disease is present when:

- (a) two or more sputa (or sputum and a bronchial washing) are positive for acid-fast bacilli and/or result in a moderate to heavy growth on culture;
- (b) failure of sputum cultures to convert to negative with either bronchial hygiene or 2 weeks of specific antimycobacterial therapy;
- (c) other reasonable causes for the disease have been excluded.

The second criterion is presumed to exclude colonization rather than a disease state. *M. chelonae* lung disease is usually non-cavitary and would be diagnosed by these criteria. A presumed colonization state should not preclude the patient from continuing observation for clinical symptoms and pulmonary findings; the indolent nature of some infections may prevent early diagnosis and the disease process may eventually progress.

3 In patients with low numbers of organisms on sputum culture and/or where another disease process cannot be excluded, a lung biopsy is often required for diagnosis [35]:

- (a) if the lung biopsy yields the organisms and shows characteristic mycobacterial histopathological features, no other criteria are needed;
- (b) if the biopsy yields no organisms but shows mycobacterial histopathological features in the absence of a prior history of other granulomatous or mycobacterial disease then (i) presence of two or more positive cultures of sputum or bronchial washings and (ii) exclusion of other reasonable causes for granulomatous disease are required.

These criteria should only be used as a guide in dealing with individual patients. Sometimes repeated positive cultures are obtained when old fibrotic lung disease has simply been colonized by the organisms. At the other extreme, progressive lung disease and evident illness may require treatment as soon as the first culture is obtained.

The diagnosis depends on the laboratory, which obtains its first clues from the cultural characteristics of the organism and its pattern of drug susceptibility. Subsequent identification requires techniques beyond the scope of most microbiological laboratories and cultures should be sent to a supraregional or national mycobacteria reference laboratory.

## Clinical features and radiology

### Clinical features

Most patients are middle-aged or elderly males and most have pre-existing lung disease, usually chronic bronchitis and emphysema or old healed tuberculosis [29–31,36–39]. The patient may have worked in a noxious or dusty environment or even have pneumoconiosis [40]. Sometimes, the patient is immunosuppressed by disease or drugs; the possibility of HIV infection, particularly in the young, must be constantly remembered. Chronic pulmonary disease resembling pulmonary tuberculosis is the most common presentation, with symptoms of cough, sputum, haemoptysis, weight loss, malaise, fever and increasing dyspnoea. Acute illness at presentation is uncommon and the picture is usually one of a subacute or chronic illness.

### Radiology

The radiological features are typically upper zone fibrosis with cavitation (Fig. 20.1), although miliary spread is occasionally seen in the immunosuppressed. The appearances may be impossible or difficult to distinguish from classical tuberculosis or from chronic fibrosis with bronchiectasis due to, for example, allergic alveolitis, pulmonary aspergillosis or sarcoidosis. Occasionally the appearances may be of centimetre-sized nodular or patchy irregular infiltrates in both lungs [35]. Attempts to usefully differentiate opportunistic mycobacterial diseases from each other and from tuberculous mycobacterial disease on the basis of radiological appearances have failed [41,42].

### Differential skin testing

At present species-specific skin-test antigens are neither sufficiently standardized nor specific to have any place in the diagnosis of opportunistic mycobacterial disease.

## Management

### *Mycobacterium avium-intracellulare* disease

As already indicated, *M. avium-intracellulare* is resistant to most, if not all, conventional antituberculosis drugs on susceptibility testing. Routine susceptibility testing for this organism is not recommended [32]. Most recommended chemotherapy regimens for disease due to this organism are based on published series of treated cases. Controlled clinical trials have not been reported to date.

### Pulmonary disease

A small number of patients with *M. avium* complex lung



**Fig. 20.1** Chest film of a patient with chronic airflow obstruction and infection with *M. kansasii*. Note the fibrosed and cavitated right upper lobe.

disease may be relatively asymptomatic and have stable radiographic appearances. They may be managed by observation only, even if their sputum clears. However, the majority of patients have significant symptomatology and/or evidence of progressive or extensive radiological disease. Recommended initial therapy for *M. avium* complex disease consists of isoniazid 300 mg, rifampicin 600 mg, ethambutol 25 mg/kg for 2 months and 15 mg/kg thereafter, with streptomycin for the first 3–6 months (see Nallace *et al* [32] for dosage regimens). Therapy is recommended for 18–24 months and for at least 12 months after sputum culture conversion. Several clinical trials using the four-drug regimen have shown sputum conversion rates of up to 80% [29,43–45].

Sputum smear and culture should be assessed monthly, at least initially, following the start of treatment to assess response. Occasional positive sputum cultures after apparent sputum conversion do not necessarily indicate treatment failure or relapse. Definite relapses after discontinuation of therapy are common, averaging 20% or higher even with the recommended four-drug regimen [44].

Patients who fail to convert their sputum cultures after 12 months of therapy should probably have their treatment discontinued. If stable, then observation is in order, but if they have clearly progressive symptomatic disease then an alternative multidrug regimen incorporating cycloserine (250 mg twice daily), ethionamide (250 mg

twice or thrice daily), clofazimine (100–200 mg daily), a rifamycin such as rifabutin (600 mg daily), a fluoroquinolone such as ciprofloxacin (1000–1500 mg daily) or a macrolide such as clarithromycin (1000–2000 mg daily) may be successful [46,47].

Many, if not most, patients will have been started on standard antituberculosis chemotherapy (rifampicin, isoniazid, ethambutol, pyrazinamide) when sputum smear positivity for acid-fast bacilli has been detected. If clinical progress is satisfactory at the time *M. avium* complex is confirmed by sputum culture testing, it would be reasonable to continue treatment with rifampicin, isoniazid and ethambutol for 18–24 months as per the above guidelines.

Where disease is progressive in spite of treatment, or sufficiently localized and where lung function permits, surgical resection under chemotherapeutic cover should be considered. Resection may result in cure [48,49]. Resected solitary pulmonary nodules that prove to be due to *M. avium* complex disease require no further therapy in the absence of evidence of other *M. avium* complex disease or immunosuppression.

#### *Clarithromycin*

Clarithromycin (1000–2000 mg daily) has been shown to be an effective single agent in the treatment of *M. avium* complex disease in the non-immunocompromised host

[50,51]. Clarithromycin resistance develops in 16% of isolates [50]. The potential for relapse remains to be fully assessed. Clarithromycin-sensitive *M. avium* complex strains contain  $10^{-8}$  to  $10^{-9}$  resistant mutants and development of drug-resistant disease and relapse is due to multiplication of these pre-existing mutants [52]. Given its efficacy in not only non-HIV-related but also HIV-related *M. avium* complex disease (see below), clarithromycin is clearly a powerful additional drug in the armamentarium available for treating this disease. Clinical trials incorporating clarithromycin in treatment regimens for *M. avium* complex disease have been started and the results are awaited.

### **Disseminated *Mycobacterium avium* complex disease**

Disseminated *M. avium* complex disease is usually a late opportunistic infection in severely immunosuppressed patients with AIDS [53]. Multidrug regimens similar to those used for pulmonary disease (but including clofazimine) have resulted in symptomatic and clinical improvement in most patients [54–57]. Clarithromycin is extremely effective against *M. avium* [58] and monotherapy with this drug in AIDS patients with disseminated disease abolishes bacteraemia in 99%; however, relapse occurs due to the emergence of clarithromycin-resistant organisms [53]. It seems likely that clarithromycin will emerge as one of the most important, if not the most important, antibiotic in treating disseminated *M. avium* complex disease. As in the early developmental days of tuberculosis chemotherapy, it will be necessary to determine by appropriate trials of multidrug therapy incorporating clarithromycin which combinations are most effective in preventing the emergence of drug-resistant organisms. At present a combination of rifampicin (or rifabutin) plus ethambutol, ciprofloxacin, isoniazid and clarithromycin might theoretically be recommended but the results of clinical trials are awaited.

### ***Mycobacterium kansasii***

*M. kansasii* disease that is positive on sputum and chest radiography progresses clinically and radiographically if no treatment is given [59]. Treatment of pulmonary disease is therefore mandatory. Current American Thoracic Society recommendations are for 18 months of combined treatment with isoniazid (300mg), rifampicin (600mg) and ethambutol (15mg/kg) [32]. Long-term relapse rates with rifampicin-based therapy are low [39]. A recent study from Spain [60] suggests that therapy with rifampicin, isoniazid and ethambutol can be abbreviated to 12 months (ethambutol given for the first 6 months) without increasing the risk of relapse. A UK study has also shown effective treatment of *M. kansasii* disease with a 9-month rifampicin and ethambutol regimen [61], although

the relapse rate, which may have been 9.7%, can be regarded as unacceptably high [62]. Until these studies are confirmed the standard regimen of rifampicin, isoniazid and ethambutol for 18 months is recommended.

Patients with organisms resistant to rifampicin as a result of previous therapy have been shown to respond well to oral therapy with high-dose isoniazid (900mg), pyridoxine (50mg), ethambutol (25mg/kg) and sulfamethoxazole (sulphamethoxazole) (3g) for 18–24 months, combined with daily amikacin or streptomycin for 2–3 months given intermittently thereafter for a total of 6 months [63]. Subsequent studies from the same group [64] have shown 90% sputum conversion in patients with rifampicin-resistant infection when treated with four-drug regimens selected on the basis of *in vitro* susceptibilities.

Disseminated *M. kansasii* disease is the second most common opportunistic mycobacterial infection in AIDS patients [65]. In the absence of suitable guidelines, standard chemotherapy should be employed.

### ***Mycobacterium mageritense***

Rifampicin and ethambutol appear to be the most important drugs for inclusion in chemotherapeutic regimens for disease due to *M. mageritense*. Treatment for 18–24 months with ethambutol- and rifampicin-containing regimens fared better than other regimens in retrospective studies [15,31,36]. The organisms may be sensitive *in vitro* to ciprofloxacin and/or clarithromycin but their role *in vivo* remains to be determined. Many patients are elderly with quite severe pre-existing lung disease [66] and death may ensue before the infection is eliminated, not necessarily because of the infection.

### ***Mycobacterium xenopi***

*M. xenopi*, so named because it was first isolated from a toad, also lives in water. Its existence in the tap water used to clean and consequently contaminate fiberoptic bronchoscopes led to an apparent epidemic of disease in Michigan, Ontario [67]. The organism shows very variable patterns of drug susceptibility *in vitro* and is often resistant to rifampicin, isoniazid and ethambutol [68]. Moreover, resistance patterns may change on sequential culture. *In vitro* drug susceptibility tests do not always predict *in vivo* clinical response [30,38]. On presently available evidence [30,38,69] treatment with ethambutol, isoniazid and rifampicin for at least 2 years is recommended. Relapse of *M. xenopi* infections, even when the organisms are sensitive *in vitro* to rifampicin and ethambutol, is common [70] if the duration of therapy is inadequate.

### ***Mycobacterium fortuitum***

Pulmonary disease due to this rapidly growing mycobacterium is uncommon. *M. fortuitum* is usually susceptible *in vitro* to amikacin, ciprofloxacin, sulphonamides, imipenem and doxycycline [71]. Such infections have been successfully treated with ciprofloxacin-containing regimens [72,73].

### **Other opportunistic mycobacteria**

The most commonly encountered opportunistic mycobacterial infections have been discussed above. As a general rule discordance between *in vitro* tests of drug susceptibility and *in vivo* therapeutic response as clinically assessed is not uncommon. This should always be borne in mind when considering treatment interventions and modifications in the management of these mycobacterial infections.

Most patients with opportunistic mycobacterial disease are likely to have been started on treatment with standard

quadruple antituberculous chemotherapy (rifampicin, isoniazid, ethambutol, pyrazinamide) prior to the isolation, characterization and drug susceptibility testing of their infecting mycobacterium. As a general rule if the patient is improving clinically on standard therapy, then this should not be modified *whatever* the results of *in vitro* susceptibility testing. Treatment should be continued for at least 18 months and preferably 2 years with all four drugs.

If there has been no clinical response or deterioration has occurred then at least two additional drugs, preferably those to which the organism is sensitive *in vitro*, should be added to the regimen. Ciprofloxacin and clarithromycin are likely to play an important role in this scenario, although reports supporting this role are still awaited. Treatment should be continued for at least 18–24 months. When treating opportunistic mycobacterial disease it is always important to consult not only the literature but also those with accumulated experience of treating the disease and also, and certainly not least, the laboratory mycobacteriologist.

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# ACTINOMYCOTIC AND FUNGAL DISEASES

ANTHONY SEATON

This chapter follows the traditional practice of considering together, albeit incorrectly, the higher bacterial actinomycetes and the fungi. The practice is justified by the similarities of the diseases with which they may be associated and, in some respects, their morphology. However, the differences between them are large in biological terms and, clinically, in terms of response to chemotherapeutic agents. Also discussed is the increasingly important organism *Pneumocystis carinii*, now generally agreed to be classifiable as a fungus.

## Actinomycetes

The bacterial order Actinomycetales includes the familiar Mycobacteriaceae (see Chapters 16–20), the Actinomycetaceae and the Nocardiaceae, together with the Thermomonosporaceae and Thermoactinomycetaceae (Table 21.1).

The Actinomycetaceae include the genera *Actinomyces*, *Actinobacillus* and *Arachnia*. *Actinomyces* spp. are slow-growing, Gram-positive filamentous organisms that differ from fungi in lacking a nuclear membrane, having no chitin in their cell walls and reproducing by fragmentation of their filaments rather than by spore formation. Most strains, including *Actinomyces israelii*, are anaerobic or microaerophilic and grow best at 37°C, forming mature heaped-up colonies within about 1 week. *Arachnia* spp. are very similar in cultural characteristics but produce smoother colonies. *Nocardia* spp. are filamentous, weakly Gram-positive organisms with a tendency to break up into coccobacillary forms. They grow aerobically over a wide temperature range and growth is promoted in 10% carbon dioxide. Growth may be slow and the pigmented colonies may be obscured by faster-growing organisms.

*Nocardia* spp. are soil saprophytes, living in decaying organic matter and are normally introduced into humans or animals by inhalation of particles in dust or by trauma and wound infection. In contrast *Actinomyces* and *Arachnia* spp. live as saprophytes in the mouths of humans and animals, causing infection as a result of oral trauma or

disease, or following aspiration of infected matter into the lungs.

## Fungi

Fungi are a group of spore-bearing, often filamentous, organisms that lack chlorophyll and therefore obtain their food by either a saprophytic or a parasitic existence. Most live by breaking down dead organic matter and, in their turn, they or their spores may provide food for other organisms such as amoebae and insects. They reproduce by producing spores, either sexually or asexually, or by budding or fragmentation.

The classification of fungi is complex and of little relevance to an understanding of their pathogenic effects. Confusion arises partly from their pleomorphism, i.e. their ability to produce two or more phenotypes from one genotype. In the sexual form the fungus is said to be in a perfect state, while in the asexual form it is said to be in an imperfect state. Many fungi, including several of medical importance, were first described and named in the imperfect state and were then found to produce, under appropriate cultural conditions, a sexual form that had a different name. Fungal taxonomy now uses the name of the perfect form, although in medical terminology the original imperfect form names have been retained. Moreover, a whole group of fungi, the fungi imperfecti, are classed together not on morphological or biochemical grounds but because they have no known perfect form; this group includes *Aspergillus*, *Paracoccidioides* and *Penicillium*. An abbreviated classification of some fungi of medical importance is given in Table 21.2.

## Growth and reproduction of fungi

Fungi have nuclei and cell walls [1]. In filamentous organisms the latter generally consist of polysaccharide, glycoprotein and chitin [2]. The filament elongates and branches, and is often divided incompletely by the development of septa. The filament is called a hypha, and a



Family	Genus	Disease
Actinomycetaceae	<i>Actinomyces</i> <i>Arachnia</i> <i>Propionibacterium</i>	Actinomycosis
Mycobacteriaceae	<i>Mycobacterium</i>	Tuberculosis, other mycobacterioses
Nocardiaceae	<i>Nocardia</i> <i>Micropolyspora</i>	Nocardiosis Allergic alveolitis
Thermoactinomycetaceae	<i>Thermoactinomyces</i>	Allergic alveolitis
Thermomonosporaceae	<i>Thermomonospora</i>	Allergic alveolitis
Streptomyetaceae	<i>Streptomyces</i>	Actinomycosis

**Table 21.1** Classification of actinomycetes of medical importance.

**Table 21.2** Classification of fungi of medical importance.

Class	Genus	Main disease
Zygomycetes	<i>Absidia</i> <i>Mucor</i> <i>Rhizopus</i>	Mucormycosis
Ascomycetes	<i>Ajellomyces</i> * <i>Didymella</i> <i>Emmonsia</i> † <i>Leptosphaeria</i> <i>Saccharomyces</i> ‡	Blastomycosis Asthma Histoplasmosis Asthma Asthma
Basidiomycetes	<i>Filobasidiella</i> § <i>Ustilago</i> <i>Puccinia</i> <i>Lycoperdon</i> <i>Merulius</i>	Cryptococcosis Asthma Asthma Allergic alveolitis Asthma
Hypomycetes	<i>Aureobasidium</i> <i>Aspergillus</i> <i>Alternaria</i> <i>Blastomyces</i> <i>Cladosporium</i> <i>Coccidioides</i> <i>Cryptosporium</i> <i>Fusarium</i> <i>Histoplasma</i> <i>Paracoccidioides</i> <i>Penicillium</i> <i>Pseudallescheria</i> <i>Sporothrix</i>	Asthma Aspergillosis Asthma Blastomycosis Asthma Coccidioidomycosis Allergic alveolitis Asthma Histoplasmosis Paracoccidioidomycosis Asthma Mycetoma Sporotrichosis
Blastomycetes	<i>Candida</i> <i>Cryptococcus</i> <i>Sporobolomyces</i>	Candidiasis Cryptococcosis Asthma

\* *Blastomyces* is the imperfect form.

† *Histoplasma* is the imperfect form.

‡ *Candida* is the imperfect form.

§ *Cryptococcus* is the imperfect form.

mass of hyphae a mycelium. The hypha absorbs nutrients and growth occurs from its tip; spores may develop on a specialized hyphal extension, the conidiophore. In their development they assume the cell wall of the hypha but take a roughly spherical or ovoid shape. They are adapted to survival in adverse conditions and are dispersed by air, water or animals. Germination of spores occurs in appro-

priate conditions and is associated with splitting of the cell wall and emergence of a germ tube. The process initiating germination is ill understood, but requires sufficient moisture and oxygen and involves uptake of water by the spore. The spore swells and its metabolic rate increases.

Many fungi exist in a unicellular form, when they are known as yeasts; most of these also exist in a mycelial form, making life difficult for taxonomists. The yeast cell wall consists mainly of mannans and glucans, with less chitin than that of filamentous fungi. Yeasts reproduce by budding, the bud arising from the inner layer of the cell wall. *Candida* and *Cryptococcus* are familiar pathogenic yeast forms.

Fungi are of considerable importance to humans in both a positive and a negative sense. Their metabolic products are exploited widely in biotechnology, the best-known being alcohol and penicillin. These, together with such products as the cephalosporins, citric and gluconic acids, glucose oxidase and catalase, form the basis of a substantial industry. On the other hand, many are plant parasites that damage food crops, for example the potato blight *Phytophthora* has had a major effect on populations. Toxic materials produced by fungi include the carcinogen aflatoxin. In addition many fungi are able to cause allergic sensitization in humans and animals, while relatively few cause direct infection.

### Pathogenic effects

With very few exceptions, humans and the animal kingdom are incidental to the life history of fungi and pathogenic effects result from the accidental intrusion of fungal spores into the animal environment.

Generally, therefore, fungal diseases affect the skin and the lungs, organs in direct contact with the air in which spores are carried. Occasionally soft tissue infections may occur as a result of penetrating injuries that introduce soil-borne spores. The pulmonary syndromes associated with fungi in humans are asthma, hypersensitivity pneumonitis, saprophytic colonization and infection. Fungal spore asthma is discussed in Chapter 34 and hypersensitivity pneumonitis in Chapter 37. These syndromes may be pro-

voked by a large, and potentially limitless, number of fungal spores. In contrast, fungal infection and saprophytic colonization of the lungs occur with only a relatively small number of species, some of which (like *Candida*) are specialized to life within the animal organism and some of which (like *Aspergillus*) have developed mechanisms for survival in their natural habitat that coincidentally improve their chances of survival in animal lungs.

Thus, apart from hypersensitivity reactions, fungal diseases of human lungs are relatively uncommon and usually arise from the coincidence of an appropriate habitat, such as pulmonary inflammation or cavitation or reduced host immunity, and an organism with defence mechanisms appropriate to its survival in that environment. These matters are discussed further under the individual diseases.

### Sources of fungi

When a patient is shown to have fungal lung disease, the physician often wonders where the organism came from. The answer is almost invariably that it was inhaled from the ambient air. The air is full of fungal spores, liberated from organisms growing on dead or living vegetable matter [3]. Most of these spores are small and of appropriate size and shape to be respirable. In the summer in the UK, *Cladosporium*, plant rust and smut and *Fusarium* spores may be found in their tens of thousands in every cubic metre of air, while *Penicillium* and *Aspergillus* spores occur (in smaller numbers) predominantly in the autumn and winter months [4,5]. The numbers and species of spores differ in different climates, weather conditions and local vegetation. Many spores, such as those of *Coccidioides* or *Histoplasma* in the USA, may be found in soil and become liberated into the air when the soil is disturbed [6,7]. Huge numbers of spores have been observed to be released into the air in the meteorological conditions immediately prior to a thunderstorm [8], and may have some relevance to epidemics of asthma that occur in such circumstances. *Aspergillus* may be liberated from compost heaps [9] and when earth is disturbed by construction operations. Many species of fungal spore form an allergenic cloud round farmers at harvest time as the plant pathogens and saprophytes are disturbed [10]. Growth of fungus indoors may cause problems for asthmatics, and occasional outbreaks of fungal disease may result from, for example, careless removal of air filters in operating theatres or from fungal growth in air conditioners [11,12].

## Actinomycosis

### Aetiology

Actinomycosis may be caused by any one of the normal

mouth commensals, *Actinomyces israelii* (the most common), *A. naeslundii*, *A. viscosus*, *A. odontolyticus* (an important agent of dental plaque), *A. meyeri*, *Actinobacillus actinomycetes* and *Arachnia propionica*. There are no important differences in terms of the resultant clinical picture or response to therapy between these organisms. Infection has been reported from all over the world; malnutrition, immunosuppression and alcohol abuse may be predisposing factors but the primary cause of infection appears to be poor dental hygiene, oral trauma and aspiration of infected material into the lungs. All actinomycotic infection is in fact polymicrobial, the actinomycetes acting synergistically with anaerobes, particularly *Actinobacillus* and *Bacteroides* spp. This means that eradication of the main pathogen may not always result in complete resolution of the clinical condition.

### Clinical features

The most frequent manifestation of infection is a cervicofacial abscess [13–16]. Sometimes this can extend downwards directly into trachea or lung. Actinomycosis characteristically transgresses tissue planes and infection of the lung results in necrotic abscesses that invade adjacent structures, such as chest wall, mediastinum or pericardium [17,18]. In earlier times the patient often presented with abscesses pointing on the chest wall, but this is now very unusual in developed societies [19]. More frequently the patient presents with cough, purulent sputum and, occasionally, haemoptysis. Systemic symptoms of fever and weight loss are often not very prominent until the disease is well advanced. Metastatic spread to subcutaneous tissues, brain and other organs may occur in severe disease [20].

The diagnosis may be difficult and is often not suspected until the organism is demonstrated microbiologically [21]. Symptoms are non-specific and the radiograph may present any of a wide variety of changes; diffuse consolidation, fibrosis, cavitation and empyema all occur, and may be bilateral or unilateral. As the lesion may mimic bronchial carcinoma, resection is sometimes carried out before the diagnosis is made, suggesting that needle biopsy of such lesions might have prevented this intervention [22]. Associated periostitis of ribs or destruction of bone may be seen. The patient has often been treated with antibiotics, which makes the organism difficult to culture. Indeed, culture of actinomycetes from sputum may be of no relevance to coincident pulmonary disease in view of their normal presence in the mouth. However, the presence of chest wall or metastatic abscesses is a strong pointer to the diagnosis, which may be confirmed by microscopy of pus or biopsy material [23]. Specific stains for the various species may be used, but there are no serological tests of proven value.

The most characteristic feature of actinomycotic

infection, and one that allows the diagnosis to be made from examination of the pus, is the presence of 'sulphur granules'. These are yellow or white flecks, hard to the touch and about 2 mm in diameter, consisting of masses of hyphae cemented by a polysaccharide–protein complex and calcium phosphate [24]. Under the microscope they appear light brown, with a granular centre and radiating bands with eosinophilic clubs at the periphery (Fig. 21.1). They may sometimes be found in sputum if it is fixed directly in formalin rather than smeared for cytology.

The differential diagnosis is from other chronic lung infections (and tuberculosis may be very closely mimicked), other causes of empyema, and carcinoma. With modern techniques of investigation, such as transbronchial and needle aspiration, the diagnosis should be missed less frequently than in the past. In view of the difficulties in culturing the organism, the importance of its histological recognition in pus, sputum or tissue specimens cannot be overstressed.

### Management

All species of *Actinomyces* and *Arachnia* are sensitive to penicillin, and as soon as the diagnosis is made treatment should be started with 10–12 megaunits (6–7 g) daily intravenously [25]. Smaller doses orally may sometimes be adequate but have not always been effective in reported cases. If the patient is allergic to penicillin, tetracyclines, erythromycin, clindamycin, lincomycin and parenteral cephalosporins may be used and all have been shown to be active *in vitro* [26]. In chronic lung infection it is advisable to continue high-dose penicillin for 4–6 weeks followed by oral penicillin in a lower dose for up to 6 months. The presence of mixed infection with anaerobes should be

anticipated and appropriate antibiotics used. *Actinobacillus actinomycetem comitans*, the most frequent of these, is usually resistant to penicillin and requires treatment with a third-generation cephalosporin [27]. Abscesses, and particularly empyema, need to be drained and, in the absence of a satisfactory response to antibiotics, lung resection may be necessary. However, in view of the difficulties in a chronic, fibrosing infection, including the complication of bronchopleural fistula, this should be postponed until after a lengthy trial of medical treatment.

## Nocardiosis

### Aetiology

The family Nocardaceae consists of a number of species of Gram-positive, branching, filamentous aerobic bacteria that do not produce spores. They live on decaying organic matter in soil and are not natural inhabitants of humans, either as commensals or parasites. Nevertheless, fragments may become airborne and the primary route of infection in humans is via the respiratory tract. The usual organism found in human disease is *Nocardia asteroides*, but *N. brasiliensis*, *N. farcinica* and *N. transvalensis* have also been described as pathogens [28–30]. Infections occur predominantly in debilitated or immunosuppressed patients; alcohol abuse, chronic disease and corticosteroid therapy are frequent predisposing factors [31]. The most common causes of infection identified in a recent survey were immunosuppressives used to prevent rejection of transplants and for treating chronic pulmonary fibrosis, tumours and blood disorders, and immunosuppression as a consequence of human immunodeficiency virus (HIV) infection [32].



**Fig. 21.1** Photomicrograph of the edge of an actinomycotic 'sulphur granule' obtained from pus from a chest wall abscess. Note the strands of filamentous organisms. (Courtesy of Mr Michael Croughan.)

### Clinical features

Infection with *Nocardia* spp. cannot be distinguished clinically from other chronic pulmonary infections [25,31,33–35]. Non-specific symptoms of cough, loss of weight and appetite, purulent sputum and malaise are usual. The radiograph shows a wide range of abnormalities, including patchy opacities, streaky fibrotic-looking shadows, and diffuse infiltration; however, cavitation (single or multiple) is a frequent feature [36]. This infection, as well as that by *Aspergillus* spp., should be suspected when radiographic pulmonary nodules develop following transplantation [37]. Spread of infection by direct extension to pleura or mediastinum may occur [38], although chest wall fistulae are an unusual feature. Metastatic spread can occur to any part of the body, and brain abscess occurs in about one-third of all patients with disseminated disease.

The clinical course is of progressive deterioration and widespread dissemination in the absence of appropriate treatment. However, acute self-limiting pneumonic forms of the disease may occur. Other opportunistic infections may complicate the picture. The differential diagnosis includes tuberculosis, other mycobacterial infections, actinomycosis and fungal infections, especially aspergillosis. Diagnosis is made by demonstration of the organism in pus or histological material by Gram stain [39]; as stated previously, culture may be difficult and take several weeks. The absence of sulphur granules tips the diagnostic scales heavily in favour of nocardiosis rather than actinomycosis, although atypical granules may occasionally be seen. Serological tests are not generally considered to be of much value in making the diagnosis, but may be useful in following response to treatment.

### Management

The generally recommended treatment is with a sulphonamide such as sulfadiazine (sulphadiazine) (up to 9 g daily in ill patients) or trimethoprim–sulfamethoxazole (sulphamethoxazole) [25,32,33]. The treatment should be continued for several months, as metastatic abscesses may occur even after several weeks of treatment. Unfortunately, sulphonamides are not always effective and when this is the case, or when the patient is allergic to them, alternative therapy must be found. *In vitro* tests are not always a reliable guide to *in vivo* response, but the results should probably be taken into account in planning therapy. In various reports, minocycline, erythromycin, tobramycin, cycloserine, imipenem and amikacin have been shown to be effective. There is a case for combining two or more of these drugs in seriously ill patients. The importance of draining abscesses should be borne in mind when treating such patients.

### Diseases caused by fungi

As stated above, fungi can exert pathogenic effects by allergic sensitization (causing asthma or allergic alveolitis), saprophytic colonization of the lung, or invasion and tissue damage. All airborne fungal spores have at least the potential to cause asthma; many of appropriate size, if inhaled in high dosages, may cause alveolitis. Saprophytic colonization of lung cavities may occur if spores can gain access to, and germinate in, the cavity. The specific factors that allow this are presence in the air in adequate numbers, sufficiently small size to be respirable (<10 µm in aerodynamic diameter) and ability to germinate in the presence of the lung's defences and at 37°C. These factors are discussed further in the section on *Aspergillus*. Pathogenicity in the sense of causing lung and systemic infection is a characteristic of relatively few fungi that have developed specific mechanisms for overcoming the body's defences, but a larger number of organisms have the potential to cause infection if the immune system is impaired. However, relatively few of these opportunistic pathogens cause disease other than very occasionally. In this section, the diseases are considered under the various fungal genera, the normally pathogenic organisms being discussed first and then the opportunistic ones.

### *Blastomyces*

#### Aetiology

North American blastomycosis is caused by *Blastomyces dermatitidis*, a dimorphic fungus that exists in both yeast-like and mycelial forms. The proper name, associated with its perfect or sexual form, is *Ajellomyces dermatitidis*. Little is known about the ecology of the organism which, though generally believed to be a soil inhabitant, nevertheless does not apparently survive well in soil [40,41]. It is introduced into humans by inhalation of either spores or the yeast form [42]. Small outbreaks of infection have been reported, suggesting point sources of heavy exposure, although most cases are sporadic and reported relatively uncommonly even in endemic areas [43,44]. The disease does not seem to be a particular hazard of the immunosuppressed, although episodes of infection in patients with neoplasms and those on corticosteroids have been described [45], and it has been reported as a late and serious disseminated infection in patients with AIDS [46]. It seems likely that exposure to a heavy infecting dose is more important than impaired defences in the aetiology of blastomycosis. This concept is supported by the occasional occurrence of laboratory infections [47]; clearly care has to be exercised in handling the organism. However, person-to-person infections do not seem to occur.

Study of the distribution of the organism and its

infectivity has been hampered by the lack of a sufficiently sensitive skin or serological test. The distribution of cases of disease is largely confined to areas surrounding the major waterways of North America, the Ohio and Mississippi basins, the southern Great Lakes and the St Lawrence seaway [43,48]. However, cases have also been described in people from many parts of Africa and from Saudi Arabia [49,50].

Once inhaled, the organism exerts a strong chemotactic effect towards polymorphonuclear leucocytes, causing a mixed leucocytic and granulomatous reaction. Although the organism appears to become associated with phagocytic cells, it is resistant to killing, and may be seen to multiply within macrophages and giant cells [50,51]. Nevertheless, human bronchoalveolar macrophages do have some fungistatic and fungicidal activity against the organism [52].

### Clinical features

Blastomycosis may present as an acute or chronic form [53–55]. The acute disease is clinically indistinguishable from other pneumonic illnesses, with general malaise, fever, cough and pleurisy. Sputum, if produced, is purulent. The radiograph shows lobar or segmental consolidation, which may be confluent or patchy; effusion is uncommon [56]. The acute illness may remit spontaneously over a few weeks [57], but more commonly progresses to an indolent form of the disease. Sometimes the progression is rapid, with diffuse intrabronchial spread leading to the adult respiratory distress syndrome and death [58,59].

Chronic blastomycosis may follow the acute disease or may occur without an obvious clinically acute episode. Irregular streaky and nodular radiographic densities on the chest radiograph, together with persistent malaise, weight loss and cough, mimic tuberculosis [56–60]. Cavitation occurs frequently and miliary mottling occasionally, making the distinction even more difficult. Alternatively, the disease may present as a solid mass in one lung, simulating bronchial carcinoma. Chronic fibrosing mediastinitis has been described leading to superior vena caval obstruction, though this is more commonly caused by histoplasmosis [61]. Chronic blastomycosis is very frequently associated with metastatic disease in organs other than the lung. Skin and subcutaneous tissues (from which manifestations the organism acquired its specific name), bone, prostate and epididymis are frequently the sites of chronic abscesses, and other organs may be affected rarely.

### Diagnosis

The diagnosis should be borne in mind if a patient lives in or has recently visited an endemic area, especially North

America. Serological methods now provide a specific test, though false negatives occur in up to 25% of patients. An enzyme immunoassay for the A antigen of *B. dermatitidis* seems to be the most sensitive test so far available [62,63]. Nevertheless diagnosis depends on demonstration of the organism in sputum, pus, lavage fluid, needle aspirate or tissue sections. It is a characteristic yeast-like organism, about 8–15 µm in diameter, with a highly refractile cell wall and multiple nuclei. It can be seen in unstained sputum preparations, preferably treated with potassium hydroxide to digest other cellular debris. In histological sections it may be stained by Gomori's method or by periodic acid–Schiff stain. It may be cultured on enriched media at 30°C; the mycelial form may grow and need to be subcultured to produce the yeast form for identification.

### Treatment

In view of the high risk of progression and death in blastomycosis, it is advisable to treat all patients in whom the diagnosis is made. Amphotericin remains the treatment of choice and should be given in a total dose of at least 2 g over 10–12 weeks [64,65]. Up to 50 mg daily may be given in seriously ill patients; in less sick individuals the same dose may be given on alternate days. The drug should not be withheld in pregnant patients in view of the seriousness of the disease and the absence of reports of fetal toxicity [66]. Ketoconazole has also been used to good effect in blastomycosis, in a dose of 400 mg daily for up to 6 months. However, not only is it a rather toxic drug with teratogenic effects but failures have occurred in seriously ill patients, so it should probably be reserved for people with relatively mild infections [67,68]. Fluconazole has also proved moderately effective in non-life-threatening infections, given at up to 400 mg daily for 6 months or more [69]. A new triazole has proved effective in murine blastomycosis and is likely to be available for trial in humans in the near future [70].

## Coccidioides

### Aetiology

Coccidioidomycosis (known familiarly and understandably by physicians in the south-western USA as 'coxy') is caused by *Coccidioides immitis*, a dimorphic fungus known only in its asexual or imperfect form. It grows as a hypha in hot, dry soil and its known habitat is confined to desert and semi-desert regions of the south-western USA, Mexico and South America. It has been noted that it shares this habitat with the creosote bush and that its presence in soil is most profuse around rodent burrows [71,72]. The hyphae become septate and reproduce by segments (or arthrospores) breaking off. These can germinate again in suitable soil or, if inhaled by an animal, can reproduce by

the production of endospores within the original spore capsule, now called a spherule. This ruptures to liberate several hundred spores which, aside from causing an inflammatory response in the host, return to the soil via sputum or other infected body fluids or in animal carcasses; the cycle is then completed by germination in the hyphal form.

The organism excites an immune response in the host, with influx initially of macrophages and neutrophils and later of mononuclear cells. The end-result is a granulomatous lesion pathologically and a T lymphocyte-mediated immune response. There is some evidence that the infection itself may cause impairment of T-lymphocyte function [73,74].

The disease coccidioidomycosis is confined to those who live in or have recently visited endemic areas, or laboratory workers exposed to the hyphal form of *C. immitis*. In particular, outbreaks have been described following dust storms and among archaeology students digging Indian sites in southern California, Arizona and New Mexico [6,75,76]. Epidemiological studies have shown infection to occur in a high proportion of people living in these areas; although subclinical infection is common, clinical illness is also frequent and, because of its debilitating nature, of considerable economic importance [77,78]. There is evidence of an increase in the numbers of people infected in endemic areas, to the extent that the disease is reaching epidemic proportions [79,80]. The infectivity of the organism is illustrated by the observation that 8 of 27 Marine Corps reservists training in the Californian desert contracted infection, seven showing symptoms [81]. Not unexpectedly, in endemic areas coccidioidomycosis has become an important and highly fatal pathogen in patients with HIV infection [82].

### Clinical features

Up to two-thirds of those infected exhibit either very mild or no symptoms [83–86]. Most of those with significant symptoms have an acute illness, with fatigue, cough, fever, malaise and chest pain. Systemic manifestations of a hypersensitivity reaction are common; arthralgia, erythema nodosum or multiforme and phlyctenular conjunctivitis may occur. The radiograph may show bilateral hilar node enlargement, although pneumonic changes are usually unimpressive [87]. However, lobar, patchy or bronchopneumonic consolidation may occur and severe confluent pneumonitis may precipitate acute respiratory failure [76,88]. Miliary dissemination may also occur, with involvement of bone, meninges and skin in particular. This potentially fatal progressive syndrome is more common in the immunosuppressed, dark-skinned races and women in the later stages of pregnancy [88,89]. It is associated with failure to produce a delayed skin hypersensitivity reaction, which may be due to antigenic over-

load in those subjects who are not immunosuppressed [90,91].

Most patients improve gradually without treatment over a few weeks, though fatigue and general debility may last for some months. A few, less than 1%, progress to the chronic disease, in which persistent lung infection may cause chronic pulmonary fibrosis, cavitation or solitary nodules [92–94]. Cavities may resolve spontaneously but more frequently persist and enlarge. This chronic syndrome may be associated with symptoms of malaise and is usually the cause of productive cough. It may lead eventually to respiratory failure. Chronic pulmonary coccidioidomycosis occurs particularly in patients with disorders of cell-mediated immunity.

### Diagnosis

Coccidioidomycosis should be suspected in anyone with an acute systemic illness with pulmonary features who has recently visited an endemic area. Reactivation of disease may also be suspected in someone treated with immunosuppressant drugs or with HIV infection who previously lived in such an area. Diagnosis is made by demonstrating the characteristic spherule in sputum or pus aspirated from a lesion. If sputum studies are negative, fiberoptic bronchoscopy with washing and brushing are helpful diagnostic tests [95]. Any endobronchial inflammatory lesion should be biopsied; transbronchial biopsy should be carried out if a radiographic lesion is present and accessible. Fine-needle biopsy is used increasingly, and diagnosis depends on demonstration of the spherule or, less commonly, culture of the organism [96]. Finally, in some cases of unexplained pulmonary shadows or nodules, thoracotomy may be necessary.

The spherule can be stained with Gomori's or Papanicolaou's stains, and may also be demonstrated on sections stained with haematoxylin and eosin. The organism can be cultured on mycological media, but this should only be attempted in specialized laboratories because of the hazard of infection by arthrospores [97]. Newer molecular techniques have resulted in production of nucleic acid probes to coccidioidal RNA, and commercially available probes hold hope of identifying the organism in culture within a few days [98]. IgM precipitating antibodies to coccidioidin antigen from the mycelial phase may be demonstrated in a high proportion of patients within 3 weeks of onset of disease, while IgG complement-fixing antibodies occur later but may persist for about 6 months; one or other of these antibodies can be demonstrated in 90% of patients [99]. Skin tests with antigens derived from mycelial phase (coccidioidin) and spherule phase (spherulin) are available, and delayed reactions can be shown in most infected patients quite early in the illness [100]. However, they are not of much use diagnostically unless the patient's reaction was known prior to the

illness, and these tests have their main application in epidemiology and control programmes.

### Treatment

Most patients require no treatment other than that needed for amelioration of acute symptoms. However, if symptoms persist for over 6 weeks, progressive or disseminated disease occurs or very high titres of IgG antibody are found, it is generally recommended that antifungal agents should be used [64]. Amphotericin, in doses as for blastomycosis, seems the most effective therapy [101,102], but ketoconazole has also been shown to be a useful alternative. While ketoconazole penetrates relatively poorly into the cerebrospinal fluid, in high (800 mg daily) doses it may be effective in meningeal disease [103]. In chronic cavitating pulmonary disease, resection of lesions may occasionally be necessary. Because of time lost from work and medical costs, the economic importance of coccidioidomycosis in endemic parts of the USA is such that a vaccine would be extremely useful. One that showed good protection against experimental disease in laboratory animals has to date shown no significant benefits in a human trial [104].

## Cryptococcus

### Aetiology

Cryptococcosis (previously called torulosis) is caused by the yeast form of the dimorphic basidiomycete *Filobasidiella* spp. [105]. The organism was originally thought to exist only as a yeast and the name of this imperfect form, *Cryptococcus*, has been maintained in medical usage. Disease is normally caused by *Cryptococcus neoformans*, of which several different serotypes have been described [106]. The serotype *C. neoformans* var. *gattii*, found especially in Australia and Papua New Guinea, is associated particularly with infection of the immunocompetent, whereas the more widespread variety *neoformans* is increasingly associated with infection of the immunosuppressed [107,108]. Two other species, *C. laurentii* and *C. albidus*, have also been implicated in pulmonary disease [109,110]. The organism may be found in soil, although it is not known whether the yeast or the hyphal form is predominant. It is most readily found in bird, especially pigeon, droppings and in soil contaminated with such excreta [111]. The variety *gattii* has been associated with eucalyptus trees, although little is known of its natural habitat. The perfect form produces spores sexually that may become airborne and are of appropriate size to be inhaled to alveolar level. Likewise, the yeast form is only about 5 µm in diameter and therefore potentially respirable; the evidence now strongly suggests that the primary route of infection in pulmonary, neurological and

disseminated cryptococcosis in humans and in experimental animals is via the respiratory tract [112].

The organism occurs widely throughout tropical and temperate zones and is probably inhaled by many people and animals without causing disease. There is clear evidence of different degrees of resistance to infection by different species of animals. High rates of skin sensitization to *Cryptococcus* have been shown in groups of healthy pigeon-breeders and exposed laboratory workers [113,114]. When disease does occur, it appears to be sporadic and there is no evidence of transmission from humans or other animals to humans. Although the disease is recognized increasingly in AIDS patients and in those on corticosteroids or immunosuppressant drugs [115–117], pulmonary infection has been reported quite frequently in otherwise healthy people. In those parts of the world where *C. neoformans* var. *gattii* occurs, such as Australia and Papua New Guinea, pulmonary infection often in association with meningitis is not uncommon in such previously well people.

Infection with *Cryptococcus* is not associated with a brisk inflammatory response. Instead, there is evidence of profuse growth of organisms with a predominantly macrophage and giant cell reaction; some plasma cells and lymphocytes may be present but well-formed granulomas are not common. In these infected tissues, *Cryptococcus* is seen to be surrounded by a thick capsule. This is composed of polysaccharide and may be of value to the organism by preventing its recognition by host defences and by enlarging it sufficiently to be too big for ingestion by macrophages. The organism appears to excite a cell-mediated immune response, although humoral antibodies are also produced [118,119]. When severe infection occurs, the most dangerous lesions are found in the brain and meninges. Presumably the organism is carried there by the bloodstream and finds appropriate conditions for growth; it has been shown that cerebrospinal fluid is a good culture medium and that inflammatory responses to *Cryptococcus* are delayed or absent in the brain [120,121].

### Clinical features

Pulmonary disease due to *Cryptococcus* is rare and in many cases appears to have been asymptomatic and self-limiting [111,122–125]. However, the lungs are important as the site of entry of the organism when it causes neurological or disseminated disease; very occasionally, pulmonary manifestations are the dominant or only clinical feature. Patients with pulmonary cryptococcosis may be free of symptoms or have non-specific complaints. The radiological features vary, but solid lesions resembling pulmonary or mediastinal tumours or abscesses are most frequent. Lobar collapse due to intrabronchial mass and Pancoast's syndrome are two presentations mimicking carcinoma that have been described [126,127]. The find-



ings may also mimic tuberculosis, pneumonia or metastases and the diagnosis can only be made by demonstrating the organism.

In view of its rarity, pulmonary cryptococcosis is usually not suspected before the lesion has been removed. However, it should be borne in mind in the differential diagnosis of unusual radiological appearances in patients with immunosuppression due to drugs, AIDS or malignant disease. In such patients, meningeal and encephalitic features occur commonly, and the insidious onset of headache, behavioural changes and cranial nerve lesions should alert the physician to this possibility [117,128].

### Diagnosis

The organism may be cultured on Sabouraud medium from sputum within 48 h, but this is not necessarily diagnostic unless it can be found repeatedly [123]. Antibodies to *Cryptococcus* may be helpful, and a latex agglutination test has been developed that is specific (in the absence of rheumatoid disease and if IgM antibody has been removed) and reasonably sensitive [129]. The presence of the organism in cerebrospinal fluid can be regarded as diagnostic of neural involvement. Generally, however, diagnosis depends on direct demonstration of the organism in biopsied or aspirated tissue (Fig. 21.2), when the doubly refractile cell wall, the presence of budding and the clear capsule (as shown by Indian ink or nigrosin preparations) are characteristic. Bronchoalveolar lavage fluid or needle aspirates guided by ultrasound if necessary are useful methods of making the diagnosis in cases of diffuse lung infiltration and nodular changes on the radiograph [116,130].

### Treatment

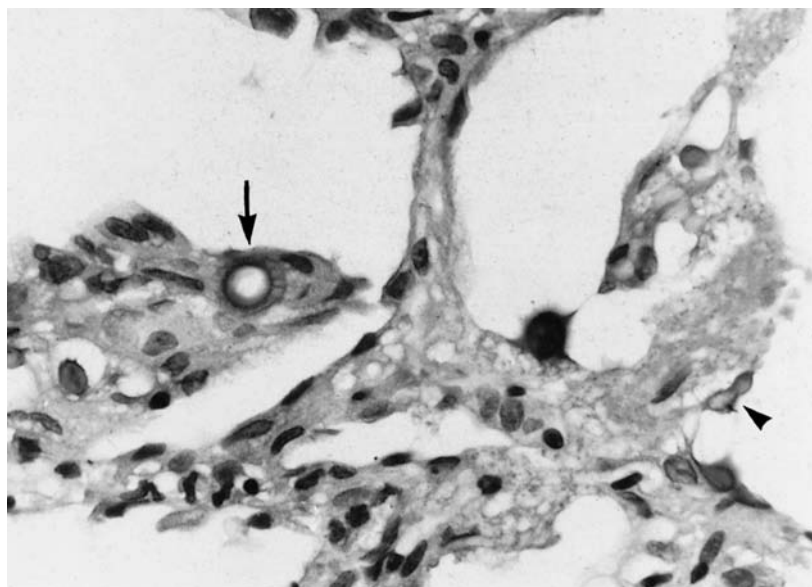
While there may be a case for withholding treatment from patients with minimal pulmonary disease that has been diagnosed by removal of the lesion, in most cases it is advisable to treat the patient with antifungal drugs once the diagnosis has been made in order to prevent both progressive pulmonary disease and involvement of the brain and meninges. Standard doses of amphotericin and flucytosine in combination over 6 weeks are regarded as the best therapy [131].

### *Paracoccidioides*

#### Aetiology

Paracoccidioidomycosis, also known confusingly as South American blastomycosis, is caused by the dimorphic fungus *Paracoccidioides brasiliensis* [132]. The organism probably lives in soil and has been found in the faeces of bats and other animals, although little is known of its natural history. The mycelial phase produces spores of respirable size when grown on culture media with reduced carbohydrate content at 25°C, while at higher temperatures the organism grows as a yeast form and reproduces by budding, usually in a characteristic daisy-wheel pattern. The yeast phase varies considerably in size, from 4 to 40 µm.

Paracoccidioidomycosis is confined to patients from Central and South America, particularly in areas of tropical and subtropical forestation. Most cases have been reported from Brazil, although occasionally the disease is diagnosed in patients from South America who have



**Fig. 21.2** Alveoli of patient with AIDS showing organisms of *Cryptococcus* (arrowed). There is also granular material of *Pneumocystis* infection and one of the cryptococcal organisms is budding (arrowhead) (alcian blue  $\times 410$ ). (Courtesy of Dr Nick Francis.)

migrated to other countries, often after a long latent period. Skin-test surveys have suggested a higher rate of infection than might be anticipated from the relatively small number of clinical case reports. Overt disease seems to occur predominantly in adult males, and especially those engaged in agriculture. It seems very likely that infection occurs through inhalation of spores, and primary complexes have been shown in lungs. However, transmission between patients has not been described.

### Clinical features

Two syndromes, acute and chronic, have been described [132–134]. In the acute condition, which mainly affects young people, there is involvement of lymph nodes, liver and spleen with a systemic illness, the lungs being involved by bronchopneumonic consolidation occasionally [135]. It is a serious and often fatal condition, and the most important cause of adrenal insufficiency in endemic areas. The chronic form affects older males primarily and is often severe, with progressive pneumonic consolidation causing cough, chest pain and breathlessness. Fever, weight loss and anorexia are common and the disease runs a slowly progressive course, often disseminating to other organs; mucosal and facial ulcers and lymphadenopathy are common accompaniments. The pulmonary manifestations are very varied, ranging from calcified granulomas to diffuse infiltration. Dense consolidation, cavitation and tumour-like masses may occur and may lead to fibrosis and acute or chronic respiratory failure. Occasional reports have documented its occurrence in individuals on immunosuppressant drugs, when presumably latent infection is reactivated [136].

### Diagnosis

The condition should be suspected in people from Latin America with appropriate symptoms. In many cases the organism can be demonstrated in sputum cleared with potassium hydroxide. If this is unsuccessful, bronchial brushings and washings and transbronchial biopsies should give the answer. The organism can be cultured on Sabouraud medium. An immunodiffusion test for precipitating antibodies is available, though a positive test may not necessarily mean active infection.

### Treatment

*P. brasiliensis* is unusual among pathogenic fungi in being sensitive to sulphonamides, although treatment with these drugs needs to be continued in high dosage (e.g. sulfadiazine 4–6 g daily in adults) for several months and then in lower dosage for 3–5 years. In severe cases, amphotericin is used in addition. These measures may be insufficient, and reports of treatment with ketoconazole and

itraconazole have been encouraging [136–138]. This treatment should also be continued for at least 1 year, depending on therapeutic response, as the disease has a tendency to relapse and up to 25% of patients die of it. When treatment is successful, healing occurs by fibrosis.

## Histoplasma

### Aetiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. Its misleading name stems from the fact that it was originally thought to be a plasmodium and because in fixed tissue it shrinks and looks as if it is surrounded by a capsule. In fact it is the imperfect yeast form of the mycelial fungus *Emmonsia capsulata*, an organism that lives in soil and prefers habitats heavily contaminated by bat or bird faeces [139]. Although it has been reported from many tropical and subtropical parts of the world, pulmonary and systemic histoplasmosis can only be considered to be endemic to North America, mainly in the states bordering the Mississippi, Missouri and Ohio rivers [140]. Only very occasionally has histoplasmosis been reported from the UK and Ireland, usually in patients who had spent parts of their lives in India, the Far East or Africa [141,142]. An African form of histoplasmosis caused by the same organism occurs, in which skin and bone lesions predominate and lung infection has been rare.

The fungus in its mycelial phase produces spores of two sizes: the larger, about 8–10 µm, have multiple fine projections from their surfaces, while the smaller, 2–6 µm, tend to be smooth. Both are potentially respirable and inhalation is the mechanism whereby humans are infected. On inhalation the spore germinates at body temperature into the yeast form, which attracts and is phagocytosed by macrophages. However, it is resistant to killing and reproduces within the macrophage by budding until the cell may be full of organisms [143,144]. Animal studies have shown that, in the unsensitized, within about 2 weeks the infection excites a strong local vasculitic response, with necrosis of lung and lymph nodes. The initial response in mice has been shown to be a neutrophil alveolitis, followed by an influx of lymphocytes at about the second week after challenge. Subsequently a granulomatous reaction occurs and this seems effective in killing the organism and leading to resolution of the pathological changes [145]. At this stage the macrophages' ability to kill the ingested *Histoplasma* is enhanced and healing occurs by fibrosis. In previously sensitized animals, the process is repeated but with much less initial proliferation of the organism and with the necrotic and healing process starting within 48 h. The accelerated reaction is due to an immune response mediated by sensitized lymphocytes [146].

Epidemiological surveys have shown evidence of high

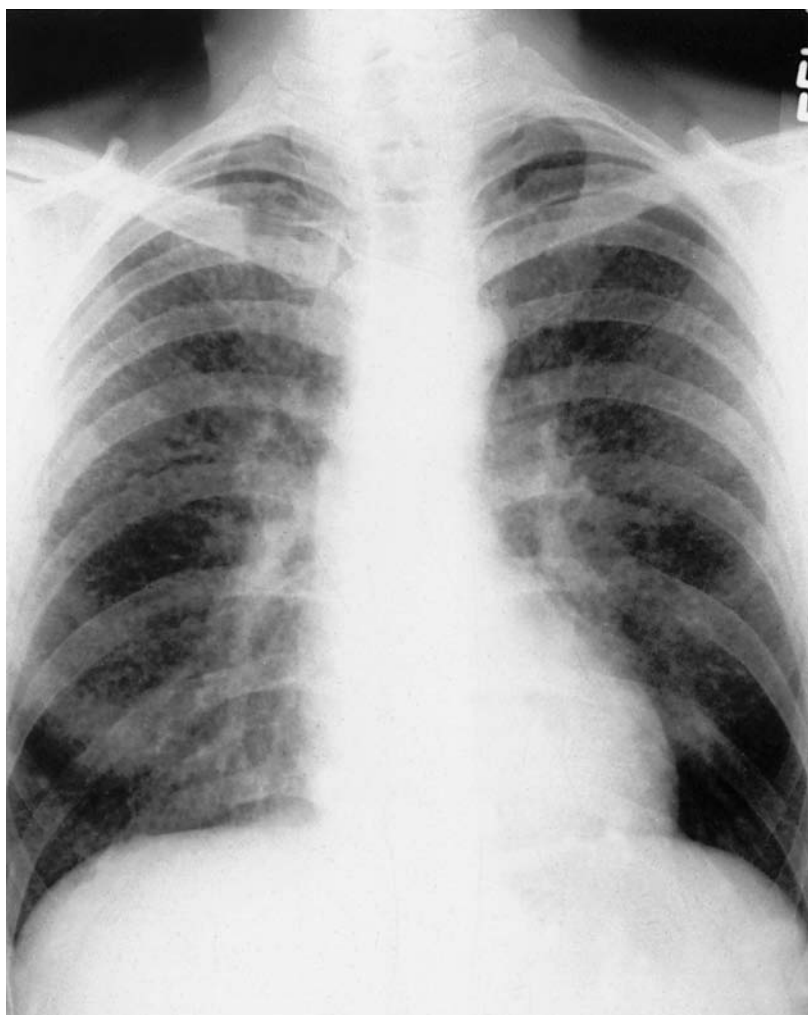
levels of skin sensitivity to *Histoplasma* in endemic areas [140], and the finding of healed, calcified pulmonary foci in well people in such areas is commonplace [147]. Infection sufficient to cause clinical disease is probably related to the exposure dose of spores and many outbreaks have been described as a consequence of heavy exposure to point sources, for example clearing out chicken roosts or pigeon lofts, digging contaminated soil and exploring bat-infested caves and belfries [148–150]. Such exposures result in acute disease. Chronic pulmonary disease seems more related to the presence of pre-existing lung disease, such as emphysema or bronchiectasis, where the organism can gain a foothold [151], while disseminated disease largely afflicts the immunosuppressed and infants [152].

### Clinical features

Acute histoplasmosis may range from a mild, influenza-like illness with no pulmonary signs, through an acute episode with cough, chest pain and hilar adenopathy on

chest radiography, to a severe illness with fever, dyspnoea, cough and extensive radiographic changes [148,153]. There may be a history of recent exposure in an endemic area. While the symptoms of acute disease are non-specific, the radiological changes in severe cases may be characteristic, with bilateral, multiple fluffy or coarsely nodular infiltrates in association with hilar node enlargement (Fig. 21.3). In such patients there may be dissemination of disease, in that the organism can sometimes be cultured from bone marrow, but obvious clinical involvement of tissues other than lung is rare. Pleural effusion occurs uncommonly and is usually small [148].

In most cases, acute histoplasmosis is a self-limiting illness, the symptoms gradually resolving over a period of a week or two while the radiographic shadows consolidate into small nodules that in time calcify (Fig. 21.4). Rarely the disease progresses to respiratory failure and death, or symptoms occur from local effects of necrotic lymph nodes; rupture into pericardium, compression of trachea, oesophagus or superior vena cava, and production of mediastinal infection and fibrosis have been



**Fig. 21.3** Bilateral diffuse nodular infiltrates in a patient with acute histoplasmosis. (Courtesy of Dr N.L. Lapp.)



**Fig. 21.4** Calcified nodules of healed histoplasmosis. (Courtesy of Dr N.L. Lapp.)

described. Solitary, slowly enlarging pulmonary nodules may occur and the diagnosis may often be suspected because of a calcified centre, sometimes with surrounding calcified laminae [154].

Disseminated histoplasmosis may follow pulmonary infection [152,155,156]. In infants and immunosuppressed adults, this may take an acute form with general malaise, fever, hepatosplenomegaly and generalized lymphadenopathy. Anaemia and leucopenia are common and some patients have radiographic evidence of a diffuse interstitial pneumonitis. This disease is fatal if not treated. However, subacute and chronic forms of disseminated histoplasmosis are also recognized, and these are the types most likely to be imported into the UK [141]. Weight loss, malaise and fever are common symptoms, chronic upper lobe pulmonary fibrosis may be present, and Addison's disease, skin or mucous membrane ulcers, intestinal ulcers, endocarditis or meningitis may occur. Such patients may develop this form of disseminated disease after starting immunosuppressant drugs or when they develop autoimmune disease or neoplasia.

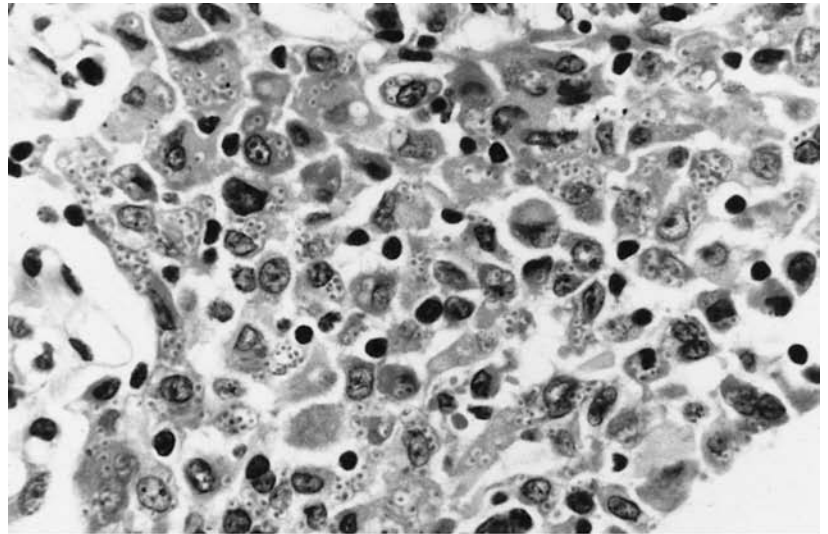
Chronic pulmonary histoplasmosis occurs largely in patients with pre-existing lung disease [151]. The lesions are normally in the apical and posterior segments and appear as a combination of streaky and fluffy opacities, with a tendency to harden and contract. Cavitation may occur and the cavities may enlarge progressively. Differentiation from tuberculosis or atypical mycobacterial infections is difficult. Symptoms may be few or absent until the disease is well advanced, when respiratory failure may

supervene as a result of the combination of primary lung disease and secondary infection with *Histoplasma*.

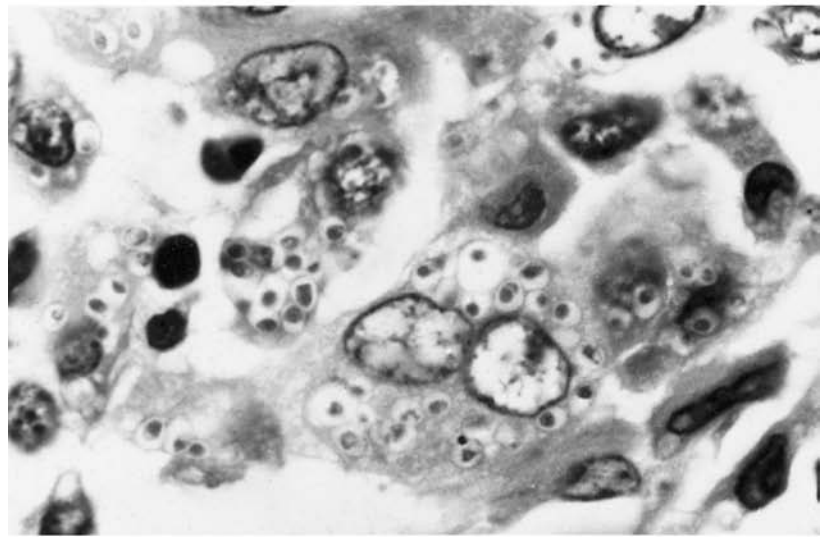
In Africa a variant, *H. capsulatum* var. *duboisii*, has been described as a cause of a chronic form of histoplasmosis [157]. The lungs have rarely been involved, lesions predominating in skin, bones and reticuloendothelial system; however, the epidemic of AIDS is probably changing this and lung and systemic infection is now being reported [158].

### Diagnosis

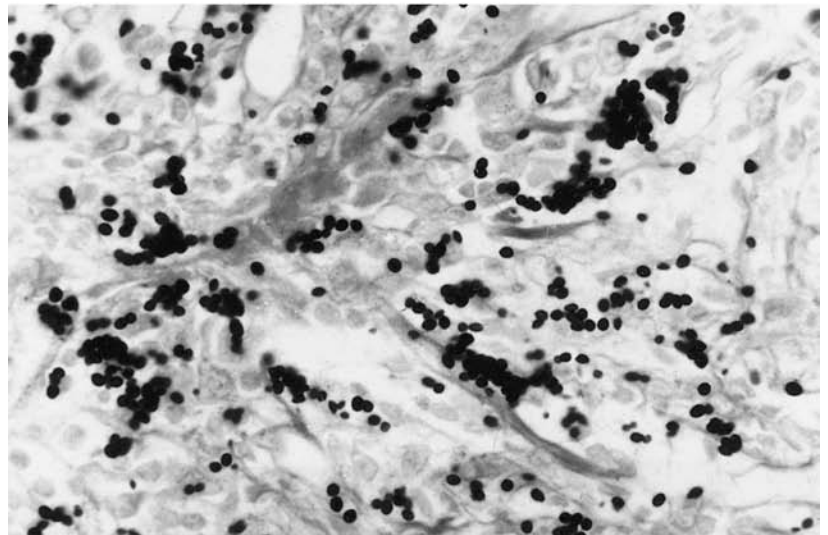
In endemic areas, acute histoplasmosis may be diagnosed on clinical grounds with the support of a positive complement fixation test; titres greater than 1/32 or a fourfold rise are strong evidence of infection if the clinical features are consistent with the diagnosis [159]. Other serological tests that may be of help (but which are of greater value in epidemiological studies) are radioimmunoassays for specific *Histoplasma* IgM and IgG antibodies [160,161]. In disseminated disease the diagnosis depends on demonstration of viable organism in macrophages or giant cells, in either tissue biopsies, blood, bone marrow or urine [156]. Blood cultures are usually positive in acute disease whereas liver and marrow biopsies are better in the subacute and chronic forms. When the lung is involved, either in disseminated disease or in chronic pulmonary histoplasmosis, brushings, washings and transbronchial biopsies may be helpful if sputum cultures are negative (Fig. 21.5). A radioimmunoassay for capsular antigen in blood, urine or



(a)



(b)



(c)

**Fig. 21.5** (a) Lung biopsy of AIDS patient showing alveoli filled with macrophages and chronic inflammatory cells; many of the former contain *Histoplasma capsulatum* (haematoxylin & eosin  $\times 410$ ). (b) Higher power view of the same section showing the organisms (haematoxylin & eosin  $\times 1025$ ). (c) Same biopsy stained for *Histoplasma* (Grocott  $\times 410$ ). (Courtesy of Dr Nick Francis.)

bronchoalveolar lavage fluid is available and has proved particularly useful in the detection of disseminated disease [162–164].

### Treatment

Most patients with acute histoplasmosis will settle without treatment [64,165–167]. The few that show progressive disease require amphotericin. Disseminated disease should also be treated with amphotericin 0.6 mg/kg daily up to a total of about 3 g. Less acute cases of disseminated disease and chronic pulmonary histoplasmosis may alternatively be treated with ketoconazole 400 mg daily for up to 1 year, with cure rates of over 80%. Fluconazole and itraconazole have both been used successfully as oral treatment in less severe infections, in which they may be used as initial treatment, and as continuation therapy after initial control with amphotericin [168–170].

### Sporothrix

#### Aetiology

Sporotrichosis is caused by the dimorphic fungus *Sporothrix schenckii*, which may be found in soil and living or dead plants [171]. The organism may be inhaled either as spores or in the yeast form, both being of respirable size. Usually, however, it enters the body via abrasions and causes chronic granulomatous skin lesions [172]. Cat scratches and handling of sphagnum moss are important causes in endemic areas. Disease occurs only sporadically, most commonly in Mexico and Brazil, but also very occasionally in many other countries including the USA and Japan. Epidemics have been described in South African gold miners exposed to the organism in rotten timber [171]. Cases have not yet been reported in the UK.

#### Clinical features

Pulmonary sporotrichosis is rare and has most usually presented with localized shadowing in an upper lobe that may progress to cavitation [173–175]. It is usually thought to be tuberculosis or another mycobacterial infection, thus delaying the diagnosis which is best made by excision of the lesion and culture of the organism. Apart from skin lesions, other organs occasionally involved include bones and joints, conjunctiva and, very rarely, the nervous system.

#### Treatment

Pulmonary sporotrichosis is often treated by excision prior to the diagnosis being made [176]. Amphotericin is effective but the newer and less toxic oral antifungal drug

itraconazole has been used successfully and will probably become established as first-line treatment in severe infections [177,178]. Skin lesions may respond to oral potassium iodide.

### Aspergillus

#### The organism

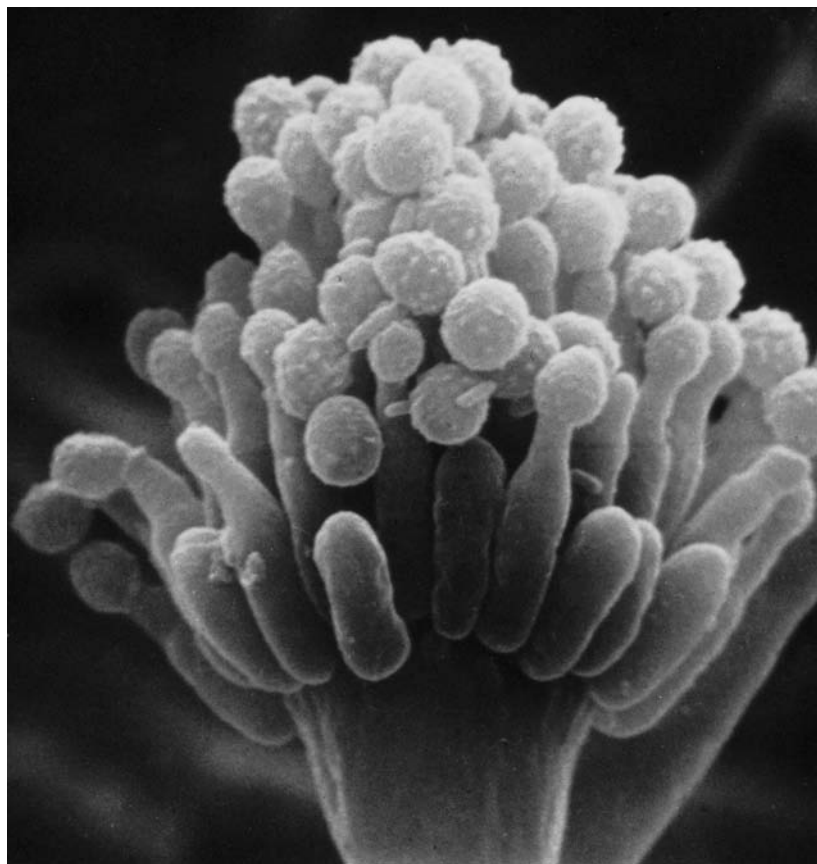
The genus *Aspergillus* includes several species known to have pathogenic effects on humans. *A. fumigatus* is the one most frequently associated with disease, but *A. niger*, *A. flavus*, *A. terreus*, *A. clavatus*, *A. glaucus* and *A. nidulans* among others have been described as causes of pulmonary or disseminated disease [179–182]. Air sampling has shown that, of these, only *A. fumigatus* and *A. niger* occur with any frequency in the ambient atmosphere in the UK [183]; they are present most profusely in the winter and this is explained by their need for dead organic matter as a substrate [9]. Thus they thrive on fallen leaves and in compost heaps, and may be found widely throughout vegetated parts of the world. As would be expected, different species of *Aspergillus* may be the dominant organisms in different climates; thus *A. terreus* has been shown to be more prevalent than *A. fumigatus* in Texas [184].

*Aspergillus* is one of the large group of imperfect fungi having no known sexual stage. It has a hyphal form and reproduces by producing spores generally less than 3 µm in diameter and which are dispersed by wind. In general, *Aspergillus* spp. (particularly *A. fumigatus*) have temperature optima for growth at about 37°C. These two characteristics fit them well for a pathogenic role in warm-blooded animals, though it seems unlikely that animals are anything other than an unnecessary diversion from their normal life cycle. The organisms grow readily on standard mycological media at 37°C and may be recognized by their septate, branching hyphae and the swollen conidiophores. It is from its resemblance to the aspergillum of the Catholic ritual that the organism takes its name (Fig. 21.6).

#### Diseases associated with *Aspergillus*

*Aspergillus* spp. are unique among the fungi in the number of different pathological reactions with which they may be associated. Nevertheless, they are opportunistic organisms with respect to infectivity. In common with many other fungi that produce spores they may be allergenic, provoking exacerbations of asthma when natural air counts rise, as in the winter, or in proximity to compost heaps. Furthermore certain asthmatic patients may develop a hypersensitivity reaction, allergic bronchopulmonary aspergillosis [185], while non-asthmatic individuals exposed to very high doses of spores may develop typical allergic alveolitis [186]. Spores may also land in old





**Fig. 21.6** Scanning electron micrograph of conidiophore of *Aspergillus fumigatus*.

pulmonary cavities or cysts and germinate there, causing aspergilloma [187]. Finally, the spore may take advantage of the presence of local lung disease (such as infarct, tumour or pneumonia) or of generalized impairment of defences (such as leucopenia, leucocyte dysfunction or immunosuppressant therapy) either to become locally invasive or to cause disseminated disease [188].

#### Factors associated with pathogenicity

*Aspergillus* illustrates particularly well the importance of the two factors involved in pathogenicity: the inherent properties of the organism and the defences of the individual host. Some animal species, such as penguins and other birds, have very little inherent resistance to the organism and thus it is an important cause of severe lung infection. Humans on large doses of corticosteroid and immunosuppressant drugs are in the same position. The atopic individual may develop asthma as a result of exposure to levels of spores that would otherwise have no pathogenic effect. Large doses of spores may have an antigenic effect through complement activation in otherwise normal people. Of course, patients with defective leucocytes, for example in leukaemia, lymphoma or chronic granulomatous disease, are at special risk of disseminated disease [188,189].

On the other hand, why should *Aspergillus*, of all the fungal spores in the air, have the potential to cause so much trouble to the animal kingdom, on which it does not depend for its natural survival? Its spore size and optimum temperature and oxygen requirements clearly mean that, probably by chance, it is ideally suited to survival within the airways [183]. However, in addition, it seems to have developed sophisticated defence mechanisms against macrophages and neutrophils. *In vivo* experiments in mice have shown that injected spores may be killed by both macrophages and neutrophils [190,191]. However, *A. fumigatus* is certainly resistant to phagocytosis by these cells from both rodents and humans [192,193] and, moreover, appears to produce a substance, as yet unidentified, that inhibits phagocytosis, macrophage migration and macrophage spreading [193–196]. It may be that it has evolved such a mechanism in order to protect itself from protozoa in soil, the natural predators of fungal spores [197–199].

#### Asthma and allergic bronchopulmonary aspergillosis

*Aspergillus* is one of many fungal spores that can provoke attacks of asthma. Several allergens have been described, one of which (*Asp*fI) appears to be present only in hyphae and is therefore only of relevance when the organism is



germinating in airways as in allergic aspergillosis [200], while another, gp55, is a glycopeptide of about 50kDa [201]. Allergenecity becomes of practical importance in three situations.

1 In atopic individuals and in children with cystic fibrosis [202], who may become sensitized and develop asthmatic symptoms and allergic aspergillosis.

2 When high levels of spores (or antigen derived from spores or hyphae) are present in the air in a workplace. This has been described in workers on farms, in sugar mills and in those producing citric acid by fermentation of molasses with *A. niger* [203,204]. In such circumstances, atopic individuals seem to be at greatest risk of developing sensitization and the organism is apparently a rather weak sensitizer [205].

3 When the immune responses of the individual are such as to provoke extrinsic allergic alveolitis. This condition may occur in workers exposed to mouldy hay or compost heaps [186], *A. fumigatus* being one of the organisms associated with attacks of farmers' lung. In these circumstances, the disease may present as a combination of asthma and alveolitis, with evidence of immediate and delayed skin sensitivity, and both airflow obstruction and reduction in lung volumes and transfer factor.

Allergic bronchopulmonary aspergillosis usually occurs in asthmatic individuals, although the first sign of the asthma may be an episode of aspergillosis. It may also occur occasionally in the absence of clinical evidence of asthma, in otherwise healthy people, although most of these prove to be atopic on skin testing [206]. Patients with cystic fibrosis are also at risk of developing bronchial colonization by *Aspergillus* and may show evidence of bronchopulmonary aspergillosis [207–209]. It is important to recognize that there is a spectrum of response to aspergillar antigen, from simple skin sensitization in atopic individuals, to sensitization with asthmatic symptoms, to asthma plus occasional episodes of aspergillosis, to persistent aspergillosis with progressive lung damage. The patient with allergic aspergillosis typically presents with an exacerbation of wheeze and cough, often associated with fever and malaise [210–212]. Such attacks occur more usually in autumn and winter than in summer [213]. The cough is unproductive at first but subsequently, especially after treatment with corticosteroids, may be associated with the production of viscous sputum containing plugs. Haemoptysis is not uncommon, though rarely more than minor. The radiograph shows features that distinguish the episode from a simple exacerbation of asthma: patchy infiltrates and band shadows, typically confined to one or two segments, are present. Occasionally segmental or lobar collapse may be a feature. Recurrent episodes are associated with similar shadows, sometimes in the same part of the lung and sometimes elsewhere [213,214] (Fig. 21.7). Bronchiectasis is often present in parts of the lung previously affected by inflammatory change.

This is sometimes confined to the proximal segmental bronchi, sparing the more peripheral, but this is far from always the case [213,215] (Fig. 21.8). The blood count typically shows eosinophilia, and immediate skin sensitivity to aspergillar antigen is present on prick testing. Intradermal tests, which are rarely necessary, often show delayed reactions of the Arthus type as well. Strong IgG precipitating antibodies are present in about 70% of patients and high levels of specific IgE are usual [216]. While cross-reactivity between different species of *Aspergillus* is frequent, it should be noted that in some patients negative tests for delayed hypersensitivity to *A. fumigatus* and other species may occur when the organism is *A. terreus* [217]. The sputum may show hyphae (Fig. 21.9) and the organism may sometimes be cultured from it; only the presence of hyphae can be regarded as confirmatory of the diagnosis, as fungi can commonly be cultured from anyone's sputum whenever the appropriate spores are available to be inhaled from the ambient air [183].

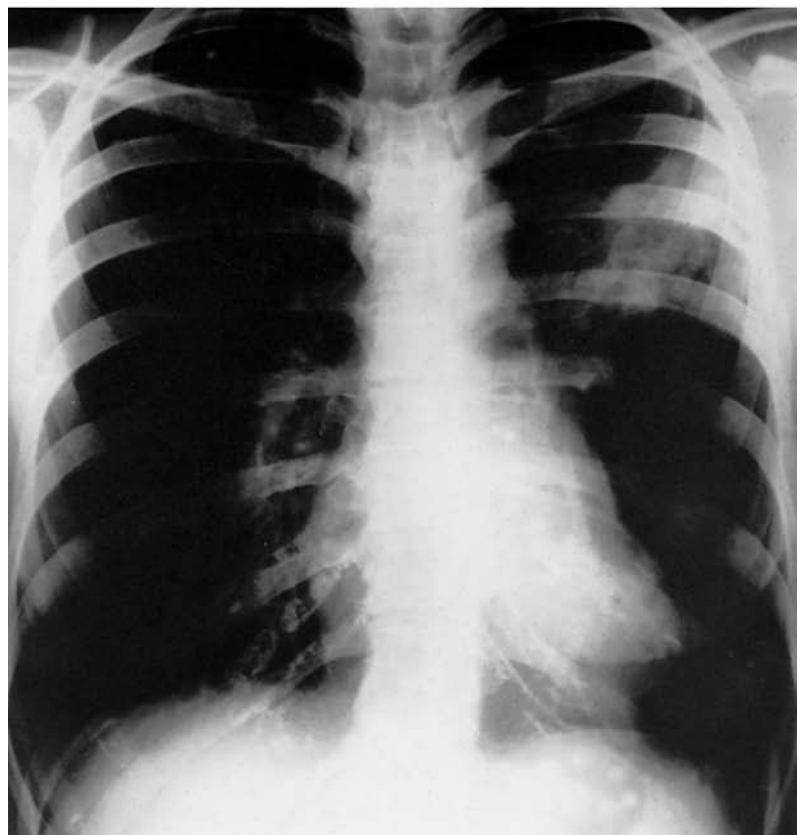
The sputum is typically viscous and contains plugs or casts of bronchi. Histologically these show, apart from hyphae, the stigmata of asthma, namely eosinophils and desquamated epithelial cells. These changes are a reflection of the pathological changes in the bronchi from which they came. The lung itself distal to the bronchial reaction shows an eosinophilic infiltration.

There is some confusion about the natural history of allergic aspergillosis, since many descriptions in the literature are of patients from the severe end of the spectrum who had been investigated in specialist centres. However, most episodes resolve rapidly without permanent lung damage on the administration of corticosteroids. Early treatment of acute episodes with corticosteroids therefore normally brings about prompt resolution of symptoms and radiographic signs; between attacks most patients remain well simply with inhaled bronchodilators and, if necessary, topical corticosteroids. Such patients can be taught to administer their own oral steroids when an exacerbation starts and to attend clinic for a chest film when they feel that they have recovered. It is the author's experience that if the diagnosis is made at an early stage in the course of the disease, long-term administration of oral steroids is unnecessary [213]. However, rarely, patients with aspergillar sensitivity may develop progressive lung damage, sometimes in spite of long-term corticosteroids [212]. Some of these have no clinical symptoms during attacks and are not therefore in a position to know when to use corticosteroids; they may require long-term treatment with the drug. These patients probably have permanent colonization of their airways with *Aspergillus*, and in some cases this may invade locally into bronchial walls. An extreme example of this syndrome is recognized as the asthmatic form of bronchocentric granulomatosis [218] (see Chapter 40).

The rare patient with chronic persistent, rather than



(a)



(b)

**Fig. 21.7** Two radiographs taken at different times of a patient with allergic bronchopulmonary aspergillosis showing (a) collapse of right upper lobe and (b) consolidation in left upper zone.

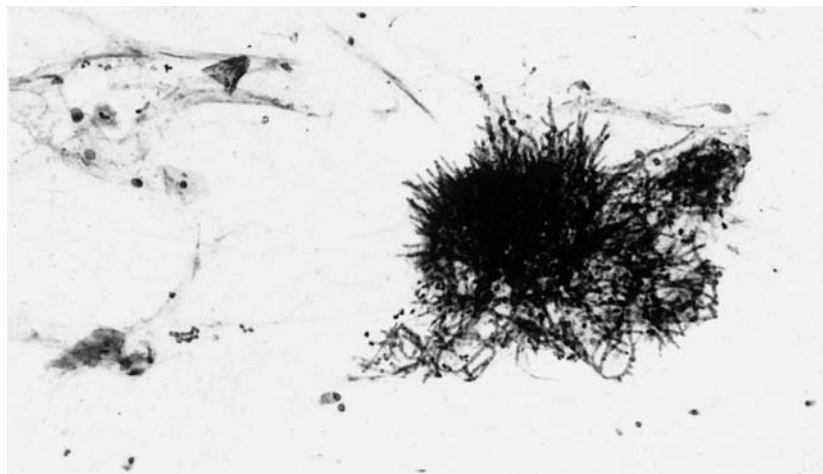


**Fig. 21.8** CT of patient with bronchopulmonary aspergillosis showing bronchiectatic changes.

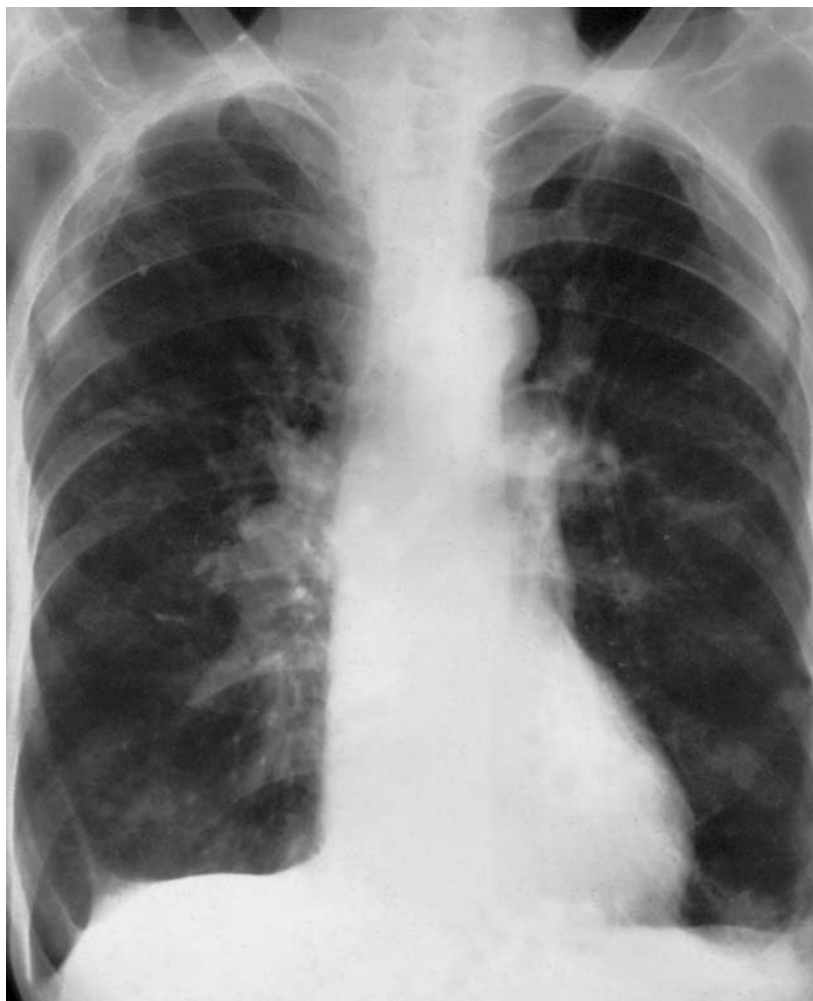
recurrent acute, manifestations of bronchopulmonary aspergillosis more typically shows residual fibrosis and bronchiectasis after the acute episode has subsided and may ultimately have extensive lung destruction [212,214] (Fig. 21.10). The clinician must be wary in the treatment of this condition since although corticosteroids are necessary to suppress the allergic manifestations, too high a dose may promote further local tissue invasion and damage. Nevertheless, in general, treatment depends on the long-term administration of adequate doses of corticosteroids, usually 10mg prednisolone daily or more, to suppress recurrences of pulmonary infiltrates [219]. If there is evidence of increasing lung damage in association with persistent bronchial colonization with *Aspergillus*, a trial of antifungal treatment is justified. This is particularly

important because amyloidosis has been described as a complication of chronic allergic aspergillosis [220]. Preliminary studies of the long-term administration of ketoconazole have suggested that this drug or one of its derivatives may be worth further investigation [221]. If during an acute episode the patient fails to respond to corticosteroids and local invasion is suspected, treatment with amphotericin is justified.

In passing, it should be noted that the syndrome of allergic bronchopulmonary mycosis, which is identical clinically to aspergillosis, may be caused by a number of other fungi as well as by several different species of *Aspergillus*; *Candida* spp., *Curvularia* spp., *Dreschlera* spp. and *Pseudallescheria boydii* are four such organisms, and doubtless others will be described [222,223].



**Fig. 21.9** Smear of sputum stained by Papanicolaou's method showing segmented hyphae of *Aspergillus fumigatus* ( $\times 85$ ).



**Fig. 21.10** Radiograph of patient with chronic bronchopulmonary aspergillosis showing contracted upper lobes with changes of bronchiectasis.

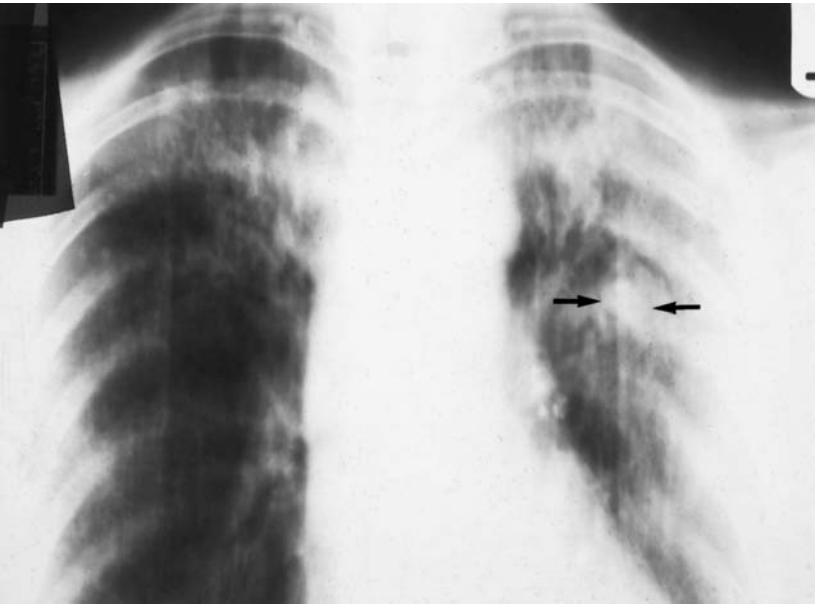
### Mycetoma

Mycetoma is the name given to a mass of fungal hyphal material growing in a lung cavity. The usual organism is *A. fumigatus* and thus the lesion is usually called aspergilloma [224,225]; however, other fungi and other species of *Aspergillus* may occasionally be found. In most patients there is pre-existing lung disease, although the condition may occasionally arise in apparently normal lung or may be the consequence of an aspergillar pneumonia [226]. The most common predisposing conditions are old tuberculous cavities and the bronchiectasis associated with upper lobe fibrosis in chronic sarcoidosis, allergic alveolitis, ankylosing spondylitis or rheumatoid disease. Other conditions in which mycetoma has occurred include pulmonary infarcts [227], pneumonia, lung abscess and bullae.

Many mycetomas cause no symptoms and are simply noticed on radiography as the typical dense rounded shadow containing a crescentic lucent area, which outlines the top of the fungus ball and the upper part of its sur-

rounding cavity (Fig. 21.11). The patient usually has strongly positive IgG precipitins to *Aspergillus* (though not necessarily to *A. fumigatus*) [181,225]. There is sometimes also a positive immediate skin-test reaction. Some studies have commented on the frequency of associated asthmatic symptoms, although whether this is because asthmatic patients are more liable to harbour the organism or that the aspergilloma provokes the asthma is not clear. These patients may also show the features of bronchopulmonary aspergillosis.

Mycetomas are commonly multiple and usually occur in the upper zones of the lungs. They occupy the cavity and do not grow, except when they form in the course of invasive aspergillosis or when they complicate an infarct or pneumonia. Occasionally they may disappear spontaneously by lysis and this should be borne in mind when assessing the results of treatment [224,228]. There are two important complications of the condition, haemorrhage and invasion [229,230]. Haemorrhage may be trivial or exsanguinating, though most patients with severe bleeds have had smaller ones before. The combination of



**Fig. 21.11** Tomogram of patient with chronic sarcoidosis showing mycetoma in old tuberculous cavity (arrowed).

haemorrhage with the previous lung damage frequently associated with mycetoma may constitute a serious emergency. Invasive aspergillosis only rarely complicates mycetoma, but might be anticipated if such patients require corticosteroid or immunosuppressant therapy.

The appropriate management of mycetoma has been much debated [229]. The clinical outcome is determined more by the underlying lung disease than by the fungal lesion, but severe haemorrhage occurs in up to one-quarter of patients and causes death in about 5%. It is not easy to predict which patients will suffer this fate, although those with recurrent moderate-sized haemoptyses must be regarded as being at greatest risk. It is therefore logical to attempt curative treatment in such patients while adopting a more conservative line of management with asymptomatic subjects or those with only occasional and minor haemoptysis.

Curative treatment, in the form of surgical resection of the mycetoma (or mycetomas), is likely to be suitable for only relatively few patients because of the hazard of operating on subjects with severe lung disease and functional impairment [181]. It has an appreciable mortality, due to haemorrhage, bronchopleural fistula, pleural infection with *Aspergillus* and respiratory failure [224,231–233]. However it offers the only hope of removing both cavity and mycetoma. Preoperative bronchial arteriography and selective embolization, and the use of staplers in the resection, may decrease the risks of operation [234,235].

If resection is thought inadvisable, severe haemorrhage may be arrested by bronchial artery embolization or by radiotherapy [236]. Fungus may also be eradicated by cav-

ernoscopic evacuation followed by irrigation of the cavity with antifungal drugs or gentian violet and sometimes simply by local administration of antifungals into the cavity [237,238]. Cavernostomy, an earlier procedure in which the cavity is exteriorized on to the chest wall and irrigated with antifungal agents, seems to be attended by a high risk of death from bleeding or infection [229]. There have been occasional reports of eradication of fungus by treatment for prolonged periods with oral itraconazole, and this drug might be considered when other methods are thought to be too risky [239].

If the fungus becomes invasive, the patient usually shows symptoms of fever, malaise and increased cough. The organism would be expected to be found in the sputum in hyphal form and the chest film shows extension of consolidation from the original lesion. Such patients require antifungal chemotherapy. However, systemic antifungal therapy has not been shown to be of benefit in mycetoma without evidence of invasion. A scheme for the management of mycetoma is given in Table 21.3.

**Table 21.3** Management of mycetoma.

No symptoms:	leave well alone
Minor haemoptyses:	symptomatic treatment
Larger haemoptyses:	elective treatment, i.e. bronchial arteriography and resection or cavernoscopy, fungal evacuation and irrigation
Massive haemoptysis:	embolization or radiotherapy followed by elective treatment as above

### Invasive aspergillosis

Invasive aspergillosis is a disease of the immunosuppressed, particularly of those with defective granulocyte function. Thus it affects patients with acute leukaemia, patients on high doses of corticosteroids and children and young adults with chronic granulomatous disease [188,240,241]. It is also seen in patients immunosuppressed after transplantation of bone marrow or solid organs [242,243]. It is less common in AIDS, occurring as a late and usually fatal complication, sometimes manifesting as a necrotizing tracheobronchial infection [244–246]. It may also occur in a wide variety of other clinical situations, for example following influenzal or other pneumonia, pulmonary infarction, treatment of chronic air-flow obstruction with corticosteroids and resection of aspergilloma [247–250]. Very occasionally it may appear to occur *de novo* [251].

Again, it should be stressed that there is a spectrum of invasiveness. In some patients there may be a rather slow progression of local invasion of lung from a site at which the organism is primarily a saprophyte; for example infarcts may be invaded while adjacent living tissue is unaffected [227]. At the other extreme, some patients with acute leukaemia or on corticosteroids may suffer a fulminant course with extensive necrotizing pneumonia and widespread dissemination to brain, liver, kidneys, heart and other organs [240].

The diagnosis is usually suspected on clinical grounds. Thus, in a patient at risk, the development of fever and progressive pulmonary shadowing of a localized pneumonic type should arouse suspicion, though clearly other possible organisms should be considered. The white cell count and precipitating antibodies are rarely helpful in the acute illness but the presence of hyphae in sputum is a strong indication of the cause. Repeated culture of *Aspergillus* from sputum also gives strong support, although sputum may be culture-negative in invasive disease and there may not be time to wait for repeated cultures. Since several *Aspergillus* spp. produce oxalic acid, the presence of this material and a low pH in the sputum has been suggested as a simple diagnostic test [180]. However, it seems unlikely to be sufficiently specific or sensitive. Strong support for the diagnosis also comes from the development of apparent mycetomas on the chest film [226] (Fig. 21.12). These result from infarction of infected tissue (probably due to vascular invasion by the fungus), cavitation and retraction of the infarct [240]. The rapid development of such lesions may be taken as almost pathognomonic of invasive fungal infection. In leukaemic patients, it is interesting that the cavitation occurs in subjects in whom the granulocyte count is recovering, and may be complicated by life-threatening haemorrhage [252]. Those in whom the white cell count remains low after treatment show widespread dissemination without cavitation and die rapidly. In many cases it is necessary to



**Fig. 21.12** Bilateral areas of consolidation, several containing fungus balls, in an immunosuppressed patient with invasive aspergillosis.

make the diagnosis by biopsy of the involved lung, either by transthoracic needle or via the transbronchial route (Fig. 21.13). The course of untreated invasive disease is progressive. Both local and disseminated spread may cause death. Urgent treatment is therefore necessary and intravenous amphotericin combined with ketoconazole is recommended.

### Mixed syndromes

It should be clear from the foregoing that the above syndromes are not infrequently combined in the same patient. Thus the author has seen locally invasive aspergillosis successfully treated only to be followed by the development of mycetoma, asthma and allergic aspergillosis, and conversely allergic aspergillosis converted (probably by high-dose corticosteroids) into invasive disease. Mycetoma may be complicated by asthma, and allergic aspergillosis by mycetoma. The clinician should keep an

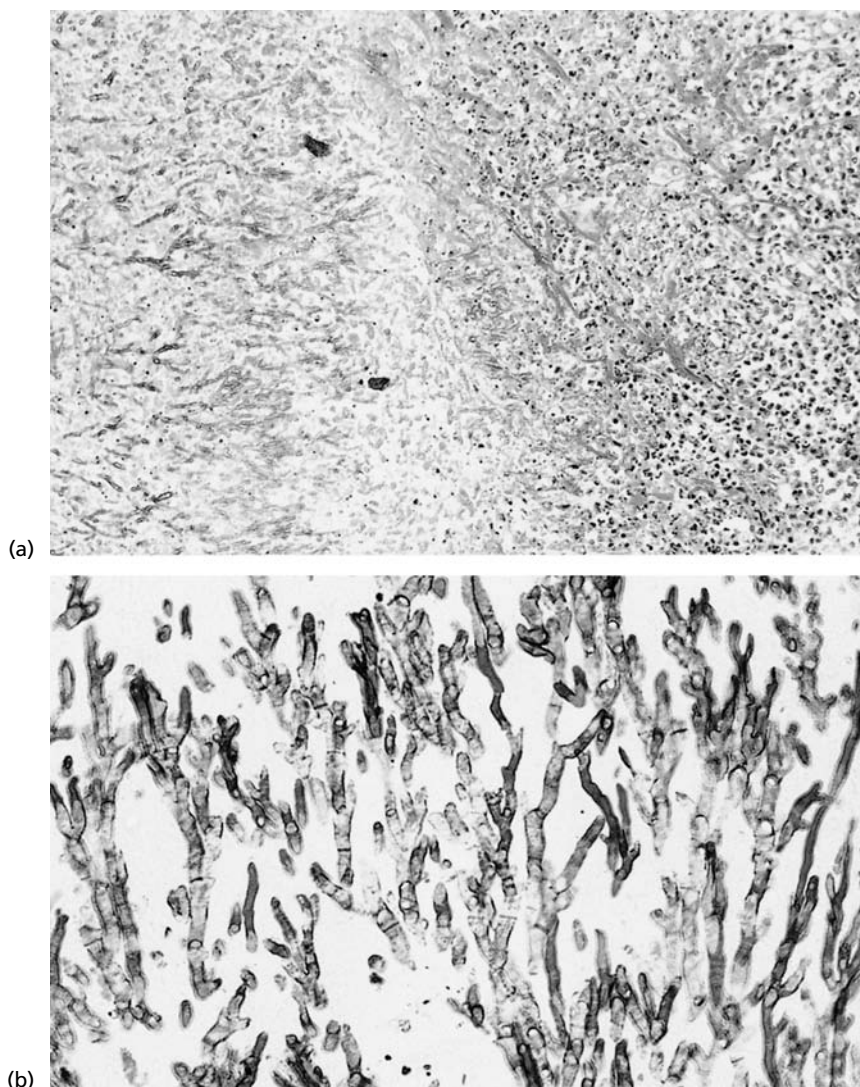
open mind when *Aspergillus* is found in the lung and be prepared to treat both allergy and infection if necessary.

## Candida

### Aetiology

*Candida* spp. are imperfect forms of the ascomycete genera *Saccharomyces* and *Pichia*. Most species, including the most important, *C. albicans*, are commensals in the mouth and gastrointestinal tract of humans. They are held in check by an intact mucosa and only become pathogenic when mucous membrane or skin is damaged or when the body's defences are impaired. They show some resistance to attachment by polymorphonuclear leucocytes, but are normally phagocytosed readily and are also susceptible to attack by T lymphocytes and macrophages [253–256].

Disease occurs as a result of local invasion of damaged skin or mucosa, aspiration into lung or introduction into



**Fig. 21.13** (a) Lung biopsy from patient with leukaemia showing hyphae in necrotic tissue to the left and an inflammatory reaction on the right (haematoxylin & eosin  $\times 90$ ). (b) Higher magnification of the same biopsy showing septate branching hyphae of *Aspergillus* sp. (Grocott  $\times 360$ ).



the tissues or bloodstream. Thus, surgical operations and indwelling intravenous cannulae can lead to disseminated candidiasis, whereas local disease may manifest as thrush, oesophagitis, lung abscess or infection of skin burns. Infection is promoted by diabetes, malnutrition, immunosuppression and, in the case of local infection, by the use of broad-spectrum antibiotics that remove competing bacteria.

### Clinical features

Lung involvement with *Candida* is rare and usually takes the form of patchy pneumonic shadowing associated with fever and tachypnoea in a debilitated or diabetic patient [257–260]. Lung abscess may occur. In cases without dissemination to other organs it is probably more usually caused by aspiration from the mouth or gastrointestinal tract [261]. Diffuse finely nodular dissemination may occur with haematogenous spread in the immunosuppressed and those undergoing cancer chemotherapy. The pathological features are bronchopneumonia with haemorrhage and necrosis.

The more familiar manifestations of candidal infection are thrush, seen not infrequently in patients on broad-spectrum antibiotics and inhaled corticosteroids, and oesophageal candidiasis, seen in debilitated patients with oral thrush. Disseminated disease involves any organ of the body and occurs in patients with acute leukaemia, *Candida* endocarditis and immunosuppression due to drugs used to prevent rejection after transplantation or for treatment of tumours [243,262,263]. Mucocutaneous candidiasis is an increasing problem with the rapid increase in the number of AIDS patients [264].

### Diagnosis

Pulmonary candidiasis is only diagnosed reliably by demonstration of the organism in lung tissue. Culture from sputum is of no value in view of the organism's normal habitat [183,265]. The yeasts, budding pseudohyphae and true hyphae may be demonstrated in tissue as Gram-positive organisms and may be cultured on routine bacterial media; special fungal media are not required. Demonstration of fungaemia and funguria may be suggestive of the diagnosis of disseminated disease but is not necessarily evidence of pathogenicity. Serological tests are not regarded as having much value in diagnosis.

### Management

Local oral and oesophageal infection can be managed most satisfactorily by amphotericin lozenges, sucked slowly five or six times daily. It is important to do this with the dentures removed. The condition can usually be prevented in asthma patients if they rinse their mouth and

throat after using inhalers. Lung infection and disseminated disease should be treated by a combination of amphotericin and ketoconazole as for aspergillar disease [258].

### *Pneumocystis* (see also Chapter 52)

#### *Pneumocystis carinii* and its epidemiology

*P. carinii* has been found in the lungs of humans and a wide range of animals [266]. Studies of antibody to *P. carinii* in children have shown a progressive rise in prevalence from birth until, at the age of 4 years, about two-thirds of normal children have a titre of 1/16 or more [267]. The organism has a life cycle involving an amoeboid trophozoite of about 2–5 µm, a somewhat larger pre-cyst, and a cyst in which up to eight sporozoites are formed [268,269]. These are liberated as trophozoites, which are capable of binary fission. Morphologically it has been thought to be a protozoon, and this has found support from its response to pentamidine and its failure to respond to antifungal drugs. However, molecular biological studies have shown its genome to have much more in common with fungi than with protozoa, hence its presence in this chapter [270,271]. It first came to prominence as a cause of severe pneumonia in malnourished infants in eastern Europe in the years following the Second World War [272,273], and subsequently was shown to cause a similar syndrome in immunosuppressed patients following treatment for acute leukaemia or other neoplasms [274]. Latterly, it has been recognized as the most important pathogen infecting the lungs of patients with AIDS, and is now the main cause of death in such patients [275,276]. While transmission of the organism from person to person has not been clearly demonstrated, there is good evidence of airborne transmission by droplets in the experimental immunosuppressed rat and mouse models [277,278]; studies of lungs of people without *Pneumocystis* pneumonia have failed to demonstrate the organism using sensitive molecular techniques [279]. It seems therefore that *Pneumocystis* is an environmental organism acquired by inhalation that only gains a foothold in the immunosuppressed and people suffering severe protein deficiency. The common factor is almost certainly suppression of T-lymphocyte function.

### Clinical features

*Pneumocystis* pneumonia occurs predominantly in infants in the first few months of life and in immunosuppressed adults and children. Originally seen most frequently in malnourished children and in patients being treated with immunosuppressant drugs for malignant disease [266,280], it is now recognized especially in sufferers from AIDS [279].

The illness usually starts with fever and cough followed

by increasing tachypnoea, the onset often being quite sudden, over a few days, in patients immunosuppressed by drugs but more insidious in patients with AIDS [281]. Inspiratory crackles are audible in a minority of patients and wheezes are rarely heard, the airways being unaffected. The chest film is almost always abnormal [282], usually showing a bilateral interstitial pneumonitis, ultimately leading to diffuse ground-glass opacification with air bronchograms. This may initially be perihilar in distribution, later spreading throughout the lungs (Fig. 21.14). These features, while indicative of a diffuse pneumonitis, are not diagnostic of *Pneumocystis* infection. The blood gases usually show increasing hypoxaemia with hypocapnia, and the carbon monoxide diffusing capacity is reduced. In the absence of treatment the disease is progressive and commonly fatal.

The condition in malnourished infants is somewhat different in presentation, usually coming on rather insidiously over a few weeks. There may be cough and associated diarrhoea but usually no fever. The infant shows signs of respiratory distress and becomes cyanosed. Again, auscultatory signs are sparse [283].

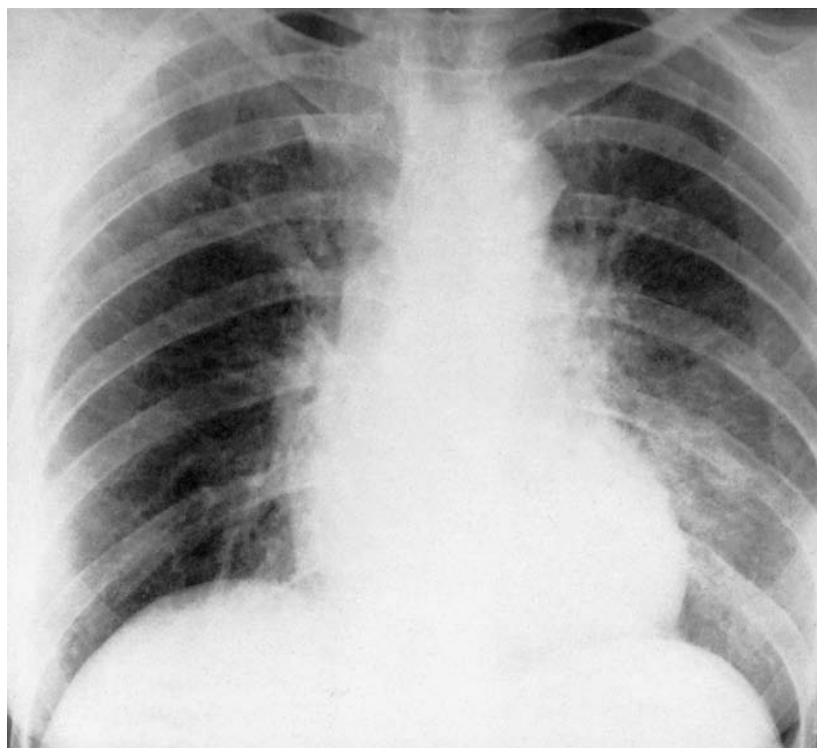
### Diagnosis

In general, the diagnosis requires demonstration of the organism in the lungs in a patient with consistent clinical features. Suspicion is aroused if an immunosuppressed patient or one with risk factors for AIDS has persistent

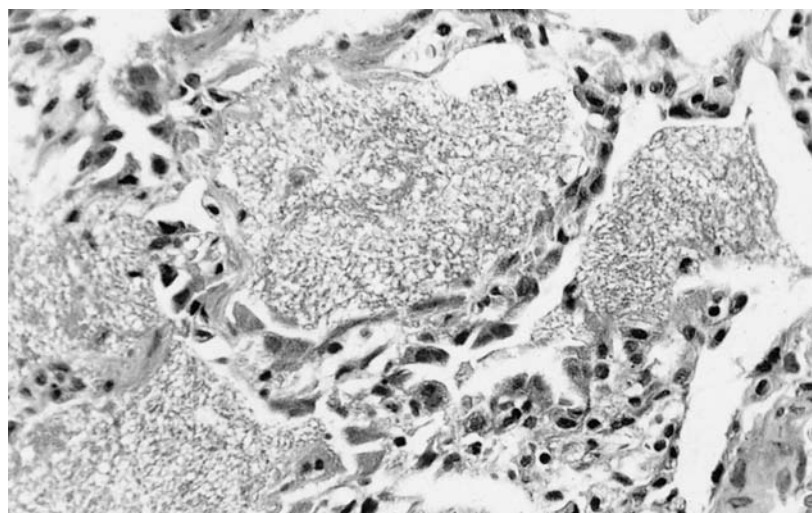
fever, even if the chest radiograph is normal. In this circumstance, a positive gallium scan may be the first indication of pulmonary disease [284–286]. The organism is demonstrated by staining induced sputum, bronchoalveolar lavage fluid, brushings or lung biopsy with Gomori's methenamine–silver nitrate stain, when cysts show as dark brown (Fig. 21.15). Trophozoites and sporozoites may be shown by Giemsa or polychrome methylene blue stains. However, these traditional methods result in a proportion of positive diagnoses being missed and newer techniques give a higher yield, for example monoclonal antibodies in immunofluorescence tests and DNA amplification with ethidium bromide staining; both techniques have been shown to be of high sensitivity and specificity in diagnosis on both induced sputum and bronchoalveolar washings [287,288]. In view of the poor physical condition of these patients, the simplest procedures should be tried first. It is encouraging to note that induction of sputum production by a 10–20 min inhalation of 5% saline through an ultrasonic nebulizer may allow demonstration of the organism by one or other of these techniques in a high proportion of patients, thus obviating the need for bronchoscopy and biopsy [288–290].

### Treatment

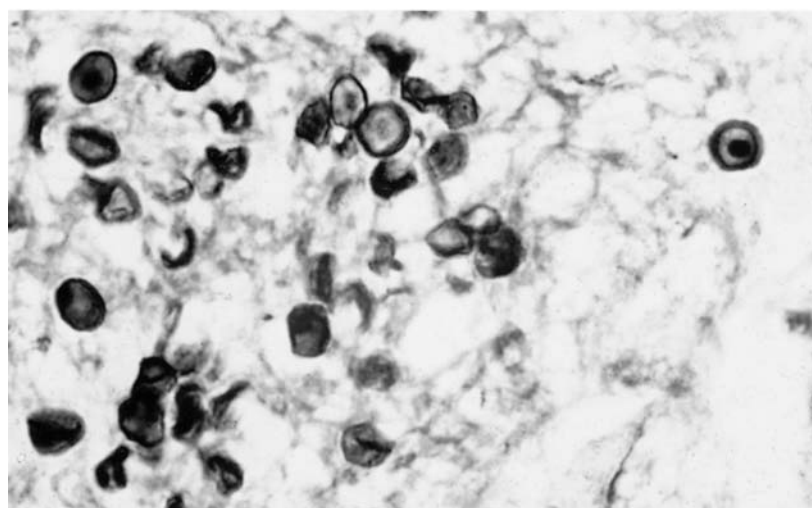
The organism is sensitive to co-trimoxazole (trimethoprim and sulfamethoxazole), dapsone–trimethoprim, and pentamidine. The standard therapy in drug-immunosup-



**Fig. 21.14** Diffuse ground-glass infiltrates due to *Pneumocystis carinii* infection in patient treated with immunosuppressant drugs for acute leukaemia.



(a)



(b)

**Fig. 21.15** (a) Section of lung biopsy from bone marrow transplant patient showing alveoli filled with the characteristic foamy and granular infiltrate of *Pneumocystis pneumonia* (haematoxylin & eosin  $\times 230$ ). (b) Some tissue stained to show the typical cysts of *Pneumocystis carinii* (Grocott methenamine-silver  $\times 900$ ).

pressed patients is co-trimoxazole (sulfamethoxazole 100 mg/kg and trimethoprim 20 mg/kg daily) in divided doses [291,292], but lower doses are necessary when renal failure is present. A 10–14 day course is usually sufficient, although in patients with AIDS it may be necessary to give more than one course or to continue treatment for a month or more as there is evidence that organisms persist in the lung and relapse occurs in patients treated only for 2 weeks [281,293]. Moreover, these patients appear to be unduly sensitive to the co-trimoxazole, often developing rash, fever and leucopenia, and for this reason lower doses or alternative regimens have been tried. It is now conventional to treat AIDS patients according to the severity of the pneumonia [279]. In mild cases without hypoxaemia, oral dapsone-trimethoprim for 21 days is usually effective. In severe cases with a  $PaO_2$  of 8 kPa (60 mmHg) or below, intravenous co-trimoxazole or pentamidine should be used together with high-dose corticosteroids. Side-effects of pentamidine include leucopenia, hypoglycaemia, uraemia and pain at the injection site. Apart from

the pain, these are not particularly common in AIDS patients. The use of these and other second-line drugs in the management of AIDS pneumonia are discussed in detail in Chapter 52.

Such treatment given early may be expected to produce a cure in most patients, although relapse may occur, particularly in patients with AIDS. However, it should be noted that immunosuppressed patients may have several coexisting pulmonary infections, and a combination of *Pneumocystis* with cytomegalovirus or mycobacterial infection is not uncommon. If treatment is successful, the lungs may be expected to revert to normal and fibrosis does not appear to be an important complication. This has been shown to be the case in the less confusing situation of children who have developed the infection in the course of cytotoxic therapy for leukaemia and lymphoma; all survivors in one large study had normal lung function within 6 months of completing therapy for *Pneumocystis pneumonia* [294]. Because of the frequency of infection and relapse in AIDS patients, prophylactic therapy is used when the

CD4 count falls to  $0.15 \times 10^9/L$ . Either oral co-trimoxazole (trimethoprim 160 mg and sulfamethoxazole 800 mg daily) or inhaled nebulized pentamidine 300 mg monthly are used. Chemoprophylaxis is also given for up to 1 year to children treated for acute lymphoblastic leukaemia or receiving transplants, using appropriate doses of co-trimoxazole.

### Other rare fungal opportunist pathogens

In immunosuppressed or debilitated patients, particularly those on steroids, and occasionally in diabetics, infections with other fungi may occur. Three zygomycetes, *Mucor*, *Absidia* and *Rhizopus*, are saprophytic organisms familiar as the mould that grows on bread. They may rarely be responsible in immunosuppressed subjects for mucormycosis, a disseminated disease with a predilection for invading sinuses and brain; diffuse pneumonitis may occur, particularly in patients being treated for lymphoma and leukaemia. The pathological lesion is usually fungal invasion of vessels with infarction of lung tissue [295,296].

They may also be discovered as the cause of pulmonary granulomas or mycetoma [297,298]. Diagnosis is made by demonstration of broad, non-septate hyphae in tissue samples. Spread of the organisms from contaminated air-conditioner filters has been described [299]. *Pseudallescheria boydii* (or, in the imperfect state, *Monosporium apiospermum*) is a soil saprophyte that has been described as producing mycetomas as well as having caused bronchial colonization and lung abscess in the immunosuppressed [300,301]. *Penicillium* spp. are ubiquitous saprophytes that produce large numbers of airborne spores, yet only very rarely have they been associated with disease. Spores may provoke asthma or allergic alveolitis (e.g. cheesewashers' disease due to *P. casei* [302]). Very occasional examples of pneumonitis and disseminated disease in the immunosuppressed have been described [303]. Similarly, *Torulopsis glabrata*, a yeast-like organism that is a commensal in the female vagina, may occasionally occur as a pathogen, causing pneumonitis and disseminated infection in patients receiving cancer chemotherapy [304].

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# PARASITIC DISEASES

ANTHONY SEATON

Animal parasites, though a major cause of morbidity and mortality worldwide, are only rarely direct causes of lung disease (Table 22.1); those that belong to the phyla Protozoa, Nematoda, Platyhelminthes and Arthropoda. Among the protozoal diseases in which lung involvement may occur are amoebiasis, malaria and toxoplasmosis. In Western countries, a number of these parasites now feature among those multiple organisms infecting the immunocompromised. Of the platyhelminths, infection with *Schistosoma* may lead to pulmonary hypertension while paragonimiasis and hydatid disease involve the lungs directly. Cysticercosis may cause diagnostic confusion on chest films. Many of the nematode worms may provoke pulmonary eosinophilia and *Toxocara* infection is associated with the symptoms of visceral larva migrans. One nematode, *Mammomanogamus*, actually lives in the bronchi. *Trichinella* is another cause of multiple calcifications in muscles that may be seen on a chest radiograph. Finally, one class of arthropod parasite appears to cause lung disease in humans, the worm-like Pentastomida, though mites are a ubiquitous and important source of antigen involved in the provocation of asthmatic attacks.

## Protozoal parasites

Pneumonia may occur as a complication of chronic debilitating diseases such as sleeping sickness (*Trypanosoma brucei*) and kala-azar (*Leishmania donovani*). Aspiration pneumonia and pulmonary embolism may result from the oesophageal dilatation and intraventricular thromboses of Chagas' disease (*Trypanosoma cruzi*) [1–3]. However, direct involvement of the lungs by protozoa occurs with severe episodes of *Plasmodium falciparum* malaria [4–6] and in infection with *Entamoeba* and *Toxoplasma*. Obliterative bronchiolitis has been described as a complication of *Plasmodium vivax* infection [7]. Lung disease due to *Pneumocystis carinii* is discussed in Chapters 21 and 52, this organism having been reclassified as a fungus.

## Thoracic amoebiasis

### *Entamoeba histolytica* and its epidemiology

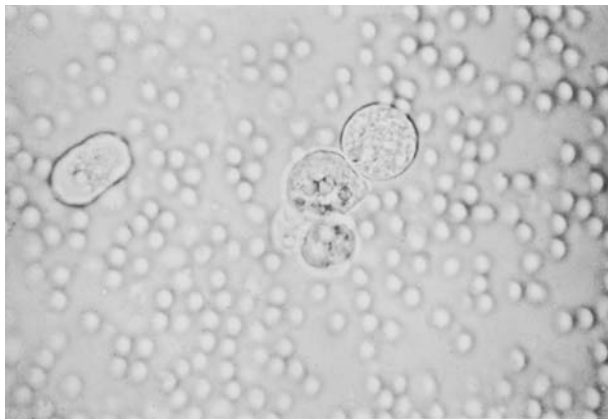
The causative organism of amoebiasis is an obligatory parasite that lives anaerobically in the colon of humans, feeding on bacteria and desquamated epithelial cells [8–10]. Its prevalence in a population is dependent on the local standards of hygiene, since transmission of the organism depends on one person ingesting the cysts passed in the faeces of another. In some areas of the tropics and subtropics infection (usually asymptomatic) is widespread, whereas in Europe and North America it is rare. Nevertheless, even in developed countries poor hygiene may allow transmission of imported amoebiasis among close contacts [11], while pockets of high prevalence may be found in areas with high immigrant populations, among homosexuals (when genital infection may occur) or in long-stay institutions for the mentally retarded [12,13].

*E. histolytica* exists in two forms, the trophozoite or motile amoeba (Fig. 22.1) and the cyst. Trophozoites have pathogenic potential, although they may live in the colon as commensals. The commensal amoeba is responsible for cyst formation, acquiring a rigid wall that can protect it from gastric juice and chlorine for example. The amoeba may divide up to twice within the cyst, but its lifespan is limited to a few days at most unless ingested by a suitable host. Excystation does not occur in the colon of the original host or in the outside environment, though it may occur in culture media at 37°C and in the bowel of the recipient.

The disease amoebiasis results from a change in behaviour and structure of the commensal amoebae or, more probably, from a change in the predominant type of amoeba to a larger and more active organism, which invades through the mucous membrane and ingests red blood cells rather than bacteria. The reasons for this change are not clear, although it is more likely to occur if the patient is malnourished, alcoholic or has other bowel disease.

**Table 22.1** Parasites causing thoracic disease.

Phylum	Class	Genus	Disease
Protozoa	Mastigophora	<i>Trypanosoma</i>	Chagas' disease
	Rhizopoda	<i>Entamoeba</i>	Amoebiasis
	Sporozoa	<i>Plasmodium</i>	Malaria
		<i>Toxoplasma</i>	Toxoplasmosis
Nematoda (roundworms)	Aphasmidia	<i>Trichinella</i>	Trichinosis
	Phasmidia	<i>Ascaris</i>	Pulmonary eosinophilia
		<i>Ancylostoma</i>	
		<i>Necator</i>	
		<i>Strongyloides</i>	
		<i>Toxocara</i>	
		<i>Dirofilaria</i>	Visceral larva migrans
		<i>Mammomanogamus</i>	Lung nodules
Platyhelminthes (flatworms)	Trematoda	<i>Schistosoma</i>	Schistosomiasis
		<i>Paragonimus</i>	Lung fluke
	Cestoda	<i>Taenia</i>	Cysticercosis
		<i>Echinococcus</i>	Hydatid disease
Arthropoda	Pentastomida	<i>Linguatula</i>	Pentastomiasis
		<i>Armillifer</i>	

**Fig. 22.1** *Entamoeba histolytica* enjoying its diet of red blood cells.

### Clinical features

Most carriers of *E. histolytica* are free of symptoms. Invasion of bowel wall by the organism results in amoebic dysentery, with abdominal pains, colonic tenderness, diarrhoea and fever [14–18]. The symptoms can range from a mild transient abdominal disturbance to acute abdomen with peritonitis or toxic megacolon. Involvement of the liver, which is the usual precursor of lung disease, may occur in the acute attack but usually only becomes apparent months or years later; indeed many patients with amoebic hepatitis give no history of previous bowel disease.

Pulmonary involvement usually results from direct spread of a hepatic abscess through the diaphragm. The liver lesion develops from the coalescence of multiple small abscesses as a result of embolism of amoebae

through the portal vein. The lesion is most usually found in the right lobe and pathologically consists of necrotic liver surrounded by active amoebae. The amoebae are capable of detaching and lysing adjacent cells, and the abscess can extend across tissue planes. The patient with an amoebic liver abscess usually feels ill, loses weight and has fever, tender hepatomegaly and rib tenderness. The lesion may point through the skin or, more commonly, rupture into the lung or the pleura (see Plate 22.1, facing p. 630). Such rupture is usually associated with cough, sometimes productive of 'anchovy sauce' sputum if a hepato-bronchial fistula is present. There may be pain, sometimes referred to the right shoulder. Much less commonly, metastatic lung abscesses may occur as a result of rupture of a liver abscess into the hepatic veins. In such patients the clinical features are no different but the lesions may be multiple and occur anywhere in the lung. A liver abscess may also rupture into the pericardium and may cause acute or gradually progressive signs of tamponade [19]. Involvement of lung or pericardium is a serious complication of amoebic infection, particularly as a high proportion of patients are already debilitated by malnutrition or alcoholism. If treatment is not initiated promptly the infection may often prove fatal.

### Radiographic appearances

Liver abscess is frequently associated with elevation of the right hemidiaphragm; some inflammatory changes may be seen at the right lung base, together with a small pleural effusion, before rupture occurs [20]. Rupture may be accompanied by a large pleural effusion, streaky consolidation or abscess formation in the right lower lobe [21]



**Fig. 22.2** Chest film of patient in Plate 22.1 showing amoebic lung abscess and pleural effusion.

(Fig. 22.2). Enlargement of the cardiac shadow may indicate rupture into the pericardium. Metastatic amoebic abscess or abscesses are indistinguishable radiologically from other causes of lung abscess.

### Diagnosis

The key point in diagnosis is to suspect amoebic infection in anyone who has visited areas where such disease is endemic and who is likely to have been exposed to poor food hygiene. Such patients with appropriate physical and radiological signs may need to be given a therapeutic trial of antiamoebal treatment if diagnostic facilities are poor. Motile amoebae should be sought by an experienced microscopist in fresh, warmed stool specimens and in anchovy sauce sputum or the last aspirates from liver abscess, and can be typed by the electrophoretic pattern of their zymodemes or by DNA probes. Cysts may be found in stools. Serological tests, including indirect haemagglutination and gel diffusion for precipitating antibody, are frequently positive in the invasive stage of the disease [22–24]. Liver abscess may be demonstrated by gallium scan, ultrasound or conventional isotope scan; in many circumstances, diagnostic liver aspiration remains the most reliable way of making the diagnosis.

### Management

As with many tropical and subtropical diseases, prevention of amoebiasis depends on good hygiene. The traveller should avoid local water, salads and cooked food from markets. The treatment of choice is metronidazole 800 mg three times daily for 5–8 days [25]. Aspiration of liver, lung or pericardial abscesses may also be necessary. If this drug is not available, a combination of chloroquine and emetine may be necessary. Other regimens may be effective and the advice of a specialist in tropical diseases should be sought. Other drugs include diloxanide and diiodohydroxyquin, which eliminate persistent bowel organisms but are not active against tissue amoebae. Chloroquine is effective against organisms in the liver, while dihydroemetine is useful because of its rapid action in seriously ill patients. Side-effects may occur: dihydroemetine is cardiotoxic, chloroquine may cause nausea and rashes, and metronidazole also causes nausea and a disulfiram-like syndrome with alcohol.

### Toxoplasmosis

#### *Toxoplasma gondii* and its epidemiology

*T. gondii* is an obligatory intracellular parasite found widely in humans and animals. A high proportion of the human population shows evidence of past infection, although a history of disease is rare. The organism exists in three forms. Tachyzoites are crescentic or oval bodies about 5 µm long that are able to penetrate living cells, where they divide repeatedly and either form a tissue cyst or disrupt the cell. The tissue cyst is a walled structure up to 200 µm in size containing many organisms, found particularly in brain, heart and skeletal muscle. It is the form in which infection is transferred between meat-eaters, including those humans who prefer their meat undercooked. The third form of *T. gondii* is the oocyst, which is a 10-µm ovoid body formed only in the intestine of members of the cat family [26]. Cats are infected by eating animals containing either tachyzoites or tissue cysts; these develop in the gut into oocysts, which in turn are passed in the faeces where they are a source of infection to other animals. Humans are usually infected either by eating infected meat or *in utero* from a maternal infection acquired in pregnancy [27]. Antibody studies have shown that up to 70% of adults have at some time been infected, although only a small proportion of these infections have caused clinical disease [28,29].

### Clinical features

Toxoplasmosis causes three main syndromes: congenital infection, acute infection and disseminated disease in the immunosuppressed. Congenital infection does not

usually affect the lung, the disease being primarily manifest in the eyes and central nervous system. Similarly, acute toxoplasmosis in immunocompetent adults rarely involves the lung, but causes a glandular fever-like syndrome. In contrast, infection in those who are immunosuppressed, whether by drugs, malignant disease or AIDS, frequently causes diffuse pneumonitis [30–32]. Involvement of the central nervous system with encephalitis is also common [33]. Disease may occur either as a result of a recent infection or from breakdown of a previously acquired, latent, infection.

There are no features of pulmonary toxoplasmosis that enable a clinical diagnosis to be made with confidence. The patient is usually febrile and breathless, and the radiograph may show diffuse or localized hazy or diffuse nodular infiltrates [31,34]. In the immunosuppressed there may be rash or lymph node enlargement and, more commonly, evidence of meningoencephalitis. There is, of course, other clinical evidence of the primary condition responsible for immunosuppression.

### Diagnosis

The diagnosis of pulmonary toxoplasmosis depends on demonstration of the organism in the lung [34]. Pathological studies have shown tachyzoites to be sparse and mainly intracellular in areas of acute pneumonitis and numerous both within and outwith cells in necrotic areas [35]. Fluorescent antibody tests are helpful in identification of the organism. The clinical features of infection do not differ from those of other opportunist infections in immunosuppressed patients and studies of toxoplasma antibody in such patients are of little value in that changes usually do not occur or, if they do, reflect infection elsewhere than in the lung. Thus the hope is that the organism may be demonstrated in lung biopsy or bronchoalveolar lavage specimens. The latter method, being relatively non-traumatic, is being used increasingly in such sick patients [36,37]. Specific stains for the organism and for antigen have been introduced and these may well increase the sensitivity and specificity of the diagnosis of pulmonary toxoplasmosis.

### Management

The condition is fatal in immunosuppressed patients unless treated and therefore a therapeutic trial of therapy is desirable when clinical suspicion is high, even if the diagnosis cannot be confirmed. It is recommended that treatment be continued for 1 month after clinical resolution, which may mean several months of therapy. The most effective regimen is probably a combination of sulfadiazine (sulphadiazine) 100 mg/kg daily orally up to a maximum of 8 g daily and pyrimethamine 100 mg daily for 2 days then lower, intermittent doses [38,39]. The latter

drug is a folic acid antagonist and adverse effects on the bone marrow may be prevented by folinic acid 10 mg on alternate days. Other side-effects of the sulphonamide also occur frequently, making satisfactory treatment something of an ordeal for the patient.

## Malaria

### Malarial parasites and their epidemiology

Malaria is second only to tuberculosis in importance as a cause of illness and death worldwide [40]. Some 170 million people contract the disease annually, of whom over 1 million die. Lung disease is a late feature, occurring almost exclusively in severe cases of *Plasmodium falciparum* infection. The life cycle of the parasite depends on the presence of both humans and anopheline mosquitoes. The mosquito obtains mature gametocytes in red corpuscles from the blood of humans and these undergo sexual fusion in the insect's gut prior to penetrating the gut wall to form an oocyst. This liberates into the blood many sporozoites that migrate to the salivary gland, from where they are injected into the next person on whom the insect feeds. The next part of the cycle in humans involves rapid transfer of sporozoites to hepatic cells where they first multiply as tissue schizonts and whence they are released into the bloodstream as merozoites; these adhere to and invade red blood cells wherein they multiply again as blood schizonts and are released into the blood in a cyclical manner as merozoites to reinvade further erythrocytes (Fig. 22.3). Some remain in red cells to develop into gametocytes, and thus complete the cycle by being taken in by a mosquito. The periodic rupture of red cells to liberate merozoites is accompanied by release of cytokines that are responsible for the periodic symptoms of the disease.

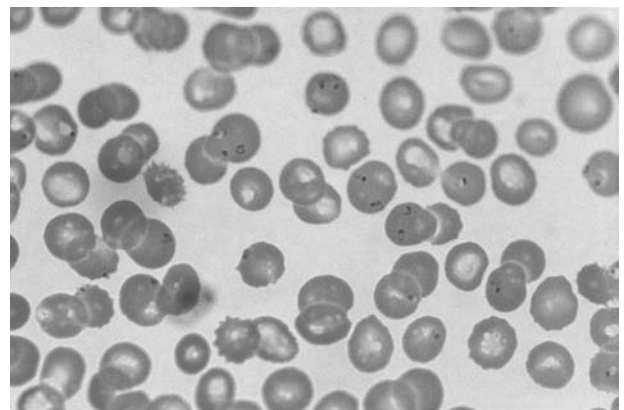


Fig. 22.3 Blood film from patient who died of cerebral malaria showing unusually heavy load of *P. falciparum* parasites in red cells. (Courtesy Dr Andrew Seaton.)

Malaria is endemic throughout the tropics, save for the southern Pacific islands. In tropical Africa and Papua New Guinea almost everyone is infected in childhood and it is at this age when most illness and death occurs, whereas in many other parts of the tropics the pattern of the disease is more epidemic, outbreaks occurring across all ages on an area basis. For visitors to the tropics, infection by *P. falciparum* can occur anywhere from a mosquito bite, and disease may appear between 1 week and 1 year later, though the large majority of infections present within 3 months. Infection with *P. vivax* and other less severely pathogenic species commonly takes longer to present and may well occur more than 1 year after return from the endemic region.

### Clinical features

Lung involvement occurs almost exclusively in patients with *P. falciparum* malaria [41–43]. The patient has a history of several days of non-specific malaise, headache and muscular pains before the first paroxysm of severe fever. Usually the condition has been untreated for several days and other serious manifestations, such as cerebral malaria and blackwater fever, may be present. At this stage, the patient is often hypotensive and extremely ill. The respiratory complications typically occur after a day or two of treatment, the patient developing cough and tachypnoea. Crackles are heard in the lungs, the chest film shows signs of pulmonary oedema and hypoxaemic respiratory failure is present. Not surprisingly, the condition is commonly fatal.

The pathology of the condition is that of adult respiratory distress syndrome and pulmonary oedema. While therapeutic fluid overload and low serum albumin levels may contribute, it seems likely that the primary pathogenesis is an inflammatory reaction provoked by arrest of parasitized red cells in pulmonary capillaries. Red cells containing the earlier ring forms of the parasite are less deformable and therefore more readily held up in the pulmonary circulation; they are also more resistant to antimalarial drugs at this stage in their life cycle [6,42,44,45].

### Management

This serious emergency should be managed with the advice of someone experienced in tropical medicine and intensive care if at all practicable. Intravenous quinine is the mainstay of treatment, given as the dihydrochloride at 20 mg/kg as a loading dose over 4 h and then 10 mg/kg infused in isotonic saline over 4 h, repeated 8-hourly [46]. Intermittent positive pressure ventilation, often with high inspired oxygen concentrations, is usually necessary. Care needs to be exercised to avoid fluid overload, but red cells may need to be transfused to correct anaemia.

## Nematode parasites

*Ascaris*, *Toxocara* and various filarial worms are associated with the syndrome of tropical eosinophilia. Two nematodes, *Dirofilaria* and *Mammomanogamus*, may cause lung disease directly, while *Trichinella* may cause multiple calcified lesions in the chest wall.

### Pulmonary eosinophilias

These conditions are described in Chapter 38. There is a spectrum of syndromes related to nematode infestation, variously grouped as transient pulmonary eosinophilia or Loeffler's syndrome, visceral larva migrans, and persistent tropical pulmonary eosinophilia. The first is usually caused by *Ascaris lumbricoides*, though *Ancylostoma*, *Strongyloides* and a number of other worms may cause it. Visceral larva migrans is associated with *Toxocara* infection, while tropical eosinophilia is related to infestation by various filarial worms.

### The parasites and their epidemiology

*Ascaris lumbricoides* is found throughout the temperate and tropical parts of the world and is a frequent parasite of humans, especially in areas of poor sanitation. It grows to 35 cm in length, the female being rather longer than the male. The eggs, which are oval and up to 70 × 50 µm in size, are passed in the faeces of the host and require a few days in moist soil to mature. When ingested by another person they hatch in the duodenum where the larvae penetrate the wall into the bloodstream and pass through the heart into the pulmonary capillaries. There they penetrate into alveoli, migrate up the bronchi and are swallowed, and develop into adult worms in the small intestine. Within 2 or 3 months the cycle is complete, the adult worms producing vast numbers of their own eggs. They survive for about 1 year in the intestine, where they may cause no symptoms or may provoke abdominal pains, biliary colic or nausea and vomiting. Pulmonary eosinophilia accompanies the period of larval migration through the lungs.

The hookworms, *Ancylostoma duodenale* and *Necator americanus*, are also widely distributed in tropical and temperate regions. The ova hatch in moist soil and develop for several weeks in that environment, moulting to form an infective larva. This waits in surface moisture for contact with human skin, which it penetrates and passes into the bloodstream and thence to the pulmonary capillaries where, like *Ascaris*, it migrates into the alveoli. It then works its way up into the trachea, is swallowed and matures by attachment to the intestinal mucosa, feeding on blood and tissue juices. Pulmonary eosinophilia may accompany the lung migration, while iron deficiency anaemia is the most serious consequence of the intestinal parasitism.



*Strongyloides stercoralis* has a similar distribution to that of hookworm. It may live free in the environment for a generation or two, but eventually produces infective larvae that penetrate the skin and migrate in the same way as hookworm, occasionally causing pulmonary eosinophilia. Heavy intestinal infections can cause malnutrition, diarrhoea and blood loss. Infective larvae can be produced in the intestine, permitting a cycle of autoinfection; in this hyperinfection syndrome, which occurs particularly in the immunosuppressed, direct lung involvement can occur.

The filarial worms that parasitize humans include *Wuchereria bancrofti*, which causes elephantiasis, and *Loa loa*, which causes Calabar swellings. They are found predominantly in Africa and tropical parts of Asia. These and other filariae are transmitted by insect intermediate hosts, which acquire the organism by feeding on the blood of an infected person and taking in microfilarial larvae. These then develop in the thorax of the insect into much larger infective larvae, which migrate to the proboscis and in turn are injected into the next person on whom the insect feeds. Further development takes place, probably in the lymphatic system, and the adult worms mature, mate and produce eggs that turn into the microfilariae. These develop a cycle of entry into the bloodstream and migration into the tissues. They probably spend part of this time lodged in pulmonary vessels, where they give rise to symptoms and allergic reactions.

*Toxocara canis* and *T. cati* are parasites of dogs and cats respectively, living in their hosts' small intestines. Their ova need to spend some time maturing in soil and develop into larvae in the intestine of the animal that ingests them. The life cycle of *T. cati* mimics that of *Ascaris lumbricoides*, with migration through the host's lung. In contrast, *T. canis* larvae migrate into the somatic tissues where they provoke the formation of granulomas. In the female dog they become active when pregnancy occurs and revert to the pattern of pulmonary migration or pass through the placenta to infect the pups. In humans, neither organism is able to complete its natural cycle. Ingestion (usually by children) of ova shed by cats, pups or pregnant bitches leads to migration of larvae to organs including lungs, liver, heart, kidney and muscles, giving rise to the syndrome of visceral larva migrans.

### Clinical syndromes

All the above parasitic infestations are associated with peripheral eosinophilia. In addition, symptoms may be associated with intestinal malabsorption, blood loss and malnutrition, and with intestinal obstruction by masses of worms. Skin rashes and urticaria may result from local hypersensitivity. Migration of larvae through the lung results in cough, breathlessness, wheeze and diffuse, often patchy, pulmonary infiltrates. In *Toxocara* infestation,

arrest of the larvae in the lungs is associated with the pulmonary component of visceral larva migrans [47–49], in which the patient's illness may range from simple blood eosinophilia to a severe disease with fever, cough, wheeze, abdominal pains and sometimes central nervous system symptoms. The patient is usually a young child, and hepatomegaly, high eosinophil count, hypergammaglobulinaemia and pulmonary infiltrates are common features. Bronchoalveolar lavage shows high proportions of eosinophils [50]. The condition usually resolves spontaneously. The microfilarial embolization of pulmonary vessels that may occur with a number of filarial worm infestations is associated with the more persistent features of tropical pulmonary eosinophilia [51,52]. The symptoms are similar to those of visceral larva migrans, with generalized malaise, fever and weight loss, together with cough, wheeze and shortness of breath. The chest film may range from normal to diffuse bilateral infiltration and a high eosinophil count ( $>3.5 \times 10^9/L$ ) is almost always present [53]. The symptoms may be present over years and may mimic asthma clinically and pneumonia or tuberculosis radiologically [54,55].

### *Strongyloidiasis*

Infestation with *Strongyloides stercoralis* is endemic throughout the tropics and subtropics, and subclinical infection is very common. It should be suspected as a cause of asthma and eosinophilia in patients from endemic areas [56]. As well as being one of the causes of tropical eosinophilia, the organism may cause a hyperinfection syndrome in which severe pulmonary disease is common [57,58]. This occurs as a consequence of arrest of larvae in the lungs and presents with general illness, urticarial eruptions on the skin and pulmonary infiltrates, often together with evidence of involvement of other systems such as malabsorption and meningitis [59]. The condition affects especially people on high doses of steroids or other causes of reduced immunity [60], though it appears not to be a particular problem in AIDS patients. The lung disease may progress to adult respiratory distress syndrome and a granulomatous interstitial pneumonitis has been described [61,62].

### Diagnosis and management

Ascariasis is diagnosed by detection of ova in the stools and treated by mebendazole 100mg twice daily for 3 days. Hookworm may be diagnosed and treated similarly, together with iron replacement if necessary. *Strongyloides* infestation is diagnosed by demonstrating larvae in stools or in duodenal aspirate and is treated with thiabendazole 25mg/kg twice daily for 3 days. Albendazole in a single dose of 400mg and ivermectin 200µg/kg have also been shown to be effective and have fewer side-effects [63,64].

Severe infections, with autoinfection, have a high mortality and longer treatment courses may be necessary, using albendazole 400 mg 12-hourly for two or more weeks. Filariasis may be diagnosed by demonstration of microfilariae in blood taken at an appropriate time or by detection of filarial antibodies. Treatment is with diethylcarbamazine 3 mg/kg three times daily for 3 weeks. This kills the microfilariae and results in relief of pulmonary symptoms; it may therefore be used as a therapeutic trial in patients with appropriate clinical features and travel history if the diagnosis has not been established. The adult worms may not be eliminated or killed by this treatment, so prevention of infection by elimination of insect vectors and avoidance of bites is particularly important.

Visceral larva migrans is suspected in children with appropriate symptoms who may have been eating soil. The diagnosis may be made by an enzyme-linked immunosorbent assay. Treatment is probably only advisable in patients with troublesome pulmonary symptoms, as the disease tends to remit spontaneously. Diethylcarbamazine or thiabendazole may be tried, usually for several weeks, but trials of ivermectin in single doses of 200–400 µg/kg have shown promise. If there is a severe hypersensitivity reaction, corticosteroids may be advisable.

### Dirofilariasis

Although not a natural parasite of humans, the dog heart worm, *Dirofilaria immitis*, may occasionally cause pulmonary disease [65–68]. It is a filarial worm usually transmitted between dogs by mosquitoes. After maturing under the skin, the worms enter the circulation and live in the animal's heart and pulmonary vessels. Accidental infection of humans may occur by mosquito bite and, though reported predominantly from the USA, is probably more widely distributed. The parasite is unable to complete its life cycle in humans but adult worms may lodge in small pulmonary arteries, causing a granuloma that presents radiologically as a peripheral patch of pneumonitis or as a coin lesion up to 5 cm in diameter. Eosinophilia is not usually present. The lesion is indistinguishable from neoplasm and is usually only diagnosed after surgical excision. The worm may be demonstrated by non-specific fluorescent whitening stains [68].

### *Mammomanogamus laryngeus*

This nematode worm has occasionally been found in the sputum or bronchial tree of humans, where it appears to provoke persistent cough [69]. Its life cycle is not known but it is probably acquired by insect bite or by eating an intermediate host. All reports have been in people who have lived in or visited the Caribbean. Symptoms respond to treatment with mebendazole 100 mg daily for 3 days.

### Trichinosis

Infection with *Trichinella spiralis* is acquired by eating undercooked meat containing larval cysts. Pork and bear are important sources in the USA, where infection is not infrequent [70]. The larvae are liberated in the stomach and develop into adult worms in the intestine. After mating, further larvae are produced that pass through the pulmonary circulation to lodge in skeletal muscles where they form cysts. The larvae eventually die in humans and the lesions may calcify, in which case they may cause diagnostic confusion on a chest radiograph until it is appreciated that they lie in the muscles of the chest wall. During the phase of larval migration, fever, myalgia, circumorbital oedema and eosinophilia may occur [71,72]. Occasionally myocarditis or pneumonia may complicate the illness, and in severe cases the myositis may mimic poliomyelitis. At least one case of ventilatory failure has been reported [73].

### Platyhelminth parasites

Representatives of two classes of platyhelminth, the trematodes and the cestodes, may cause lung disease in humans. Of the trematodes, *Schistosoma* spp. and *Paragonimus westermani* are important pathogens, while the cestode *Echinococcus granulosus* is the cause of hydatid disease. Cysticercosis, caused by *Taenia solium*, may also cause radiological opacities in the muscles of the chest wall.

### Schistosomiasis

#### The parasites and their epidemiology

Three species of *Schistosoma*, *S. mansoni*, *S. haematobium* and *S. japonicum*, are important causes of disease; they are endemic in 79 poorly developed countries and several hundred million people may be infected by one or other of them [74]. *S. mansoni* is found throughout Africa, the Arab countries, South America and some of the Caribbean, *S. haematobium* in Africa and the Middle East and *S. japonicum* in Japan, China and the Philippines. The organisms require fresh water and certain species of snail as intermediate hosts to complete their life cycles. Humans are the usual definitive host, although *S. japonicum* infects a wide variety of other exposed mammals.

Ova are excreted in the faeces or urine of humans. If they are shed into fresh water they hatch into ciliated miracidial larvae, which are able to penetrate the skin of an appropriate snail and develop into a sporocyst. This divides and the daughter sporocysts migrate to the snail's gut where they develop into cercarial larvae. These in turn are passed into the water where they swim freely and survive for several days. If during this time they come into

contact with the skin of humans, they are able to penetrate it and start the complex process whereby the life cycle is completed. Each cercaria that penetrates the skin is able to develop into one adult worm, of single sex, but not all survive the journey. On penetration, the cercaria transforms into a schistosomulum that passes into the bloodstream, through the pulmonary bed and the systemic circulation, eventually finding itself in the liver. There it develops into the adult worm and is able to migrate against the blood flow down the portal vein into the intestinal mucosa and, in the case of *S. haematobium*, through collateral vessels into the vesical venous plexus. Male and female worms mate at this site and produce enormous numbers of eggs. The mature worms may live and continue to produce eggs for many years, but the eggs need to reach the outside to restart the life cycle. A proportion of them succeed, by penetration of intestinal or bladder mucosa, but most become trapped in the local tissue or embolize in the bloodstream, setting up a granulomatous reaction that is responsible for the chronic manifestations of schistosomiasis.

### Clinical features

Penetration of the skin by cercariae, which occurs when the victim swims or bathes in fresh water in an endemic area, may cause itchy papules (swimmers' itch). This is a hypersensitivity reaction and occurs on second and subsequent exposures, though it is more common with species of *Schistosoma* that are natural pathogens of other mammals and birds. A month or two later, as the adult worms start to produce eggs, a generalized and sometimes severe episode analogous to serum sickness and called Katayama fever may occur. This also seems to be a delayed-type hypersensitivity reaction, characterized by fever, malaise, cough, aches, enlargement of liver, spleen and lymph nodes, and blood eosinophilia [75]. In massive *S. japonicum* infections this may be fatal.

Most people infected with *Schistosoma* spp. have no symptoms, the severity of disease being related to the number of worms harboured. Natural immunity does not occur, so reinfection may be frequent and such patients may develop chronic manifestations of schistosomiasis related to granuloma formation around eggs retained in tissues [76]. These lead to fibrosis, so that intestinal strictures and pseudotumours occur with *S. mansoni* and *S. japonicum* and bladder papillomas with ureteric and urethral obstruction occur with *S. haematobium*. Embolization of the portal tracts leads to periportal fibrosis, splenomegaly and portosystemic anastomoses. Systemic venous embolization leads to granuloma formation in pulmonary arterioles, which may cause solitary or multiple peripheral shadows on the chest radiograph or may lead to pulmonary hypertension and cor pulmonale [77–79]. This latter condition normally occurs as a compli-

cation of embolism of ova through portosystemic anastomoses in portal hypertension. The end-result of this can be aneurysmal dilatation of the pulmonary arteries and death from cor pulmonale. The bowel and bladder lesions are complicated by blood loss, obstructive syndromes and, in the case of *S. haematobium* infection, carcinoma of the bladder.

### Diagnosis and management

Schistosomiasis is diagnosed by finding ova in stools or urine. Since significant infection is always accompanied by the excretion of large numbers of ova, a negative finding by an experienced microscopist can be taken to exclude the diagnosis.

The infection is prevented by avoiding skin contamination by fresh water in endemic areas. Cercariae do not survive in water that has been stored more than 24 h or boiled. If the skin is contaminated, cercariae can only penetrate if it remains wet; rapid drying therefore prevents infection. There is no adequate treatment for swimmer's itch or for this initial stage of the infection. Severe Katayama fever may require suppression with corticosteroids, but it is doubtful if any antischistosomal drugs have any effect at this stage of the infestation. For chronic disease, praziquantel is effective against all species of *Schistosoma*: 40 mg/kg in one dose is adequate for *S. mansoni* and *S. haematobium* and 20 mg/kg for three doses in 1 day for *S. japonicum* [80].

Long-term control of schistosomiasis depends on improvements in disposal of urine and faeces, control of the snails by molluscicides and treatment of individuals with heavy infection. However, partial control in one area is often accompanied by spread in other areas associated with the introduction of irrigation schemes. The best hope for control is likely to be wide-scale treatment programmes and improvements in sanitation.

### Lung fluke

#### *Paragonimus* spp. and their epidemiology

There are many species of *Paragonimus* that infect humans and other flesh-eating vertebrates. The best-known is *P. westermani*, which is widely distributed throughout the Far East. Other species are found in Africa and Central and South America. The parasite is a fluke, about 1 cm in length, whose eggs are shed in the host's sputum (or faeces if the sputum is swallowed). They mature in fresh water to liberate miracidia that penetrate the first intermediate host, a snail. Several months later cercarial larvae emerge looking for a crab or crayfish. If successful, they penetrate it and form cysts in its gut and muscles. Transfer to humans or other vertebrates occurs when they eat the uncooked meat of the crustacean or drink its juices for

their supposed medicinal effect. Metacercariae excyst in the gut where the flukes develop, penetrate the wall into the peritoneum and migrate directly through diaphragm and pleura into the lung. They may go astray and end up in other tissues such as peritoneum, subcutaneous tissue, muscle or brain. Once established in the lung they reach sexual maturity and, being hermaphrodite, produce eggs. They may survive up to 10 years in the body.

### Clinical features

Many light infections are asymptomatic [81–83]. The most frequent symptoms are cough, sputum, haemoptysis and pleurisy, though the clinical features may sometimes result from involvement of subcutaneous tissues, brain or abdomen. There is blood eosinophilia and the chest radiograph may show a variety of signs, from transient infiltrates to cavities, single or multiple cysts and calcified nodules. Pleural effusions occur in almost half the patients and may be massive. CT may demonstrate multiple 5–15 mm cysts and evidence that is interpretable as worms in cysts and worm tracks [84].

### Diagnosis and treatment

The diagnosis may be suspected in someone with appropriate eating habits from an endemic area who has chronic cough, expectoration, eosinophilia and lung shadows. Increasing numbers of cases have been described in refugees to the West from South-East Asia, and the long survival of the parasite means that disease may present anywhere in the world long after leaving the site of infection. The diagnosis may be made by detection of the eggs in sputum or, occasionally, by finding an expectorated fluke. The discovery of the condition is credited to Sir Patrick Manson who when working as a young doctor in China had the curiosity to examine the sputum that a local mandarin had hawked up onto the carpet of his consulting room—a useful lesson to all doctors! However, in early or late cases eggs may not be found and complement fixation tests are generally a reliable means of confirming the diagnosis [81]. In patients with pleural effusion, the fluid should be examined for ova and detection of IgG and IgE specific to the parasite is probably a sensitive diagnostic test [85]. Treatment is with praziquantel 60 mg/kg daily in three divided doses for 1–3 days [86], together with aspiration of any pleural effusion.

### Hydatid disease

#### *Echinococcus granulosus* and its epidemiology

Humans are in the rather undignified position of being an accidental intermediate host for this parasite, whose ultimate destiny is normally to live in the intestine of the dog.

It occurs widely throughout the world, with the exception of Scandinavia, USA, Central and most of South America and West Africa. The adult worms are less than 1 cm long and very many of them may live in the jejunum of a dog. The ova are normally accidentally ingested by herbivores, although humans can do so after handling the dog or by eating contaminated vegetables. The eggs hatch in the duodenum and the embryos pass through the mucosa into portal vein or lymphatics, coming to rest predominantly in liver and lung. Each embryo then develops into a cyst, from the delicate inner membrane of which brood capsules arise. The hydatid cyst grows slowly but after a decade may contain 1 L or more of fluid. The fluid contains a granular material consisting of brood capsules, scolices budded from within brood capsules and daughter cysts. This fluid is the agent by which the life cycle is completed, when the organ containing it is eaten by a dog or other scavenging carnivores such as foxes and wolves. A closely related species, *E. multilocularis*, has a very similar life cycle but the intermediate host is usually a rodent. It is prevalent particularly in northern Canada and the former USSR.

### Clinical features

Hydatid disease occurs most commonly in areas where sheep are reared, such as Australia, New Zealand, Wales, Greece, North Africa and the Middle East. There is usually a history of contact with dogs. Cysts may occur in any organ but liver, lung and muscle are most commonly involved, with kidney, bone and brain occasionally being affected. The lesions grow steadily and, though many cause no symptoms, may eventually come to the patient's attention because they rupture or become infected or because of pressure effects.

Pulmonary lesions are usually incidental radiological findings. They present as spherical lesions with well-defined edges and of uniform density. They are frequently multiple and bilateral [87]. Rupture is accompanied by expectoration of salty-tasting fluid and the radiograph may then show a fluid level in the lesion, sometimes with the membrane floating on the surface to give the 'water-lily' sign (Fig. 22.4). Liver cysts may be present also and may be palpable as fluctuant lesions on the surface of the organ. Calcification in the walls of cysts may be seen radiologically.

Hydatid disease commonly presents as a result of complications of the presence of cysts, which may become infected or may rupture causing hepatobiliary, hepatobronchial or bronchopulmonary fistulae or pneumothorax [87–89]. Occasionally, rupture may provoke anaphylaxis and this is a well-recognized, though rare, complication of surgery of the cysts [88,90]. Rupture is also liable to cause seeding of daughter cysts through the pleura or peritoneum. Whether associated with anaphylaxis, infection



**Fig. 22.4** Multiple hydatid cysts in lungs of patient from Greece. The large cyst in the right mid zone shows the 'water-lily' sign.

or spread of disease, these complications carry a high risk of mortality.

### Diagnosis and management

The condition is suspected clinically in people from sheep-farming areas in contact with dogs and who show appropriate radiological signs. Occasionally, after pulmonary cyst rupture, scolices may be seen in the sputum. The traditional Casoni skin test using hydatid fluid is insufficiently specific or sensitive as a reliable diagnostic tool, although latex agglutination and complement fixation tests are useful for detecting the presence of antibodies.

In many cases, the lung lesions are only diagnosed definitively at surgery. In general, in view of the very serious effects of complications, all such lesions should be removed, although it has been suggested that the relatively benign variant endemic in north-west Canada causes few complications and may resolve spontaneously [91]. Uncomplicated cysts may be removed easily without lung resection; an incision is made in the outer false capsule and the complete cyst is expelled through it when the anaesthetist inflates the lung [90]. Many cysts may be removed in this way without any loss of lung. If the cyst has ruptured into a bronchus or become infected, lobar or segmental resection is necessary. Hepatic cysts also require surgical treatment, and the surgery of hepatopul-

monary rupture is complex [89,90]. There has been much debate about sterilizing cysts prior to surgery. Some authorities aspirate some fluid and replace it with dilute iodine, formaldehyde or silver nitrate solution. Others argue that this increases the risk of rupture. The best guarantee of success is probably the experience of the surgeon.

Intrapleural rupture constitutes an emergency, requiring tube drainage, antianaphylactic measures sometimes, and urgent thoracotomy to remove pleura and affected lobe after irrigation of the pleural space with formaldehyde. In the case of cyst rupture, the antihelmintic alben-dazole should be used in conjunction with surgical measures; doses of 10 mg/kg daily for 3–4 weeks may be necessary. The role of antihelmintics is not clearly established but there is now much evidence that they are capable of sterilizing cysts and curing some, though they are not always effective [92–94]. There seems to be a strong case for their use in cyst rupture, perisurgically [95] and where surgery is thought to be too risky.

Measures to prevent endemic hydatid disease have been successful in some countries, notably Iceland, Tasmania and New Zealand. These involve educating farmers and others to prevent access of dogs to offal.

### Cysticercosis

Cysticercosis is not a pulmonary disease, although the

elongated, ovoid, calcified lesions may occasionally be seen in the chest wall muscles on radiographs. The disease is acquired when humans inadvertently become the intermediate host for *Taenia solium*, the pork tapeworm. This may occur when ova excreted in infected faeces are swallowed or, possibly, from development of ova in the stomach of an infected person when gravid segments are regurgitated from the small bowel. The cysts lodge in tissues and may present in subcutaneous tissue, muscle and brain particularly. Clinical effects arise from central nervous system involvement, epilepsy being the most frequent result. Apart from appropriate symptomatic treatment, surgical removal may be tried. Drug therapy directed against the larval worm is probably of little value.

## Arthropod parasites

The only arthropods that parasitize the lungs of humans are the tongue worms of the class Pentastomida, *Linguatula serrata* and *Armillifer* spp. [96]. They have no external appendages other than two pairs of hooks by the mouth and thus resemble worms, a resemblance made all the more close in some species by the presence of rings on their bodies. The adult parasite is up to 2 cm long and lives in the respiratory tract and nasopharynx of wild

mammals. Ova may be shed in sputum or faeces and picked up by reptiles (especially snakes) or other mammals; the larvae are not species specific. The eggs hatch in the gut and the larvae burrow through into the peritoneum and tissues, encysting in muscle and liver particularly. If the host is then eaten, the cysts hatch and the developing adult migrates to the lungs and nasopharynx.

Humans may be the intermediate or definitive host. If the cysts in raw meat are ingested, what is probably an anaphylactic reaction develops, with acute nasopharyngeal inflammation, vomiting, cough and wheeze, known in the Middle East as halzoun [97]. The adults are capable of developing and may reach the lung where they cause a granulomatous reaction that leads to fibrosis and calcification and where the organism is usually an incidental finding [98–100]. Infection with *Linguatula* has been reported in Europe and the Middle East, whereas *Armillifer* infections occur quite commonly in tropical areas. Infection can be avoided by not eating uncooked meat—raw snake meat in Africa and Malaysia is apparently an important source of infection! In general, no treatment is required except for anaphylactic reactions, when epinephrine (adrenaline) and hydrocortisone may be necessary.

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# CHRONIC BRONCHITIS AND EMPHYSEMA

WILLIAM MACNEE

## Definitions and terminology

There is no universally accepted terminology or definition for the group of conditions characterized by airways obstruction that is incompletely reversible [1]. There are several problems that have to be considered. The first results from the use of the term 'chronic obstructive pulmonary disease' (COPD), which is considered inaccurate since this is not truly a disease but a group of diseases. The second relates to the British preference for the terms 'chronic bronchitis' and 'emphysema', which although describing two conditions with an apparently more precise clinical or pathological definition, lack any reference to airways obstruction in their definitions. The third problem, which is the most difficult to resolve, is the concern over differentiating this condition from asthma, which the terms 'chronic bronchitis' and 'emphysema' seem to do whereas this is not the case for COPD. In all the recent consensus statements from scientific societies, COPD is the term used and is considered as a separate condition from asthma [2–4]. This latter problem is compounded by the fact that the persistent airways obstruction in older chronic asthmatics is often difficult or even impossible to differentiate from that in COPD, although a history of heavy cigarette smoking, evidence of emphysema by imaging techniques, decreased diffusing capacity for carbon monoxide and chronic hypoxaemia favour a diagnosis of COPD [3].

*Chronic bronchitis* is defined as the presence of a chronic productive cough on most days for 3 months, in each of two consecutive years, in a patient in whom other causes of chronic cough have been excluded [5]. *Emphysema* is defined as abnormal, permanent enlargement of the distal airspaces, distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis [6]. Thus chronic bronchitis is defined in clinical terms, whereas emphysema is defined pathologically.

A group of synonyms have arisen, which in the UK include chronic obstructive bronchitis or chronic bronchitis with airways obstruction; in the USA, COPD, chronic

obstructive airways disease (COAD) and chronic obstructive lung disease are favoured. However, the term 'chronic bronchitis and emphysema' has often been used loosely to define a patient with chronic cough and associated airflow obstruction, although airflow obstruction does not appear in the definition. The most widely used term is COPD, which has been accepted in the British Thoracic Society (BTS) guidelines on the management of this condition [4] and is the title of a major British textbook on the subject [7].

Chronic bronchitis has been classified into three forms: simple bronchitis, defined as hypersecretion of mucus; chronic or recurrent mucopurulent bronchitis in the presence of persistent or intermittent mucopurulent sputum; and chronic obstructive bronchitis when chronic sputum production is associated with airflow obstruction. The use of the term 'chronic obstructive bronchitis' arose from the 'British hypothesis' that persistent recurrent infection, and thus chronic sputum production, resulted in damage to the airways and hence airways obstruction. However, the term has never found favour outside the UK.

As with chronic bronchitis, the definition of emphysema does not require the presence of airflow obstruction. Many studies in the past have attempted to predict the presence and extent of emphysema in life. However, the use of respiratory function tests and the assessment of pulmonary emphysema by plain chest radiography is imprecise [8]. Furthermore, attempts to determine the relative contribution made by airway abnormalities or distal air-space enlargement to the airways obstruction in an individual patient with COPD has proved elusive. Thus in the UK, in clinical practice the terms 'chronic bronchitis and emphysema' were used to describe patients, current or ex-smokers, who did or did not produce sputum chronically but who had persistent breathlessness and chronic airways obstruction. In contrast, in the USA in the early 1960s the term COPD was introduced to describe patients with largely irreversible airways obstruction due to a combination of airways disease and emphysema, without defining the contribution of these conditions to the airways obstruction. However, the wheel has now come

full circle since the BTS has now adopted the term COPD and produced guidelines for the treatment of this condition [4].

The guidelines published by the American Thoracic Society (ATS) define COPD as 'a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway reactivity, and may be partially reversible' [2]. The European Respiratory Society (ERS) has adopted a similar definition: 'a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs; features which do not change markedly over several months' [3]. The definition adopted by the BTS is similar: 'a slowly progressive disorder characterized by airways obstruction (reduced  $FEV_1$  and  $FEV_1/VC$  ratio), which does not change markedly over several months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilator (or other) therapy' [4].

The BTS guidelines suggest that a diagnosis in clinical practice is usually associated with:

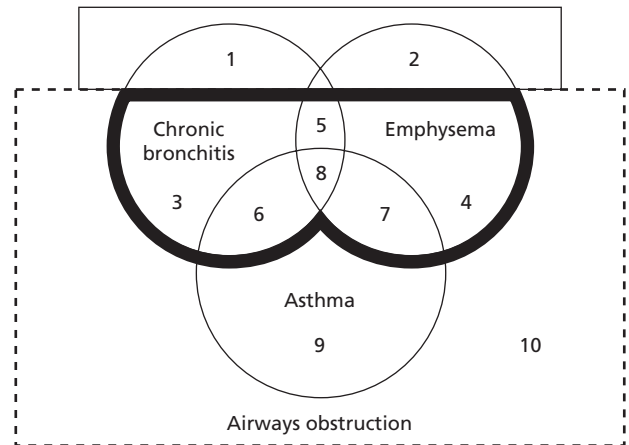
- 1 a history of chronic progressive symptoms (cough, wheeze and/or breathlessness), with little variation;
  - 2 usually a cigarette smoking history of greater than 20 pack-years (1 pack-year is equivalent to smoking 20 cigarettes a day for 1 year);
  - 3 objective evidence of airways obstruction, ideally by spirometry, that does not return to normal with treatment.
- A number of specific causes of chronic airways obstruction are not included in the term COPD, such as cystic fibrosis, bronchiectasis and bronchiolitis obliterans (e.g. associated with lung transplantation and chemical inhalation). The differentiation of COPD from asthma remains a problem, particularly as a large proportion of patients with COPD show some improvement in airflow obstruction with bronchodilators. However, in clinical practice the definition is less important than assessing whether patients show reversibility of their airways obstruction, since this influences their management.

Snider has popularized the use of a Venn diagram that shows the relationships between chronic bronchitis, emphysema and asthma (Fig. 23.1).

## Epidemiology

### Prevalence

Hypersecretion of mucus is a symptom that has been extensively studied in general population surveys over the last 40 years. In these studies, usually in middle-aged men, the prevalence of chronic cough, or chronic cough and the production of sputum, ranges between 15 and 53%, with a lower prevalence of 8–22% in women, being more prevalent in urban than rural areas [9,10]. The most



**Fig. 23.1** A non-proportional Venn diagram describing the relationship between patients with chronic bronchitis, emphysema and asthma. The broken line rectangle includes all patients with airflow obstruction. Patients in subsets 1 and 2 have clinical or radiological features of chronic bronchitis or emphysema but do not have airflow obstruction and thus have a normal forced expiratory volume in 1 s ( $FEV_1$ ) and  $FEV_1$ /forced vital capacity ratio. These patients are not classified as having chronic obstructive pulmonary disease (COPD). Patients in subsets 6–8 have partially reversible airflow obstruction. Subsets 3, 4 and 5 have no significant reversibility and patients in subset 8 have features of all three disorders. Those in subset 9 have completely reversible airflow obstruction and thus have asthma. Those in subset 10 have airflow obstruction due to specific pathology such as cystic fibrosis, bronchiectasis or obliterative bronchiolitis. Patients with COPD are those patients within the thick shaded band. (After Snider [1].)

recent study in the late 1980s showed a decline in the prevalence of chronic cough and phlegm in middle-aged men to 15–20%, with little change in women [10]. This compares with a prevalence of approximately 4% in these symptoms in people who have never smoked. Smoking low-tar cigarettes results in less cough and phlegm than smoking high-tar cigarettes [11].

Prevalence studies of COPD are normally based on values of percentage predicted forced expiratory volume in 1 s ( $FEV_1$ ), which defines individuals with and without airways obstruction. In the UK in a survey in 1987 of a representative sample of 2484 men and 3063 women in the age range 18–64 years, 10% of men and 11% of women had an  $FEV_1$  greater than 2 standard deviations (SD) below their predicted values, the numbers increasing with age, particularly in smokers [12]. In current smokers in the age range 40–65, 18% of men had an  $FEV_1$  greater than 2 SD below normal and 14% of women compared with 7% and 6% of non-smokers respectively.

Studies from the USA, which used a cut-off  $FEV_1$  of less than 65% of the predicted value, provide similar figures, with prevalence falling in men from 8% in the 1960s to 6% in the late 1970s, whereas the 3% prevalence in women did not change over this period [13]. National surveys of con-

Diagnosis	Age	Men (per 1000)			Women (per 1000)		
		1955–56	1970–71	1981–82	1955–56	1970–71	1981–82
Chronic bronchitis	45–64	32.7	29.6	12.3	12.9	12.0	6.7
	65–74		73.8	37.9		23.5	13.6
Emphysema and COPD	45–64	3.1	3.4	6.5	0.2	0.5	3.0
	65–74		11.1	26.2		1.5	7.8

**Table 23.1** Annual general practitioner consultations for chronic respiratory disease in the UK 1955–56, 1970–71 and 1981–82. (From Strachan [14].)

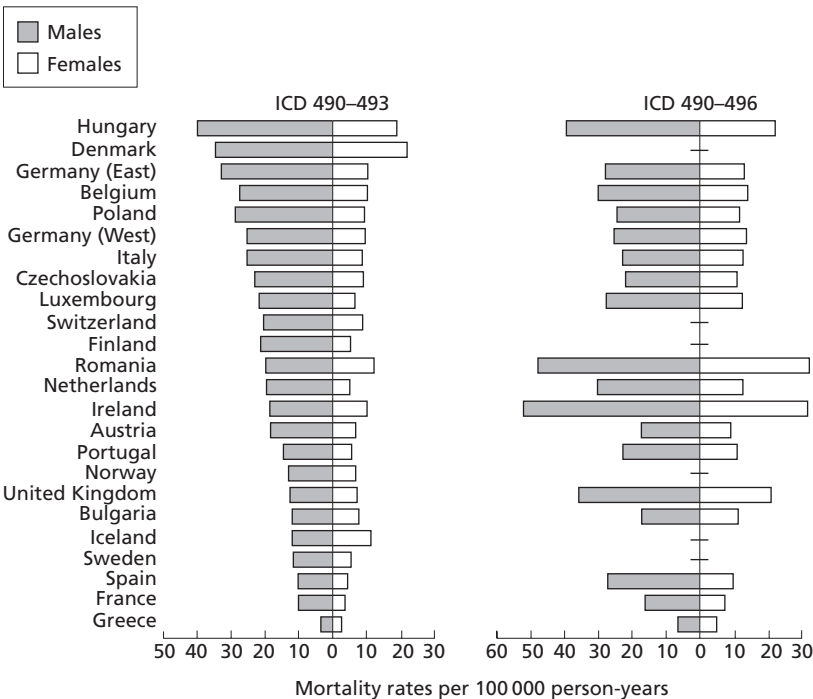
sultations in British general practices have shown the changes in prevalence of clinically diagnosed chronic bronchitis, emphysema and COPD over the last 40 years (Table 23.1). These data show a modest decline in the number of middle-aged men consulting their GP with symptoms suggestive of COPD and a slight increase among middle-aged women. These trends are confounded by changes over the years in the application of the diagnostic labels for this condition, particularly the overlap between COPD and asthma [15].

**Mortality**

There are large international variations in the death rate for bronchitis, which cannot be entirely explained by differences in diagnostic patterns and labels or by differences in smoking habits [16]. Certified cause of death can be misleading, particularly where pneumonia is often used as the underlying cause of death. Furthermore, chronic bronchitis

and emphysema or COPD is often a contributory factor to the cause of death. It is likely therefore that the use of death rates from certification of these conditions underestimates the true mortality due to COPD. Most of the mortality from this condition occurs in the over-65 age group. The highest death rates for COPD among the developed countries occur in the UK, eastern Europe and Australia, with low rates in southern Europe, Scandinavia and Japan [16]. In 1984 British death rates for COPD for both sexes were exceeded only by Romania. As mentioned above, international comparisons of mortality are complicated by the use of different diagnostic labels. In the UK, chronic bronchitis (International Classification of Disease (ICD)-8 and ICD-9, 491) was the common certification of such deaths until a separate code for chronic airways obstruction not elsewhere classified was introduced in 1978 (ICD-8,591; ICD-9, 496), thereafter termed COAD and which has been used increasingly (Fig. 23.2).

Within the UK, age-adjusted death rates from chronic



**Fig. 23.2** Age-standardized mortality rates in Europe 1988–91 for chronic obstructive pulmonary disease (COPD). ICD-9, 490–496 describes COPD and similar conditions. Shaded bars to the left indicate mortality rates in males; White bars to the right indicate mortality rates in females. (From Siafakas *et al.* [3] with permission.)

respiratory diseases vary by a factor of more than five in men and more than 10 in women in different geographical locations [17]. Mortality rates tend to be higher in urban areas than rural areas and there is a trend for higher rates in South Wales and Scotland independent of urbanization. Mortality from chronic respiratory disease (ICD-9, 490–493 and 496) in males aged 55–84 years has been falling, except in the oldest age group over 75 years of age. In the USA, similar trends have been recorded in males, whereas in women the mortality is one-third that of males; the decline in mortality, which was recorded until 1975, has since then shown a slight increase in women over the age of 65 years [18]. These trends presumably relate to the differences in the time of the peak prevalence of cigarette smoking in men and women, which occurred later in women. In England and Wales in 1992 there were 3873 deaths certified as due to chronic bronchitis, 1946 due to emphysema, 1791 due to asthma and 19963 due to COAD [17]. Together these accounted for 6.4% of all male deaths and 3.9% of all deaths in females [17]. Similar percentages of the total death rates occurred for COPD in Scotland.

### Social class

The association between respiratory diseases and social class in the UK is well recognized. Data from the 1981 census showed that standardized mortality ratios for chronic bronchitis, emphysema and asthma were three to six times greater in social classes 4 and 5 compared with social classes 1 and 2 [19]. These social class trends in men are also apparent in women (classified by their husbands' occupation), suggesting that occupational exposure does not explain these socioeconomic differences. In addition, smoking only partly explains these trends in mortality related to socioeconomic status, since population surveys have shown associations between spirometry or decline in spirometry and socioeconomic status that are independent of current smoking habit [12].

There is evidence, from a national follow-up to adult life of a cohort born in 1946, of a strong association between social deprivation in childhood, particularly domestic overcrowding, and ventilatory capacity and cough, suggesting that conditions in early life influence the development of chronic respiratory disease in adulthood [20].

### Morbidity and use of health resources

COPD places an enormous burden on healthcare resources [10]. Table 23.2 gives an estimate of the annual workload in primary and secondary care attributable to COPD and its associated conditions in an average UK health district with a population of 250 000. It has been calculated that chronic bronchitis and emphysema, COPD and asthma account for 24.4 million working days lost per year, which represents 9% of all certified sickness absence among men; the equivalent figures for women are 3.1 million working days lost, 3.5% of the total certified sickness absence [21]. Respiratory diseases in the UK rank as the third most common cause of days of certified incapacity, COPD accounting for 56% of these days in males and 24% in females [22].

### Aetiology

#### Chronic hypersecretion of mucus and persistent airflow obstruction

The landmark studies of Fletcher and colleagues [23] indicate that although both chronic hypersecretion of mucus and progressive, persistent airflow obstruction occur in cigarette smokers, their influence on survival is quite distinct. These features arise from abnormalities in different lung sites. The persistent cough and sputum production results from bronchial gland enlargement in the proximal conducting airways and improves following cessation of cigarette smoking, whereas the persistent airflow obstruction arises from damage to the peripheral airways and airspaces and is persistent after the cessation of cigarette smoking.

Population studies of respiratory symptoms show a much higher prevalence of cough and sputum among smokers compared with non-smokers. Indeed the presence of chronic bronchitis has been almost confined to cigarette smokers. For example, a survey in urban and rural populations in the UK found a history of chronic bronchitis in 17.6% of males aged 55–64 who were heavy smokers, in 0.9% of light smokers, in 4.4% of ex-smokers and in no non-smokers [24].

Pipe and cigar smokers have a much lower prevalence of chronic bronchitis and less impairment of respiratory

**Table 23.2** Estimated annual health service workload due to chronic respiratory disease in an average UK health district serving 250 000 persons. (Modified from Anderson *et al.* [10].)

	Hospital admissions	Inpatient bed-days	General practice consultations
Chronic bronchitis	100	1500	4400
Emphysema and COPD	240	3300	2700
Asthma	410	1800	11900
Total	750	6600	19000

function, despite a similar capacity for cigarette smoke and cigar smoke to cause bronchial reactivity [25]. This may reflect lower rates of smoke inhalation in pipe and cigar smokers. Filter-tip cigarettes also have less propensity to incite cough and sputum production [26].

Fletcher and colleagues [23] demonstrated that around 20% of male cigarette smokers aged 50 had an  $FEV_1$  within 2 SD of their normal value. If a smoker stops smoking, then in 90% the sputum production ceases [27]. These studies emphasized the dissociation between chronic persistent cough and phlegm and airflow obstruction. In an 8-year prospective study of working men in West London, Peto and coworkers [28] were unable to demonstrate an independent correlation between the degree of hypersecretion of mucus and an accelerated decline in  $FEV_1$ , after the data were adjusted to account for age, smoking and the absolute value of the  $FEV_1$ . There was also no association between hypersecretion of mucus and mortality. By contrast, morbidity and mortality in COPD are strongly related to the development of low  $FEV_1$  (Fig. 23.3). Recent data from Denmark suggest that the concept of a lack of association between sputum production and decline in  $FEV_1$  may have to be revised [29].

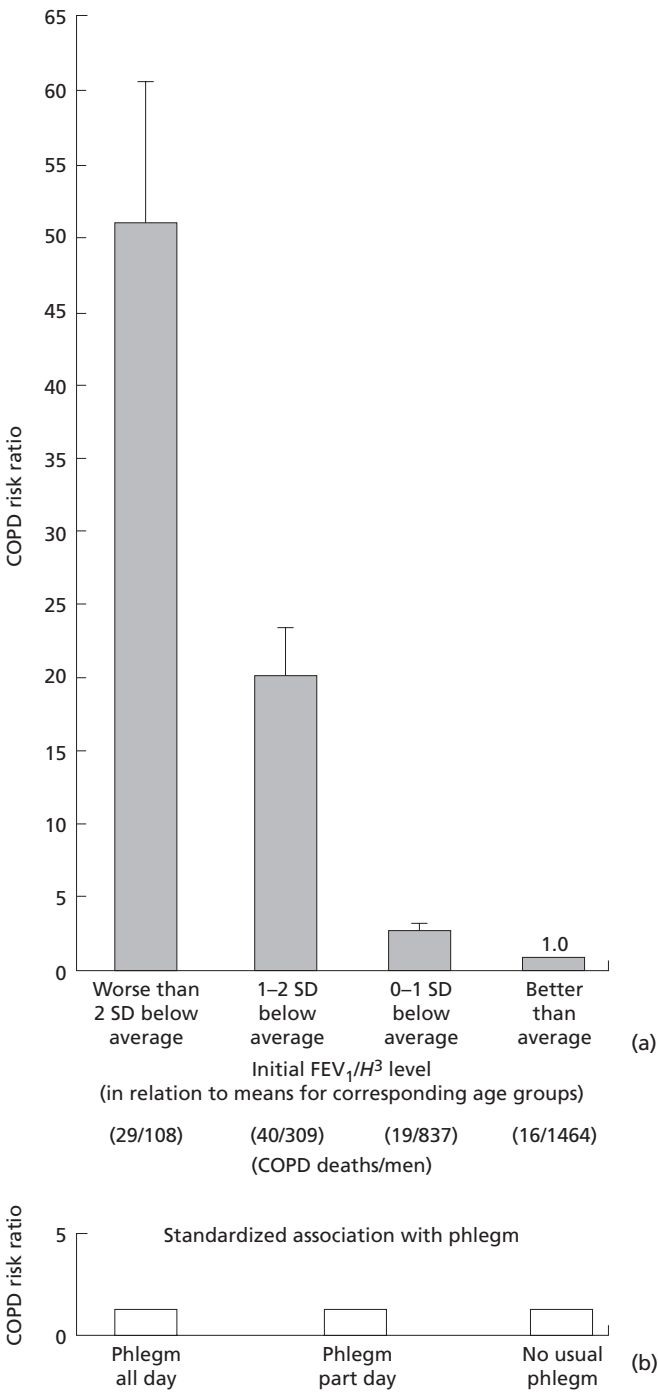
**Risk factors**

Cigarette smoking is clearly the single most important identifiable aetiological factor in COPD. However, only 10–20% of smokers develop clinically significant COPD, while approximately half never develop a clinically significant physiological deficit [30,31]. The factors that identify the cigarette smoker susceptible to the development of progressive airflow obstruction are still a matter of much debate and research. Since there is a strong association between a low  $FEV_1$  and both morbidity and mortality in COPD, risk factors are usually assessed by studying the relationship with mortality or with accelerated annual decline in  $FEV_1$ .

**Cigarette smoking**

The evidence that tobacco smoking is the most important aetiological factor in COPD is overwhelming [32,33]. The greater the total tobacco exposure, the greater the risk of developing COPD [30] (Fig. 23.4). Pipe and cigar smokers have higher morbidity and mortality rates for COPD than non-smokers, although their rates are lower than cigarette smokers [30]. Although it is generally regarded as the dominant risk factor, cigarette smoking is not a prerequisite in all definitions of COPD [2,3] since COPD can occur in non-smokers, such as patients with  $\alpha_1$ -antitrypsin deficiency [34]. However, the BTS guidelines suggest that most patients with COPD have at least a 20 pack-year smoking history [4].

On average, cigarette smokers have a high annual rate of decline in  $FEV_1$  of about 50 mL, which is nearly double



**Fig. 23.3** Risk ratios for death from chronic obstructive pulmonary disease: (a) according to initial value of height-corrected forced expiratory volume in 1 s ( $FEV_1/H^3$ , where  $H$  is height in metres) at survey 20–25 years previously (bars indicate standard errors); (b) according to presence of phlegm after standardization for  $FEV_1/H^3$ . (Modified from Peto *et al.* [28] with permission.)

the average value of 30 mL annually present in non-smokers. However, there is considerable variation in the decline in  $FEV_1$ , with some smokers showing very rapid rates of decline. In non-smokers the  $FEV_1$  begins to decline

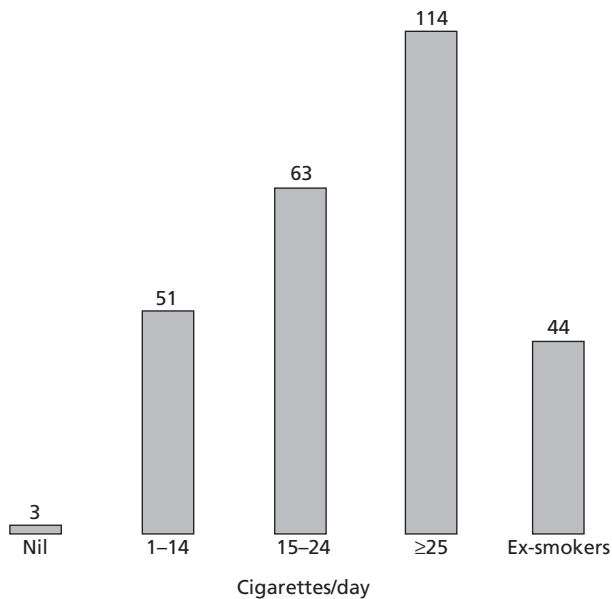


Fig. 23.4 Death rates due to bronchitis in British male doctors per 100 000 according to smoking habit. (Data from Doll & Peto [38].)

at 30–35 years of age, and this may occur earlier in smokers [35]. The decline in  $FEV_1$  may be faster early in the natural history of the disease before COPD is established [36]. Stopping cigarette smoking does not produce a substantial improvement in  $FEV_1$  but the subsequent rate of decline is decreased [23,37]. This was clearly shown in the Lung Health Study where the decline in  $FEV_1$  slowed in those smokers who quit smoking [37] (Fig. 23.5). There is a less striking relationship between annual decline in  $FEV_1$  and the reported daily number of cigarettes smoked, since there is wide variation in the annual rate of decline among smokers with the same smoking history [38]. In broad terms, however, mortality from COPD is twofold greater in those who smoke more than 25 cigarettes a day compared with those smoking fewer than 15 cigarettes a day.

There are other confounding factors that complicate the relationship between numbers of cigarettes smoked and rate of decline in  $FEV_1$ . These are the extent to which cigarette smoke is inhaled and the tar, nicotine and other constituents [11]. Although a reduction in the tar content of the cigarettes smoked reduces hypersecretion of mucus [37], it has a small, if any, effect on the progression of airflow obstruction and any improvement may be outweighed by a change in the pattern of the number of cigarettes smoked [35].

The most important evidence associating smoking and mortality from bronchitis is that from the studies of Doll and Peto [38]. In a study mainly determining the aetiology of lung cancer, 40 000 medical practitioners in the UK recorded their smoking habits. The cause of death was determined later in those who died during the follow-up period. In this study the death rate for chronic bronchitis

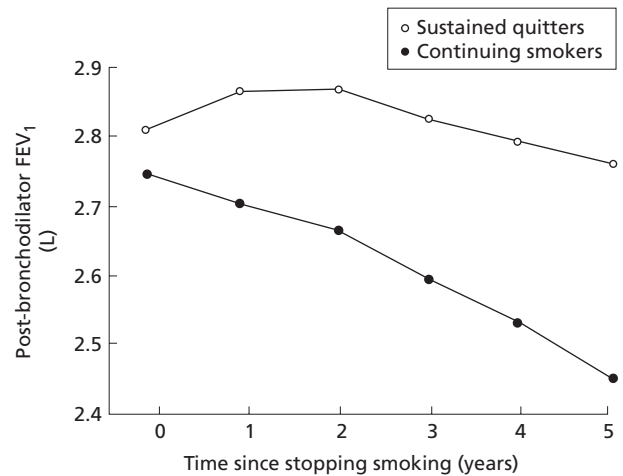


Fig. 23.5 Mean forced expiratory volume in 1 s ( $FEV_1$ ) after bronchodilator in subjects in the Lung Health Study who were sustained quitters and those who continued to smoke. (From Anthonisen [37] with permission.)

was significantly higher in cigarette smokers than in non-smokers and increased with the amount smoked. In those who stopped smoking, the mortality 10 years on was well below that for all smokers. In male doctors aged 35–64, mortality from chronic bronchitis between 1953–67 and 1971–75 fell by 24% compared with a fall of only 4% in other men in the UK of the same age. This difference was attributed to the decrease in smoking in doctors compared with an overall increase in smoking in the general population [39]. Similar results to the UK study have been published in other population studies in the USA [40] and in a 20-year follow-up study of female British doctors [41].

The effects of smoking cessation on mortality have been less clear. Randomized controlled trials fail to demonstrate a unequivocal benefit in terms of respiratory mortality from stopping smoking [36,42]. In one study on smoking habits, fewer deaths from emphysema occurred in smokers of lower tar cigarettes than in smokers of medium- or high-tar cigarettes [43].

### Passive smoking

In view of the weak but statistically significant association between lung cancer in people who have never smoked and environmental tobacco smoke, or 'second-hand smoke' exposure [44], a relationship between passive smoking and the development of chronic airflow obstruction might also be expected. This relationship has been examined using case-control studies [45,46] and a cohort study [46]. These studies show a trend towards an increased relative risk from passive smoking, similar to that of lung cancer but not powerful enough to demonstrate statistical significance.

Passive smoking does not appear to have a convincing



effect on pulmonary function in middle-aged adults [48]. However, in a study of young adult non-smokers, cumulative lifetime exposure to environmental tobacco smoke during childhood was associated with significantly lower peak levels of FEV<sub>1</sub> in adulthood [49]. Maternal smoking in pregnancy is associated with low birthweight [50] and smoking by either parent is associated with an increased incidence of respiratory illnesses in the first 3 years of life [48]. Studies of the relationship between parental smoking and lung growth in childhood have produced inconsistent findings [51,52].

Increased airways resistance occurs after smoking only one cigarette [53]. This can be blocked by atropine, suggesting that it could be an irritant receptor reflex-induced phenomenon [54].

### Air pollution

Interest in air pollution as a risk factor in chronic respiratory disease was stimulated by the London smog of December 1952 [55], to which 4000 excess deaths due to cardiorespiratory disease were attributed among the elderly, particularly those with poor cardiorespiratory reserve. Several studies in the 1950s, 1960s and early 1970s produced evidence incriminating air pollution as an aetiological factor in COPD, including:

- 1 the association, in the UK, between increasing mortality and prevalence of COPD and increasing urbanization [56,57];
- 2 the close association between atmospheric pollution and mortality from COPD both geographically and temporarily [58];
- 3 the demonstration that post office employees in foggy areas showed a higher rate of invalidity than those working in less foggy areas [59];
- 4 the increase in reported symptoms of chronic bronchitis in areas of increased air pollution [60];
- 5 a higher prevalence of emphysema in autopsy studies in areas with greater pollution [60].

The introduction of the Clean Air Acts (1956, 1965) led to a reduction in smoke and sulphur dioxide levels during the 1960s, which produced less discernible peaks of pollution related to morbidity and mortality compared with the 1950s [60]. In 1992, a World Health Organization (WHO) expert committee on air pollution [61] concluded that high concentrations of sulphur dioxide (150 µg/m<sup>3</sup>) or similar concentrations of particulate air pollution, measured as black smoke, were associated with increased morbidity in terms of symptoms and hospital admissions in adult patients with COPD. Levels of sulphur dioxide or black smoke in excess of 500 µg/m<sup>3</sup> would be expected to increase mortality among the elderly and those with poor cardiopulmonary reserve. Thus there was a belief that current air pollution, generally at lower levels even in urban areas in the UK, had no influence on the morbidity

and mortality from COPD. More recent studies, particularly from the USA, have cast doubt on this conclusion and indicate an association between respiratory symptoms in patients with airways disease, clinician consultations or hospital admissions with airways diseases and levels of particulate air pollution (black smoke) below 100 µg/m<sup>3</sup>, levels currently experienced in many urban areas of the UK [62]. Furthermore, levels of particulate air pollution are associated with deaths from all causes, particularly cardiorespiratory deaths [63].

There appears to be no threshold for the association between particulate air pollution and mortality. It is interesting that the last of the great London smogs, which occurred in the winter of 1962–63, produced an increased morbidity and mortality from bronchitis but to a level less than in 1952. The sulphur dioxide concentrations were similar in both years but the smoke concentrations were much lower in 1962 and so was the associated respiratory mortality [64]. This evidence, and the fact that the association between particulate air pollution and respiratory morbidity and mortality was demonstrated in such diverse locations as Utah (where the particulate air pollution is derived mainly from a steel mill) and Los Angeles (where it is largely motor vehicle exhaust), led to the suggestion that the composition of the particulate pollution was not the critical factor [63].

One hypothesis is that the fine particles in air pollution, with an aerodynamic diameter of less than 10 µm (PM<sub>10</sub>), or the ultrafine particles, which have a diameter in the nanometer range, may have properties related to size, acidity or ability to generate oxidants that increases the permeability of the airway epithelium [65]. This may contribute to airway inflammation, which may lead to a pro-coagulant state and hence to the increased cardiovascular mortality that has been shown to be associated with increased levels of environmental particulate air pollution [63].

Although there have been associations between exacerbations of airways diseases and photochemical air pollutants, such as nitrogen dioxide and ozone, this association has been largely confined to patients with asthma [66]. There are no studies showing an association between ozone and deaths from respiratory diseases [66]. There is an association between environmental nitrogen dioxide levels and short-term effects on symptoms or pulmonary function, both from laboratory and community-based studies of patients with chronic respiratory diseases [67]. There are a few longitudinal studies on the effects of air pollution on the decline in lung function. However, a study of a population born in 1946, who would have been exposed to high levels of smoke and sulphur dioxide in childhood, was unable to demonstrate a major effect of exposure to air pollution in childhood and the later development of chronic bronchitis on measurements of peak expiratory flow rate in this population's fourth decade



[68]. By contrast, in a study from Sheffield, where there has been a substantial decrease in the formerly very high levels of air pollutants, patients in the later less-polluted period had less productive cough, fewer winter illnesses, less severe breathlessness and only one-third the rate of decline of FEV<sub>1</sub> compared with those studied in the earlier highly polluted period [69].

### Protease inhibitor deficiency

$\alpha_1$ -Antitrypsin ( $\alpha_1$ -AT) or  $\alpha_1$ -protease inhibitor ( $\alpha_1$ -Pi) is a polymorphic glycoprotein responsible for the majority of the antiprotease activity in the serum [70]. Laurell and Eriksson [71] in 1963 were the first to describe the association between  $\alpha_1$ -AT deficiency and the development of early-onset emphysema. Their initial discovery of the absence of the  $\alpha_1$  band in a number of sera on routine electrophoresis led to the observation that three of the original five subjects with this abnormality had severe early-onset emphysema. Later the clinical, biochemical and genetic features were described in detail by Eriksson, showing that the abnormality was transmitted as an autosomal recessive gene [72].

Since the discovery of the deficiency, over 75 biochemical variants have been described. The commonly recognized alleles are designated by capital letters relating to their electrophoretic properties, which gave rise to the phase inhibitor or Pi nomenclature, e.g. PiZ. The commonest allele in all populations is PiM and the most common genotype is PiMM, which occurs in around 86% of the UK population. PiMZ and PiMS are the next two most common genotypes and are associated with  $\alpha_1$ -Pi levels of 50–75% of the mean levels of PiMM subjects, as is the much less common PiSS type. The homozygous PiZZ deficiency, in which serum levels are 10–20% of the average normal value, is the strongest genetic risk factor for the development of emphysema and the associated airflow obstruction and forms the basis of the proteolytic theory of the pathogenesis of emphysema [73]. The most important other type is PiSZ, where basal levels are 35–50% of normal values. A few rare variants that result in complete functional absence of  $\alpha_1$ -Pi account for the remainder of the severely deficient patients.

In the USA, studies in which adult blood donors were screened identified a 1 in 2700 prevalence of PiZZ subjects, of whom most had normal spirometry [74]. It has been calculated that about 1 in 5000 children in the UK are born with the homozygous deficiency (PiZZ) [75]. However, the number of identified subjects with disease is much less than predicted from the known prevalence of the deficiency [76]. Therefore it is by no means inevitable that all individuals with a homozygous deficiency develop respiratory disease. Indeed a few identified PiZZ individuals live beyond their sixth decade and escape the development of progressive airways obstruction [77].

The incidence of  $\alpha_1$ -Pi deficiency in a population study of patients presenting with COPD was 1–2% [78] but rises to greater than 50% in patients with severe disease who are less than 40 years of age [79]. Prospective follow-up of PiZZ subjects has shown a greatly accelerated decline in FEV<sub>1</sub>, but with large variations between individuals [80]. There is a clear interaction with cigarette smoking, although this cannot entirely account for the variation in decline in FEV<sub>1</sub> observed among individuals. Life expectancy of subjects with  $\alpha_1$ -Pi deficiency is significantly reduced, especially if they smoke [76].

The onset of dyspnoea and death occur at a younger age in smokers with  $\alpha_1$ -Pi deficiency. In a study of deficient subjects in New Zealand, dyspnoea began on average at age 32 years in smokers compared with 51 years in non-smokers. The mean age at death in this group was 48 years for smokers and 67 years for non-smokers with PiZZ [81].

### Occupation

It is generally accepted that there is a causal link between occupational dust exposure and the development of mucous hypersecretion [82]. However, the relationship, particularly in coal-miners, between the development of airways obstruction and dust exposure at work has been controversial [83]. Cigarette smoke has been a confounding factor since the prevalence of smoking remains disproportionately high in many workers exposed to dust at work. The problem is compounded by the fact that only 20% of smokers develop COPD, that there may be an interaction between cigarette smoking and dust exposure, and that workers in dusty occupations often live in areas of high air pollution.

Longitudinal studies by Becklake [82] on workforces exposed to dusts or gases only, or a combination of the two, show an association with dust exposure resulting in a more rapid decline in FEV<sub>1</sub>. Cross-sectional studies in the general population of single measurements of ventilatory function and symptoms by questionnaire have limitations but show a relationship between impairment of ventilatory function and exposure to dusts [84]. Longitudinal studies of British coal-miners indicate a relationship between the exposure to dust and the development of a small excess longitudinal decline in FEV<sub>1</sub> [85–87] and increased mortality [88]. The risk of disabling loss of ventilatory function (defined as a mean loss in FEV<sub>1</sub> of 942 mL, which occurred in the miners with disabling symptoms) is less than 5% among non-smoking miners with low cumulative exposures to coal dust (<100 mg/h/m<sup>3</sup>), but increases exponentially to 20% in those with heavy cumulative exposures (500 mg/h/m<sup>3</sup>). Smoking also appears to enhance the effect of increasing dust exposure levels and the risk of developing COPD.

The accumulating evidence for an association between

coal-dust exposure and the development of COPD led recently in the UK to the establishment of COPD as a disease considered for compensation in miners. The criteria for compensation are work underground for at least 20 years and a reduction in FEV<sub>1</sub> of at least 1 L from the predicted value [83].

A small but significant effect of exposure to welding fumes and the development of COPD was shown in a study of shipyard workers [89]. Workers exposed to cadmium can develop emphysema and hence COPD [90]. Cadmium is also a trace component of cigarette smoke. Since cumulative exposures to cadmium through smoking are not likely to approach those achieved occupationally, smoking-induced emphysema cannot be attributed to cadmium.

### Chronic bronchopulmonary infection

In the 1950s it seemed reasonable to hypothesize that since patients with chronic bronchitis often had bacteria in their sputum [91], recurrent bronchopulmonary infections would result in damage to the airways and progressive airways obstruction. Thus a 'British hypothesis' was developed which stated that smokers who had chronic hypersecretion of mucus were at risk of bronchopulmonary infections, which caused airway damage and progressive airways obstruction. However, studies in the 1960s and 1970s in men with chronic bronchitis demonstrated that prophylactic antibiotics to prevent recurrent infective exacerbations did not slow the decline in lung function [92,93]. Furthermore, Fletcher and colleagues [23,28], in their 8-year prospective study of working men in West London, showed that neither hypersecretion of mucus nor bronchial infection caused a more rapid decline in FEV<sub>1</sub> after adjusting for age, smoking and the level of FEV<sub>1</sub>. However, acute bronchopulmonary infection did show an association with an acute decline in lung function, which may persist for several weeks but which usually recovered completely.

Many studies from both western Europe and North America have shown a relationship between a low FEV<sub>1</sub> and an increased risk of death from COPD [94,95]. Although some studies have shown a low risk of death from COPD in relation to hypersecretion of mucus [96,97], others have found more important risk-ratios of up to three- to four-fold [29,94], though still less important than the effect of FEV<sub>1</sub> [28].

Although studies in the general population and in smokers failed to demonstrate a strong association between the annual rate of decline in FEV<sub>1</sub> and recurrent bronchopulmonary infection, these studies have been in smokers with only mild impairment of lung function. Therefore the results can only be applied to this group and not to the group of patients with established and more severe COPD, in whom recurrent bronchopulmonary

infections are more frequent. Indeed, one study in Salt Lake City did find an association between lower respiratory tract infection and an accelerated decline in FEV<sub>1</sub>, but in a group who already had established COPD [97]. Furthermore, in a large community study in Copenhagen, Lange and coworkers [29] found that hypersecretion of mucus was associated with a fourfold greater relative risk of death from COPD if the FEV<sub>1</sub> was 40% of predicted compared with a group of individuals whose FEV<sub>1</sub> was 80% of predicted.

Intraluminal airspace inflammation is a characteristic of chronic bronchitis [98–101]. Peripheral blood white cell count, which is 30% higher in smokers than non-smokers, has an inverse relationship with FEV<sub>1</sub> [102,103]. The relationship between peripheral leucocyte cell count and FEV<sub>1</sub> is perhaps more complex than the association of respiratory infection, since peripheral white cell count relates not only to the release of neutrophils from the bone marrow but also to the sequestration of neutrophils in the pulmonary microcirculation [104].

Chest illness in childhood appears to have an association with chronic respiratory morbidity and impaired respiratory function in adulthood [105]. It remains unclear whether these episodes of infection in early life cause lung damage or reflect an underlying susceptibility to lower respiratory infection [106]. There is also controversy over the relationship between childhood or infant respiratory infection and ventilatory impairment in later life. A study of health visitor records of illnesses in early childhood suggested that illnesses diagnosed as whooping cough, bronchiolitis or pneumonia in the first year of life were associated with a significant reduction in FEV<sub>1</sub> measured in the first decade [107]. In contrast, the same illnesses in children aged 1–4 years were not associated with significant defects in lung function.

However, studies of a cohort of children born in 1946 reported that cough and sputum production between the ages of 20 and 36 years were more commonly reported in those with a history of chest illness in childhood [108,109]. In contrast, respiratory illnesses below the age of 2 years had no effect on peak expiratory flow rate at age 36 years [68]. One of the problems with these studies is the confusion of diagnosing asthma in those who might previously have been diagnosed as having bronchitis, which appears to have a close association with chronic respiratory problems in adulthood [110]. Indeed, it seems that those children who do not grow out of their asthma are at increased risk of chronic cough and sputum production in their early twenties [111].

### Growth and nutrition

Several recent studies have suggested that nutrition may affect both the growth and decline in ventilatory function. In a study of men born in Hertfordshire between 1911 and

1930, mortality from chronic respiratory diseases (ICD-9, 491–493 and 496) correlated inversely with birthweight and weight at 1 year of age [107]. Since a similar association did not occur with lung cancer, it was suggested that smoking is unlikely to be a confounding factor. Thus, impaired growth *in utero* may be a risk factor for the development of chronic respiratory diseases.

The association between childhood respiratory illness and ventilatory impairment in adulthood is probably multifactorial. Several factors, such as low economic status, greater exposure to passive smoking, poor diet and housing and residence in areas of high pollution, may contribute to this finding. One study has shown that in British adults there is a correlation between consumption of fresh fruit in the diet and ventilatory function [112], a relationship that held in both smokers and people who never smoked. Dietary factors, particularly a low intake of vitamin C and low plasma levels of ascorbic acid, were related to a diagnosis of bronchitis in the US National Health and Nutrition Examination Survey [113]. A relationship between heavy alcohol intake and a risk of impaired ventilatory function has been shown in one study [114].

#### Atopy and airway hyperresponsiveness

In the 1960s Dutch workers proposed that smokers with chronic, largely irreversible airways obstruction and asthmatics shared a common constitutional predisposition to allergy, airway hyperresponsiveness and eosinophilia [115]. This proposal named the 'Dutch hypothesis' by Fletcher and colleagues was contrary to Fletcher's own data, which failed to find a relationship between evidence of allergy or increased airway responsiveness to histamine and accelerated annual decline in FEV<sub>1</sub> in cigarette smokers [23]. Numerous studies have shown that smokers tend to have higher levels of IgE and higher eosinophil counts than non-smokers; however, the levels are not as high as those seen in asthmatics [116,117]. Studies in middle-aged smokers with a degree of impairment of lung function show a positive correlation between accelerated decline in FEV<sub>1</sub> and increased airway responsiveness to either methacholine or histamine [118,119]. However, atopic status, as defined by positive skin tests, does not differ between smokers and people who have never smoked [116,117,119].

There are several important differences between the airway hyperresponsiveness (AHR) in smokers, patients with COPD and patients with asthma. Cross-sectional studies have shown that AHR occurs more commonly in middle-aged than young non-atopic smokers [120]. Whereas in asthma AHR is present in those with normal baseline respiratory function, in smokers there is a strong relationship between baseline FEV<sub>1</sub> and AHR [121]. The relationship between AHR and diurnal variation in peak

flow is stronger in asthmatics than in smokers and the relationship between AHR and eosinophil count is present in asthmatics but not in smokers [115]. The bronchial hyperreactivity in asthmatics is more intense than in patients with COPD [122] and, as with normal subjects, patients with COPD show a plateau in airway narrowing as the dose of inhaled methacholine is increased [123,124], which does not occur in asthmatic subjects [123]. There are also differences in the short-term effects of drugs on AHR in smokers and patients with asthma. The  $\beta$ -adrenoreceptor agonists have a much larger short-term effect on attenuating AHR to histamine or methacholine than antimuscarinic drugs. This is true in both asthmatics and smokers with mild airflow obstruction [125]. This contrasts with clinical studies which suggest that antimuscarinic drugs may have more important effects and thus be more useful in smoking-related COPD [126]. Short-term studies of non-steroidal anti-inflammatory drugs have shown no effect on AHR in smokers [127]. However, smokers and asthmatics differ in the response of their AHR to treatment with corticosteroids, which given over 2–3 months effectively attenuates AHR in asthma but is ineffective in smokers with mild airways obstruction [128]. These studies suggest, but do not prove, that AHR in smokers may be acquired rather than constitutional. There are several possible mechanisms for the increased AHR in smokers with COPD [129]:

- 1 geometric factors related to an increased thickening of airway walls, producing a narrowed airway, result in a proportionally greater rise in resistance in a narrowed airway for a given shortening of airway smooth muscle;
- 2 more central deposition of inhaled aerosols as a result of airways obstruction;
- 3 loss of airway wall support as a result of loss of alveolar walls in emphysema;
- 4 increased airway epithelial permeability resulting in airway wall oedema.

One structure-function study has shown that the degree of bronchiolar inflammation is related to the hyperresponsiveness in cigarette smokers [130]. However, the infiltration of eosinophils into the airways of asthmatic subjects is much more prominent than in non-asthmatic smokers [100]. There is evidence that non-asthmatic smokers display several features of allergy. They certainly have raised levels of total serum IgE and higher blood eosinophil counts compared with healthy people who have never smoked [117,131]. It has been suggested that sensitization to tobacco or to pneumococci resident in the lower respiratory tract results in increased levels of IgE or that the increased epithelial permeability which occurs in smokers [132] allows penetration of allergens into the airway wall, accounting for the increased IgE [133]. However, there is no evidence of an increased prevalence of a family history of allergic disease nor an increased prevalence of positive skin tests to common aeroallergens

in smokers [119]. The relationship between increased IgE levels and age and pack-years smoked, and the fact that the levels decline following cessation of smoking [116], again suggests an acquired rather than constitutional cause for the raised IgE in cigarette smokers.

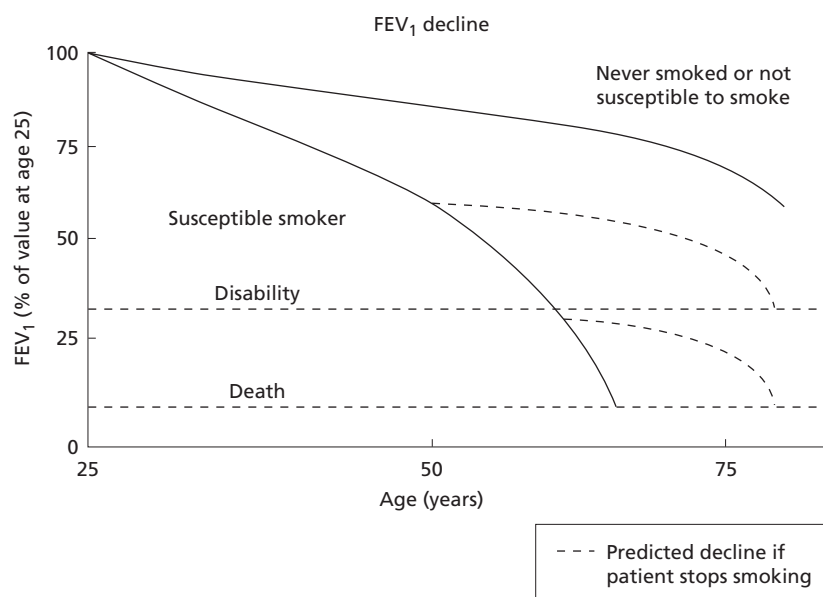
An important question is whether AHR is an important risk factor for the development of progressive airways obstruction in smokers. Since atopy and cigarette smoking occur in 30% of the population, the clear relationships between total IgE, positive skin tests, aeroallergens and AHR that occur in asthma are likely to be found also in population studies which include smokers. Smoking is not rare in asthmatics [134] but does not appear to be a risk factor for the development of asthma in middle age [135]. Indeed asthma may first develop after quitting smoking [136].

The role of AHR in the pathogenesis of airways obstruction remains unclear. It has been suggested that persistent airways obstruction in middle-aged subjects may be of two types. The first, as in the 'Dutch hypothesis', is associated with an asthmatic predisposition with associated allergic phenomenon in which AHR may be important in the pathogenesis of persistent airways obstruction [137]. In the second type, which may be considered to represent the emphysematous type of COPD, AHR may result from structural changes as described above and therefore has no significant pathogenic role in the accelerated decline in respiratory function. However, it is clear that there may be considerable clinical overlap between these two types of individuals.

## Natural history and prognosis

Severe airways obstruction in patients with COPD is

thought to occur in susceptible smokers as a result of years of accelerated decline in  $FEV_1$ . In non-smokers, the  $FEV_1$  declines at a rate of 20–30 mL/year [138] (Fig. 23.6). Smokers have an accelerated decline in  $FEV_1$  and the rate increases with increasing numbers of cigarettes smoked. Reported changes in  $FEV_1$  in patients with COPD range from 48 to 91 mL/year [36]. Fletcher and colleagues [23] found a relationship between the level of  $FEV_1$  and the annual rate of decline in  $FEV_1$  over a follow-up period of 8 years in a study of working men in London. From these data they suggested that susceptible cigarette smokers could be identified in early middle age by a reduction in  $FEV_1$  (Fig. 23.6). They assumed that there was a 'tracking' effect, whereby individuals in the highest or lowest  $FEV_1$  percentiles remained in the same percentiles over subsequent years. However, there is one other model for the development of impairment of  $FEV_1$  in the susceptible smoker: smoking-related lung damage occurs as a result of inflammation and eventual scarring of the small or peripheral airways, in which extensive changes may occur without any resultant change in tests of overall lung function, such as  $FEV_1$ . Thus such susceptible smokers might only present with an accelerated decline in  $FEV_1$  at a late stage of the disease, whereas at an earlier stage they would be indistinguishable from the general population of smokers, although having a lower  $FEV_1$  than people who never smoked. Support for the 'tracking' effect comes from a study of 2718 working men whose pulmonary function was assessed in the 1950s and subsequently followed up over 20 years. In this cohort, in those whose initial  $FEV_1$  was more than 2 SD below predicted values, the risk of death from chronic airways obstruction was 50 times greater than in those whose initial  $FEV_1$  was above average [28]. Similar results have been reported from



**Fig. 23.6** The effect of age on airflow obstruction in normal subjects and susceptible cigarette smokers. Cessation of smoking returns the rate of decline to normal. (Adapted from Fletcher *et al.* [23].)

population studies in Copenhagen [29] and from studies in six US cities [94]. The presence of tracking for the decline in  $FEV_1$  has been confirmed in middle-aged males in studies from Tucson, Arizona, but not in women smokers [139]. Furthermore, there is a tendency for annual rates of decline in  $FEV_1$  to be slower in advanced compared with mild disease [36]. There are large differences in the rate of decline between individuals in longitudinal studies. It is presumed that those who develop severe airways obstruction are those who have the fastest decline in  $FEV_1$ . Other tests sensitive to changes in peripheral airways and airspaces, such as the single-breath nitrogen test or maximum expiratory flows below 50% of vital capacity on a flow-volume curve, are abnormal when the  $FEV_1$  is normal in almost all smokers who subsequently develop a reduced  $FEV_1$  [140]. However, not all patients with an abnormal single-breath nitrogen test develop a reduced  $FEV_1$ , which has limited the value of this test. Small changes in the carbon monoxide diffusion coefficient ( $K_{CO}$ ) occur in many cigarette smokers [141] and often reverse as a result of stopping smoking, suggesting removal of a pulmonary vascular response. In some smokers there is a considerable reduction in  $K_{CO}$  at a time when spirometry is relatively well preserved [142]. There is very limited information on follow-up studies of  $K_{CO}$  or indeed of sequential measurements of lung recoil pressure [143], which is also abnormal in the early stages of airways obstruction [142,143].

### Effects of smoking cessation

Most studies of the effects of stopping smoking have been made in middle-aged or older subjects with mild airways obstruction. After smoking cessation these subjects have a rate of decline in  $FEV_1$  that approaches that found in people who have never smoked [23,32,138]. Most cross-sectional studies show a slightly higher mean  $FEV_1$  in ex-smokers than in current smokers [30,32,144]. Longitudinal measurements in the Lung Health Study demonstrated a slight improvement in  $FEV_1$  in the first months after stopping smoking in younger subjects with very mild impairment of lung function, but a subsequently slower decline than in continuing smokers [37]. Short-term studies of stopping smoking have shown improvement in small airway tests, such as the single-breath nitrogen test, although changes in maximum expiratory flow-volume curves have been variable [145]. However, a clear improvement in survival has been demonstrated in ex-smokers with advanced disease [36,38].

### Prognosis

The strongest predictors of survival in patients with COPD are age and baseline  $FEV_1$  [36]. Less than 50% of patients whose  $FEV_1$  has fallen to 30% of predicted are

alive 5 years later [146]. There is an even stronger relationship between survival and the  $FEV_1$  after, rather than before, the use of bronchodilators. Other unfavourable prognostic factors include severe hypoxaemia, a high pulmonary arterial pressure and low  $K_{CO}$ , which become apparent in patients with severe disease [36,146]. The factors that favour improved survival are stopping smoking and a large bronchodilator response. A reduced  $FEV_1$  is also a predictor of later cardiovascular mortality [96,147] and is an important additional risk factor for lung cancer, independent of age or cigarette smoking [148].

The only treatment shown to improve the long-term prognosis in patients with COPD is long-term domiciliary oxygen therapy, given for at least 15 h daily [149,150]. The use of intermittent positive pressure breathing, at least in non-hypoxaemic patients, has failed to improve survival [151]. Furthermore, regular inhaled muscarinic antagonists in the Lung Health Study did not slow the decline in  $FEV_1$  over a 5-year period [37]. Trials of long-term inhaled corticosteroids in two European studies [152,153] in mild COPD and preliminary results from another trial in moderate to severe COPD have failed to show that inhaled corticosteroids have no effect on the rate of decline in  $FEV_1$  (see p. 677).

### Pathology

The pathological changes in patients with COPD are complex and occur in both the large and small airways, and in the alveolar compartment. The difficulty in distinguishing, clinically or by respiratory function tests, the relative contributions that the pathological changes in the airways and emphysema make to the airways obstruction has been the subject of considerable study. In general, in all such 'structure-function' studies pathological changes correlate rather poorly with both clinical and functional patterns of the disease [154]. There are several reasons for this, including the fact that most studies that correlated pathological changes with function were performed on patients with relatively mild disease who were undergoing lung resection or, alternatively, were studies of autopsy material in patients with end-stage COPD. Sampling problems occur in the study of resected lung specimens when only a single lobe is resected. Other problems with these studies include the reliance on semi-quantitative scoring techniques to measure the extent of emphysema or inflammation and the inability in pathological material to recognize functional abnormalities such as bronchoconstriction.

As a result there is still no clear consensus on whether the fixed airway obstruction in COPD is largely due to inflammation and scarring in the small airways, resulting in narrowing of the airway lumen, or to loss of support to the airways because of loss of alveolar walls as in emphysema. Although the pathology of COPD is complex, it can be

simplified by considering separately the three sites at which pathological changes could, in smokers, produce a clinical pattern of largely fixed airways obstruction. These are the bronchi, where chronic bronchitis develops; the alveolar compartment, where emphysema develops; and the more peripheral airways, which develop so-called 'small airways disease'. The clinicopathological picture is complicated by the fact that these three entities, or any combination of the three, may exist in an individual patient.

### Chronic bronchitis

The pathological basis for the hypersecretion of mucus, which defines this condition clinically, is an increase in the volume of the submucosal glands and an increase in the number and change in distribution of goblet cells in the surface epithelium. Submucosal glands are confined to the bronchi, decreasing in number and size in the smaller more peripheral bronchi, but are not present in the bronchioles. In chronic bronchitis, the hypertrophy of the mucus-secreting glands was thought to be largely a consequence of the irritant action of cigarette smoke [155]. However, in animal experiments chemical stimuli, such as sulphur dioxide and nitrogen dioxide, can also result in mucous gland hypertrophy [156]. The hypertrophy of mucous glands is mainly in the larger bronchi and is evenly distributed throughout the lungs [157]. Mucous gland hypertrophy can be quantified by the Reid index [158], which is the ratio of the distance between the basement membrane of the airway epithelium and the cartilage to the thickness of the gland layer, normally 3:1. Alternatively, mucous gland size can be assessed by measurement of the absolute gland area, whereby the proportion of the wall volume occupied by glands is assessed. The Reid index was devised in an attempt to assess the gland mass independent of variations in bronchial dimensions. However, measurements of sputum production correlate better with mucous gland area or volume than with the Reid index. Neither sputum production nor gland size bear any relation to antemortem FEV<sub>1</sub> [159]. Furthermore, infection does not appear to be an aetiological factor in the bronchial mucous gland hypertrophy in chronic bronchitis [160].

In healthy people who have never smoked, goblet cells are seen predominantly in the proximal airways and decrease in number in more distal airways, being normally absent in terminal or respiratory bronchioles [161]. In contrast, in smokers, goblet cells not only increase in number but extend more peripherally [161]. The presence of metaplastic or dysplastic changes in the surface epithelium in smokers may replace the goblet cells of the normal respiratory epithelium and hence may reduce the numbers of goblet cells in the proximal airways in some smokers. Since the mass of the submucosal glands is greater than that of the goblet cells, most airway secretions are produced by the glands and there is a relationship

between the extent of the submucosal glands and the volume of sputum production [162].

Smaller peripheral bronchi may be thickened and distorted by scar tissue. Loss of cartilage in the subsegmental bronchi has been described by some authors and this may render the bronchi more susceptible to expiratory collapse [163]. Some authors have suggested that scarring of the smaller airways and airway inflammation is associated with airways obstruction [164,165]. In most studies the assessment of airway inflammation has been semi-quantitative. In one study of resected lung specimens, there was no significant relationship between a decrease in bronchiolar lumen size and measurements of airways obstruction [166].

In the presence of acute infection the bronchial walls may be macroscopically inflamed and there may be pus in the lumen. Microscopically, the bronchial walls may show infiltration with acute or chronic inflammatory cells associated with dilatation of the capillaries and oedema. The mucous membrane may become ulcerated, with squamous epithelium replacing columnar epithelium in limited areas.

### Bronchial biopsy studies

The use of bronchoscopy to obtain airway cells by bronchoalveolar lavage (BAL) and bronchial tissue samples by biopsy has added new insights into the role of inflammation in both asthma and COPD [167,168]. However, bronchoscopy is an invasive technique and recent work has suggested that examination of spontaneous or induced sputum may be an effective non-invasive method to investigate the inflammatory cells in the airways of patients with COPD [169].

Early studies reported an increased number of neutrophils in BAL fluid in COPD [170]. Although these studies characterizing the inflammation in the large airways are of some interest, the increase in airflow limitation in COPD is considered to reside largely in the peripheral airways [171]. Bronchial biopsy studies have recently described the inflammation in the bronchi of patients with chronic bronchitis, with or without airways obstruction, in much the same way as has been done in asthma [167]. These have confirmed the findings of earlier studies of resected lung material, which showed inflammation in the bronchial walls in this condition [98,172]. As with asthma, studies of bronchial biopsies in patients with chronic bronchitis have shown that activated T lymphocytes are prominent in the proximal airway walls [100]. However, in contrast to asthma, macrophages are also a prominent feature and the CD8 suppressor T-lymphocyte subset, rather than the CD4 subset, predominates. Recently, O'Shaughnessy and coworkers [173] have shown a significant negative association between the numbers of CD8+ cells in the airway walls and the degree of airways obstruction as measured by FEV<sub>1</sub> in a group of smokers. There is also a greater number of T lymphocytes and

macrophages in the bronchial walls of patients with chronic bronchitis who also have airways obstruction [173,174]. Bronchial biopsies from patients experiencing an exacerbation of chronic bronchitis indicate increased numbers of eosinophils in the bronchial walls [175], although their numbers are small in relation to the numbers present in exacerbations of asthma and, in contrast to asthmatics, these cells do not appear to have degranulated [176].

Several studies, using BAL [177,178] or spontaneous or induced sputum [178–180], have demonstrated intraluminal inflammation in the airspaces in patients with chronic bronchitis, with or without airways obstruction. There are clear differences between the cell populations sampled by these different techniques [178]. In stable chronic bronchitis the percentage of neutrophils was significantly higher in sputum than in BAL, whereas the reverse was true for macrophages and lymphocytes. The lymphocyte was the predominant cell infiltrating the bronchial submucosa. However, there was fairly good agreement between the numbers of eosinophils counted by the three techniques in exacerbations of chronic bronchitis [178]. The pathogenic significance of these findings awaits further study, and the question of a possible overlap with asthma in these subjects arises. Studies of spontaneous or induced sputum in patients with chronic bronchitis also indicate the presence of chemotactic activity, partly due to interleukin 8 and also other inflammatory mediators, such as tumour necrosis factor [179,180]. There is also some preliminary evidence that treatment with anti-inflammatory agents such as inhaled steroids can reduce the chemotactic activity of sputum, and thus play a protective role by decreasing the recruitment of neutrophils into the airspaces [179]. However, other studies have shown no effect of oral or inhaled corticosteroids on cytokine levels in induced sputum in COPD patients [180a].

Cigarette smoking is associated with an increased sequestration of neutrophils in the pulmonary microvasculature, which also occurs during exacerbations of COPD [181,182]. Increased neutrophil sequestration is due initially to a decrease in the deformability of circulating neutrophils, which delays their passage as they deform in order to pass through the smaller pulmonary capillaries [183,184]. The increased sequestration in, and migration of neutrophils from, the circulation in patients with COPD involves the upregulation of cell-surface adhesion molecules on endothelial and epithelial cells [185]. There is also some evidence that the airspace inflammation in patients with chronic bronchitis persists following smoking cessation, if the production of sputum persists [186].

These studies of sputum and bronchial biopsies in chronic bronchitis have mainly sampled the proximal airways. Recent preliminary studies suggest that inflammatory changes present in the large airways may reflect those present in the small airways and perhaps even those in the alveolar walls [187,188].

## Emphysema

The original definitions of emphysema by the Ciba Guest Symposium in 1959 [189] and by the ATS in 1962 [190] were modified as a result of a National Heart, Lung and Blood Institute workshop in the USA in 1985 [6], which defined emphysema as 'a condition of the lung characterized by abnormal, permanent enlargement of the airspaces, distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis'.

This is a morphological definition more relevant to the pathologist than to the clinician. It should be emphasized that clinical, radiographic and functional assessment of patients is an insensitive method of diagnosing emphysema. Dividing pulmonary emphysema into its subtypes could, until recent studies using high resolution CT scanning, only be undertaken by the pathologist. However, the definition of emphysema also presents problems for the pathologist, since there are no agreed criteria for normal airspace size by which abnormality can be assessed. Although the statement 'without obvious fibrosis' was included in the definition to exclude enlarged airspaces associated with gross fibrosis, as in cryptogenic fibrosing alveolitis, it is recognized that fibrosis is found in the walls of emphysematous spaces [191]. A further problem for the pathologist is the concept that the presence of emphysema implies that there has been enlargement of airspaces resulting from destruction of alveolar walls. This, by definition, excludes other conditions where overinflation is present, such as after pneumonectomy or in chronic asthma. However, in an area of established emphysema it is not possible to determine whether the absence of airspace walls has been due to a destructive process.

Emphysema has been classified by the pattern of enlarged airspaces on the cut surface of a fixed inflated lung. Air-space enlargement can be identified macroscopically when the airspace size reaches 1 mm. The distribution of these enlarged airspaces is identified within the acinar unit [158]. Three major types of emphysema are recognized, according to the distribution of enlarged airspaces within the acinar unit (Fig. 23.7).

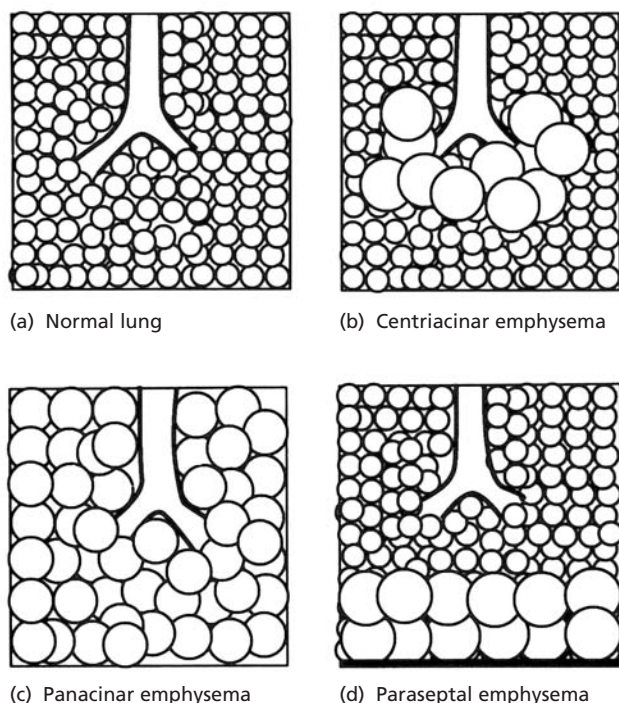
**1 Centriacinar (syn. centrilobular) emphysema**, in which enlarged airspaces are initially clustered around the terminal bronchiole.

**2 Panacinar (syn. panlobular) emphysema**, where the enlarged airspaces are distributed throughout the acinar unit.

**3 Periacinar (syn. paraseptal or distal acinar) emphysema**, where the enlarged airspaces are along the edge of the acinar unit but only where it abuts against a fixed structure, such as the pleura or a vessel.

Periacinar emphysema occurs less commonly than centriacinar or panacinar emphysema and is usually of little clinical significance, except when it occurs extensively in a subpleural position and may be associated with





**Fig. 23.7** Distribution of abnormal airspaces within the acinar unit in different types of emphysema: (a) normal lung; (b) focal enlargement of airspaces around the respiratory bronchioles in centriacinar emphysema; (c) confluent, even involvement of the acinar unit in panacinar emphysema; (d) peripherally distributed enlarged airspaces abutting the pleura in paraseptal emphysema. (From Lamb [420] with permission.)

pneumothorax. Two other types of emphysematous change have been described.

**4** Scar or irregular emphysema is used to describe enlarged airspaces around the margins of a scar, unrelated to the structure of the acinus. This lesion is excluded from the current definition of emphysema but is a useful descriptive term.

**5** Bullae represent localized areas of emphysema that have overdistended. Conventionally, only lesions greater than 1 cm are described as bullae [189]. The terms 'bullae', 'cyst', 'cavity' and 'pneumatocele' are often used interchangeably. A cyst is a generic term for an abnormal airspace greater than 1 cm in diameter, which can be congenital or acquired, such as a cavity, bulla or pneumatocele, all of which lack an epithelial lining. A cavity is an acquired cyst with non-epithelial lining and a wall thicker than 3 mm. These usually arise following pulmonary infection or fibrosis. A bulla is also an acquired enlarged airspace but has extremely thin walls of minimal thickness. The term 'pneumatocele' is usually reserved for small postinfective cysts that result from tissue lysis, such as in staphylococcal pneumonia.

Bullae arise in an area of lung that has been locally destroyed, although this destruction does not always have

to be as a result of emphysema and can also occur from lytic or traumatic causes. Bullae have been described in tuberculosis, sarcoidosis, AIDS and trauma [192]. In a minority of cases, around 20%, the surrounding lung is normal, but in the majority there is associated emphysema and chronic airways obstruction [192].

Bullae have been classified according to their size and position [193]. Type I bullae have a narrow neck, attached to a mushroom-like expansion into the pleural space; type II bullae have a broader neck, and represent distension of a moderate area of emphysema; and type III bullae occur in an area of severe emphysema within the lung and have no pleural reflection. The origins of bullae remain obscure, particularly type I [193]. Types II and III appear to arise in areas of moderate to severe emphysema. One hypothesis is that a region of local weakness in the structure of the lung is supplied by airways with a valvular structure, which allows gas to enter but impedes its exit. However, there are several problems with this theory, since it would suggest that gas enters an area of high pressure rather than distending more compliant lung. Furthermore, direct measurement of pressures within bullae measured at operation are very similar to pleural pressure [193] ( $-11$  cmH<sub>2</sub>O during tidal breathing). This is despite the appearance of bullae at operation, which give the impression of a structure containing gas under pressure. This paradoxical finding may result from the development of positive end-expiratory pressure within bullae during intermittent positive pressure ventilation during thoracotomy, resulting in artificially high pressures in the interior of the bulla that are greater than pleural pressure.

The two common types of emphysema have different distributions within the lungs. Centriacinar emphysema is more common in the upper zones of the upper and lower lobes [194], whereas panacinar emphysema may be found anywhere in the lungs but is more prominent at the bases and may be associated with  $\alpha_1$ -AT deficiency. Both types of emphysema can occur alone or in combination.

There is still debate over whether centriacinar and panacinar emphysema represent different disease processes [194,195], and hence have different aetiologies, or whether panacinar emphysema is a progression from centriacinar emphysema [196,197]. There is certainly a clearer association between cigarette smoking and centriacinar emphysema than with panacinar emphysema [198]. Indeed in surgically resected lungs the presence of centriacinar emphysema is independent of the occurrence of microscopic panacinar emphysema [199,200]. Recent studies of the morphometry and inflammatory cell populations in lungs in these two patterns of emphysema also suggest that different pathogenic mechanisms may result in these two forms of emphysema. In studies of resected lungs, Kim and coworkers [199] and Saetta and colleagues [200] showed that smokers can develop both centriacinar and panacinar emphysema, and that those patients with

centriacinar emphysema had more abnormalities in their small airways, with more muscle and smaller luminal diameters, than those with predominantly panacinar emphysema. Moreover, the patients with centriacinar emphysema had greater AHR than those with panacinar emphysema; the AHR in the former correlated with the numbers of lymphocytes in the airway walls [201].

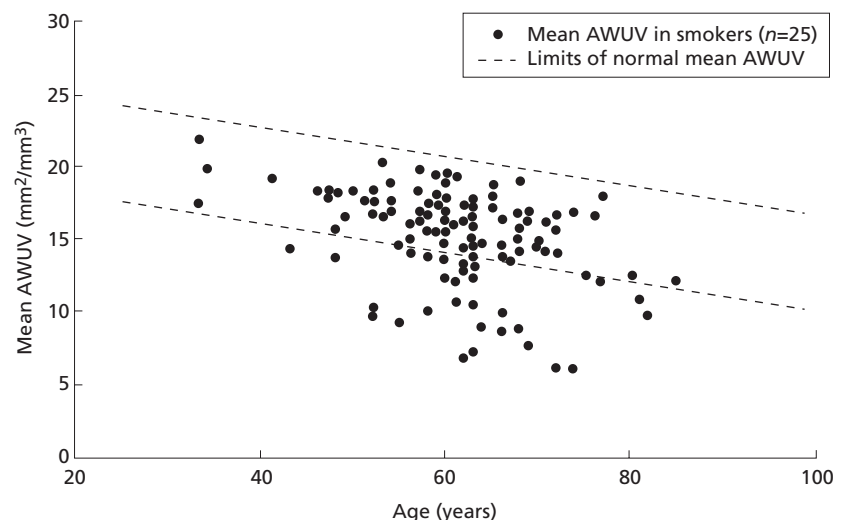
The severity of emphysema can be measured either macroscopically or microscopically in resected lung specimens. Macroscopic emphysema can be assessed by the point counting technique [202], where a grid of intersecting points is placed over the lung and the type of tissue (normal or emphysematous) a point overlies is recorded, producing a quantitative assessment of the amount of lung involved in macroscopic emphysema. Various emphysema grading techniques have been described, the best known being that of Thurlbeck and coworkers [203] who used a series of paper-mounted cross-sections of lungs with varying degrees of emphysema that were ranked from 0 (normal) to 100, which was the most extensive emphysema encountered in a series of 500 paper-mounted sections. However, this is a semi-quantitative technique that grades emphysema on a non-linear scale, since a score of 80 is not double a score of 40. Furthermore, none of these techniques makes any assessment of the pattern of emphysema. In addition all these techniques fail to identify airspaces less than 1 mm in diameter and therefore to do not measure microscopic emphysema. This is important since when an alveolus, which is normally 240  $\mu\text{m}$  in diameter, has enlarged to reach 1 mm, 75% of the alveolar surface has been destroyed [204].

Various techniques have been used to quantify microscopic emphysema including the mean linear intercept technique, which estimates the diameter of the airspaces [205]. Advances in image analysis have allowed automation of this previously time-consuming technique,

enabling detailed analysis of large numbers of lung samples [206]. Measurements of microscopic emphysema can be expressed in terms of the distal airspace size (mean linear intercept,  $L_m$ ) or in terms of the surface area of the alveolar or airspace wall per unit lung volume (AWUV) [207,208].

These quantitative morphometric techniques have begun to allow a definition of normality for airspace size. Gillooly and Lamb [209] studied lungs from a group of 38 lifelong non-smokers with a wide age range and have defined normality as values of AWUV lying outwith the 95% confidence limits of their measurements (Fig. 23.8). Using similar techniques in a population of smokers, the majority of smokers lie within the normal range. Interestingly, there was no difference in the smoking histories between those lying in or outwith the normal range. This exaggerated fall in AWUV in some smokers is the result of microscopic, panacinar emphysema, which was found in only 26% of the smoking group. Thus panacinar emphysema does not appear to be present at an early stage in all smokers. The relationship between AWUV and centriacinar emphysema is less clear since its focal nature has little effect on the overall mean airspace size, as expressed by AWUV. The fall in airspace wall surface area with age was previously thought to represent 'senile emphysema'. However, these recent studies suggest that this enlargement of distal airspace size may be part of the normal ageing process [209].

Absence of fibrosis is a prerequisite in the most recent definition of emphysema [6]. Histologically, however, fibrosis has been recognized in the region of the terminal or respiratory bronchioles, as part of a respiratory bronchiolitis described by Niewoehner and colleagues [210] that occurs in asymptomatic cigarette smokers. Furthermore, when sensitive techniques are used to measure collagen and elastin in alveolar walls, there appears to be an



**Fig. 23.8** The effect of smoking on mean alveolar or airspace wall per unit lung volume (AWUV) values. The dotted lines indicate the normal range derived from a population of non-smokers. Those lying outwith the normal range have microscopic panacinar emphysema that does not appear to be related to smoking dose. (From Gillooly & Lamb [209] with permission.)

increase in collagen in the lung parenchyma in smokers compared with non-smokers [211], which is also the case in areas of emphysematous compared with areas of relatively normal lung [212]. Scanning electron microscopy has also demonstrated fibrosis in association with end-stage emphysema [213].

The destruction of airspace walls has been assessed by Saetta and colleagues [200], who described a destructive index based on a point counting technique that estimated the proportion of the airspace walls showing evidence of damage according to set criteria. Using this technique alveolar wall damage has been described in the absence of measurable emphysema [195,200].

The bronchioles and small bronchi are supported by the attachment to the outer aspect of their walls of adjacent alveolar walls. This arrangement maintains the tubular integrity of the airways. It has been suggested that loss of these attachments may lead to distortion and irregularity of airways, which may result in airflow limitation [214,215] (Fig. 23.9). The integrity of the alveolar wall supports can be assessed by measuring the linear distance between alveolar wall attachments, the interalveolar wall attachment distance (IAAD) [216,217]. Increase in IAAD may be caused by local inflammatory changes and could result in early airway collapse during expiration, and hence contribute to the airflow limitation.

### Small airways disease

Hogg, Macklem and Thurlbeck introduced the concept of 'small airways disease' in studies of lungs *in vitro*. Using a retrograde catheter they were able to show that the increased flow resistance in the lungs of patients with COPD largely occurred in the small airways at the periph-

ery of the lungs [171]. Subsequent studies by Niewoehner and colleagues [210] on postmortem lungs obtained from young asymptomatic cigarette smokers who died of non-respiratory causes and studies by Cosio and coworkers [218] in resected lungs demonstrated several different pathological changes in small airways. These were assessed using a scoring system by Cosio and colleagues [218] as follows:

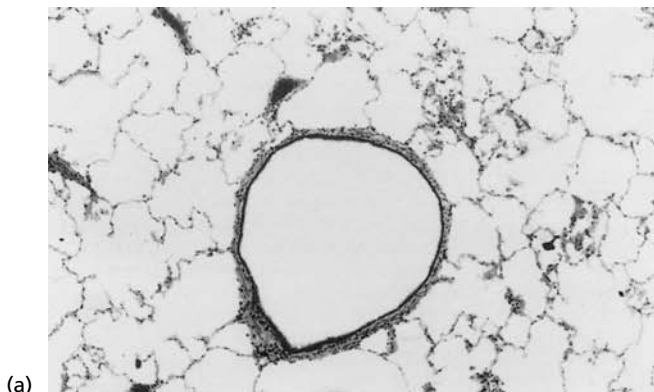
- 1 occlusion of the lumen by mucus and cells;
- 2 presence or absence of mucosal ulceration;
- 3 goblet cell hyperplasia;
- 4 squamous cell metaplasia;
- 5 inflammatory infiltrate in the airway wall;
- 6 amount of fibrosis in the airway wall;
- 7 amount of muscle;
- 8 degree of pigmentation.

From this subjective grading system a set of standard illustrations was made of the various grades of abnormality, termed the small airways disease score [219]. Others have used a more quantitative approach by measuring the dimensions of small airways. This is problematic since in histological sections most airways are sectioned tangentially. Many workers who have made measurements of small airways have ignored the associated alveolar walls that support the airways and which, as described above, can be selectively lost in microscopic emphysema, leading to tortuosity of the small airways [214,215]. Loss of these alveolar attachments may have an important role in the development of airways obstruction in early emphysema, but may be less important in the overall severity of airflow limitation in the later stages of the disease [220].

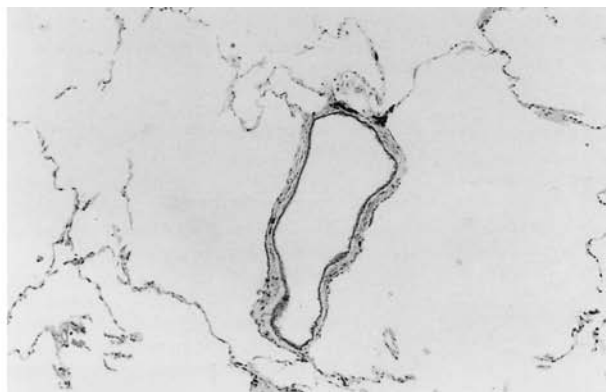
### Pathology of severe COPD

Most of the descriptions of the pathology of COPD described so far in this chapter have come from the study of resected lungs from patients who have early disease, since they are required to have sufficient respiratory reserve to allow surgery to proceed. These pathological changes may occur at the mild end of a spectrum of

**Fig. 23.9** (a) Cross-section of a small peripheral bronchiole showing a circular outline supported by adjacent alveolar walls. (b) A small bronchiole at the same magnification in a patient with very early macroscopic emphysema. The loss of alveolar supporting walls results in an elliptical airway.



(a)



(b)

disease that leads to end-stage COPD or may represent smoking-related changes, which may or may not progress. At autopsy in patients dying with end-stage COPD, severe macroscopic emphysema is the most prominent feature [221–223]. Centriacinar or panacinar emphysema may predominate, or there may be a mixture of both. Centriacinar emphysema is much more extensive and the lesions are larger in end-stage COPD than those seen in smokers without airways obstruction. Centriacinar lesions are usually confined to the upper zones of the lungs but extend throughout the lungs in patients with severe disease. Panacinar emphysema may also be widespread throughout the lungs. Type I and type III bullae are often present, both at the apex and on the diaphragmatic surface of the lower lobe. It is common to find mucous plugging and areas of bronchopneumonia at autopsy in patients with severe COPD, particularly in the lower lobes, and lung cancer is more common in these patients than one would expect from their smoking history [224].

### **Pulmonary vasculature**

The development of chronic alveolar hypoxia in patients with COPD produces characteristic remodelling of the pulmonary arteries that consists of three components. The first is an extension of the medial muscle into the pulmonary arterioles, which normally have no muscle in their walls [225,226]. The second is the presence of longitudinal smooth muscle in the intima of the small pulmonary arteries. Through a process of proliferation this muscle becomes progressively thicker and may eventually occlude the vascular lumen. Intimal fibrosis may occur that may be severe. However the significance of this is uncertain since it is clearly present in smokers without COPD [226,227]. The third component occurs in the small pulmonary arteries, which develop inner muscular tubes. External to the thickened elastic lamina is an area containing myofibroblasts. Internal to this is a coat of circular muscle bound by two elastic laminae. The zone containing myofibroblasts is eventually replaced by fibroelastic tissue.

In the large pulmonary arteries intimal atheroma may be present and the main pulmonary trunks may show aneurysmal dilatation, sometimes containing laminated thrombus, seen in about 20% of cases of severe COPD at postmortem. Attempts to quantify these structural abnormalities in the pulmonary vasculature and relate them to the degree of pulmonary hypertension is complicated by the fact that vasoconstriction, which can be seen in postmortem specimens, may alter morphometric measurements [228].

### **Heart**

Right ventricular hypertrophy and pulmonary hyperten-

sion are commonly found in patients with COPD who have chronic hypoxaemia [223]. Right ventricular hypertrophy can be measured at postmortem as the Fulton index, the ratio of the weight of the left ventricle and the interventricular septum to that of the free right ventricular wall. This ratio is normally greater than 2.2. Measurement of ventricular wall thickness alone is not considered accurate in the assessment of right ventricular hypertrophy due to the complicating effects of ventricular dilatation and heart failure [229].

Other abnormalities have been described in patients with hypoxic COPD, including a decrease in the muscle and weight of the diaphragm with increasing emphysema [230], enlargement of the renal glomeruli [231] and carotid body enlargement [232].

### **Structure–function relationships**

There are several limitations to structure–function studies in the lungs of patients with COPD. Early studies were largely performed on postmortem lungs in patients with end-stage lung disease and concentrated largely on macroscopic emphysema [194]. More recent studies have been undertaken in patients undergoing lung resection for peripheral bronchial carcinoma, where measurements of small airways disease and macroscopic and microscopic emphysema have been related to tests of respiratory function. In postmortem studies there is often a poor temporal relationship between respiratory function and the pathological assessment, whereas in surgically resected lungs respiratory function measurements have been made pre-operatively. However, these studies tend to be restricted to those with mild disease who are capable of undergoing thoracotomy. More recently CT (see below) has been used to quantify emphysema in life and has been related to both pathological measurements and lung function [8].

### **Emphysema**

There is a relatively poor relationship between semi-quantitative assessments of macroscopic emphysema and the severity of airways obstruction [221,222]. In a large study of 163 patients undergoing lung resection who had variable degrees of emphysema as assessed semi-quantitatively by the scoring system of Thurlbeck, there was no correlation between percentage predicted FEV<sub>1</sub> and the emphysema score [154]. Measurements of microscopic emphysema have also shown poor correlations with FEV<sub>1</sub> [208]. Several authors have stressed the importance of peribronchial alveolar attachments in maintaining airway shape [214,215]. Loss of airway attachments as described above appears to be related to the degree of airflow limitation. Support for this comes from both post-mortem studies [233] and studies of the early stages of the disease, where a relationship has been shown between a

decrease in  $FEV_1$  and loss of alveolar attachments [216,217]. Indeed in patients with mild COPD, Lamb and coworkers [216] showed that the best relationship with percentage predicted  $FEV_1$  was the Inter-alveolar cell attachment distance (IAAD). These workers also showed a relationship between IAAD and the slope of the single-breath nitrogen test, suggesting that loss of attachments leads to lack of homogeneity in the distribution of ventilation in the lungs.

A relationship between single-breath and steady-state  $K_{CO}$  and the degree of emphysema has also been shown in several studies [207,208,234]. However, the relationship between  $K_{CO}$  and measurements of microscopic emphysema, either  $L_m$  or AWUV (see p. 631), is closer than that between  $K_{CO}$  and measurements of macroscopic emphysema [207,208].

It has been suggested that changes in the elastic recoil of the lungs should bear the closest relationship to the severity of emphysema [235,236]. An exponential equation

$$V = a - be^{-kp}$$

can be fitted to the pressure–volume relationship of the lungs. The constant  $k$  from this equation describes the shape of the curve [237]. Studies on a group of 163 patients with variable degrees of emphysema showed no significant relationship between the exponential constant  $k$  and the macroscopic emphysema score [154]. Since the elastic recoil of the lungs is one of the major determinants of maximum expiratory flow, the lack of a relationship between macroscopic emphysema and the elastic recoil of the lungs may explain the lack of correlation between macroscopic emphysema and  $FEV_1$ . These authors suggested that patients who had decreased elastic recoil (i.e. increased  $k$ ) had evidence of microscopic emphysema, as measured by increased values of  $L_m$ , irrespective of the absence or presence of macroscopic emphysema [154]. This suggests that  $k$  reflects the structure of the lung *apart* from the macroscopic emphysematous lesions.

## Pathogenesis of COPD

Since COPD encompasses at least three pathological conditions, chronic bronchitis, emphysema and small airways disease or respiratory bronchiolitis, it is a difficult task to encompass these diverse pathologies in one simple pathogenic mechanism. The main aetiological factor in COPD is cigarette smoking, but it is clear that susceptibility to the effects of cigarette smoke determines the presence and the degree of COPD since only 15–20% of smokers develop the disease.

The majority of the work on the pathogenesis of COPD relates to the development of emphysema and derives from the observation of an association between a deficiency of  $\alpha_1$ -AT and the development of early-onset emphysema, which was first described by Laurell and

Ericksson in 1963 [71]. A second important observation was made in the same year by Gross and coworkers [238] who described the first animal model of emphysema, produced by instillation of the proteolytic enzyme papain into the rat lung.

These two important observations form the basis of the protease–antiprotease theory of the pathogenesis of emphysema. The hypothesis states that in healthy lungs the release of proteolytic enzymes from inflammatory cells does not cause lung damage because of inactivation of these proteolytic enzymes by an excess of inhibitors. However, in conditions of excessive enzyme load, or where there is an absolute or functional deficiency of antiprotease an imbalance develops between proteinases and antiproteinases in favour of proteinases, leading to uncontrolled enzyme activity and degradation of lung connective tissue in alveolar walls, leading to emphysema (Fig. 23.10). This simplified version of the theory has been elaborated over the past 15–20 years and an enormous amount of research has been focused on providing evidence to support it.

## Animal models

There have been numerous animal models of emphysema. However, many of these models involve single exposures to an insult and therefore cannot hope to mimic the repeated exposure to cigarette smoke that is thought to result in emphysema in humans. The most extensively studied of all animal models involves instillation of the protease elastase. In 1972 Lieberman [239] was the first to show that leucocyte enzymes could digest lungs deficient in  $\alpha_1$ -AT and that this could be prevented by exogenous  $\alpha_1$ -AT. The ability of purified neutrophil elastase to produce emphysema in experimental animals was demonstrated in 1977 [240] to be associated with a transient decrease in lung elastin [241]. These studies are unphysiological since instillation of elastase into the lung produces a profound inflammatory response that does not resemble the small influx of neutrophils which occurs in the lungs of cigarette smokers as a result of the repeated insult of smoking. However, these studies supported the contention that elastase was the most important proteolytic enzyme in the pathogenesis of emphysema.

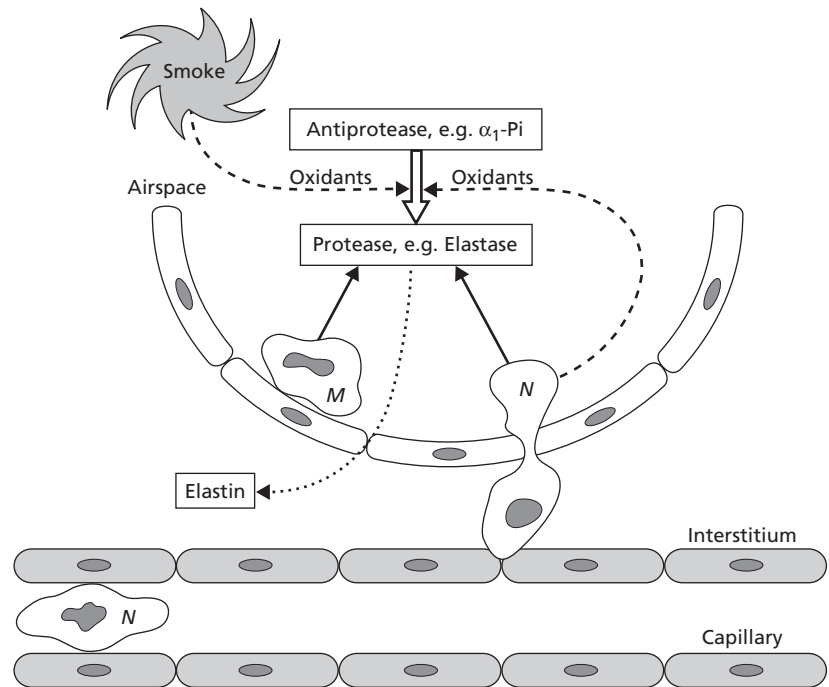
## $\alpha_1$ -Antitrypsin/ $\alpha_1$ -protease inhibitor

The fact that subjects with  $\alpha_1$ -AT deficiency develop emphysema early in life, particularly if they smoke, provides a simple concept for the development of emphysema resulting from a disturbance in the balance between elastase release and its inactivation by  $\alpha_1$ -AT. It is considered that emphysema developed in the absence of  $\alpha_1$ -AT deficiency by:

- 1 an increase in the proteinase burden, due to either the presence of increased numbers of inflammatory leuco-



**Fig. 23.10** Simplified protease–antiprotease theory of the pathogenesis of emphysema. Neutrophils (N) sequester in the pulmonary capillaries initially as a result of the oxidant effect of cigarette smoke, which decreases neutrophil deformability. Activated neutrophils adhere to the endothelial cells and subsequently migrate into the airspaces. Oxidants, either directly from cigarette smoke or released from activated airspace neutrophils, inactivate antiproteases such as  $\alpha_1$ -protease inhibitor ( $\alpha_1$ -Pi syn.  $\alpha_1$ -AT), reducing its ability to bind to and hence inactivate proteases, particularly elastase. This allows active elastase to enter the lung interstitium and bind to and destroy elastin, causing destruction and enlargement of the distal airspace walls. This simplified protease–antiprotease theory is complicated by the presence of other antiproteases, such as antileucoprotease, and other proteases, such as metalloproteases released from macrophages (M). There is also the potential for neutrophils to be activated and release elastase while sequestered in the pulmonary capillaries without the need to migrate.



cytes in the airspaces or the release of excess protease from the leucocytes;

- 2 a functional deficiency of protease inhibitors;
- 3 a combination of 1 and 2;
- 4 an abnormality in the repair mechanisms for lung connective tissue.

$\alpha_1$ -AT is a potent inhibitor of serine proteases and has greatest affinity for the enzyme neutrophil elastase [242]. It is a 52-kDa glycoprotein synthesized in the liver, and increases from its usual plasma concentration of approximately 2 g/L as part of the acute-phase response. Most of the lung  $\alpha_1$ -AT is derived from the plasma, although monocytes and macrophages can also manufacture the protein. Chromosome 14 contains a single 12.2-kb gene that encodes the  $\alpha_1$ -AT protein [243]. The protein is composed of 394 amino acids and three carbohydrate side-chains. The gene for  $\alpha_1$ -AT is polymorphic, with over 70 known alleles, resulting from changes in the amino acid sequence, none of which alter protein structure, function or expression. The activity of the protein is critically dependent on the methionine-358, serine-359 sequence at its active site. The  $\alpha_1$ -AT protein is classified phenotypically by its electrophoretic properties, resulting in the Pi system. The common Pi type is M and the deficient Pi type, which can be clearly distinguished using electrophoresis is termed Z. The average  $\alpha_1$ -AT plasma levels for the more common phenotypes are shown in Table 23.3. Over 75 different Pi types of  $\alpha_1$ -AT have now been identified. Some alleles, such as Null Null, are associated with no detectable  $\alpha_1$ -AT.

The Z deficiency state (PiZ) is associated with PAS-

positive inclusion bodies in the liver, which represent accumulations of the  $\alpha_1$ -AT protein. Although liver and mononuclear cells from PiZ patients can manufacture normal amounts of mRNA [244] and the protein can be translated, there is little secretion of the protein [245]. It is now recognized that the Z  $\alpha_1$ -AT gene is normal except for a single point mutation resulting from substitution of a guanine for adenine in the DNA sequence that codes for the amino acid at position 342 on the molecule. This produces a change in the normal amino acid sequence from glutamic acid to glycine [246]. Recently the consequences of this change, and hence the mechanisms producing  $\alpha_1$ -AT deficiency, have been elucidated. It appears that the charge of the amino acid at position 342 is important to the function of the protein [247]. The glutamic acid at position 342 is sited at the base of the inhibitory active site loop. Substitution of glutamic acid by glycine results in alteration in the normal 'hinge' mechanism at this region, thus extending the active site loop which can then fit between the A sheets of a second molecule. This results in spontaneous polymerization of the protein [248]. The consequence is that large polymers of  $\alpha_1$ -AT accumulate in the liver and are unable to pass through the rough endoplasmic reticulum, so impairing  $\alpha_1$ -AT secretion. The mechanisms of the other deficiency states have also been elucidated [249].

### Epidemiological factors in $\alpha_1$ -AT deficiency

In the UK approximately 86% of the population are PiMM and have been used to establish the normal levels of  $\alpha_1$ -AT within the population (Table 23.3). The other phenotypes

**Table 23.3** Serum  $\alpha_1$ -proteinase inhibitor concentrations and the frequency of the more common phenotypes and the risk for emphysema. (Modified from Stockley & Afford [326].)

Phenotype	Percentage in UK population	Average concentration (g/L)	Risk factor for emphysema
MM	86	2	No
MS	9	1.6	No
MZ	3	1.2	No
SS	0.25	1.2	No
SZ	0.2	0.8	Yes
ZZ	0.03	0.4	Yes

are much less common and of these SZ and ZZ are associated with severe deficiency and MZ and SS with partial deficiency. The association between emphysema and severe deficiency of the ZZ [250], SZ and the rarer Null phenotypes [251] is well known. Other variants of  $\alpha_1$ -Pi (MZ, MS, SS), with serum levels greater than 50% of the values in PiMM subjects, are not definitely associated with an increased risk of developing COPD. PiSZ subjects have significantly lower serum  $\alpha_1$ -Pi levels than other heterozygotes. However, an increased risk of developing COPD has only been demonstrated in one study [252] but not in another two [253,254].

The commonest heterozygote phenotypes, MZ and MS, affect 3 and 8% of the UK population and these subjects have been extensively studied. Although hospital-based studies have shown a two- to five-fold excess of PiMZ in patients with COPD [255,256], population surveys have shown significant changes in spirometry only in PiZZ subjects [256] and either no [257] or only minor changes in lung elasticity have been demonstrated [258]. Only one prospective study of PiMZ subjects who smoked showed an accelerated annual decline in FEV<sub>1</sub> [259]. However, recent studies from the  $\alpha_1$ -AT registry in the USA indicate that although the PiSZ phenotype confers a significant risk of developing COPD in smokers, there is probably no added risk in non-smokers [260]. Thus whether the MZ phenotype is associated with an increased risk of emphysema remains controversial, but any effect is small in comparison to other risk factors.

Although the relationship between severe  $\alpha_1$ -AT deficiency and emphysema is well established, since few patients who have a PiZZ phenotype and who smoke survive beyond 60 years of age [34], it is clear that the number of patients identified as PiZZ is much less than can be predicted from the prevalence of the deficiency. Therefore some individuals with this deficiency do not develop severe airways obstruction [250]. The true prognosis of subjects with PiZZ is unknown, since many are clearly asymptomatic and therefore do not present themselves for detailed investigation. In Sweden, Larsson [34]

identified 246 PiZZ subjects from a population calculated to contain as many as 4000 individuals over the age of 20 with this phenotype. In the UK one would expect around 2000 PiZZ subjects between the ages of 45 and 55. However, in a national survey over several years, only 100 individuals were identified [250]. Although a number may have died from hepatic disease, it seems likely that a large proportion of PiZZ individuals do not develop any significant respiratory abnormalities and thus remain undetected. From the geographical distribution of the Z deficiency, the mutation is likely to have originated in Scandinavia and spread thereafter to north-western Europe. Deficiency of  $\alpha_1$ -AT in the serum also results in a deficiency in the lung lining fluid [261], since  $\alpha_1$ -AT enters the lung largely by diffusion from the plasma.

Since  $\alpha_1$ -AT is the only major inhibitor of neutrophil elastase in the lower airways [262], the presence of increased numbers of neutrophils in the lungs of subjects with  $\alpha_1$ -AT deficiency [261], attracted by increased release of chemotactic factors from alveolar macrophages [263], may create an increased elastase burden in the presence of an antielastase deficiency. It appears that the development of emphysema, and hence the decrease in life expectancy of  $\alpha_1$ -AT-deficient subjects, occurs particularly in the presence of the additional risk factor of smoking [34]. However, there are some patients who survive to old age with relatively well-preserved lung function even if they smoke. Thus our view of the natural history of  $\alpha_1$ -AT is biased since individuals are recognized, and therefore only followed up, when they develop symptoms and thus may not be representative of the whole population of  $\alpha_1$ -AT-deficient subjects. Greater identification of subjects with  $\alpha_1$ -AT deficiency who are asymptomatic and their follow-up should give new insights into the pathogenic mechanisms of the development of emphysema in these individuals.

### Pathogenesis of emphysema in patients without $\alpha_1$ -AT

The pathogenic mechanisms of emphysema and also of small airways disease in COPD is clearly more complex in patients without  $\alpha_1$ -AT deficiency. In this case the most clear association is with cigarette smoking. There are several possible mechanisms whereby cigarette smoke can alter the elastase–antielastase balance in the lungs, assuming that neutrophil elastase and  $\alpha_1$ -AT are the main players in this protease–antiprotease imbalance. In addition the role of other proteolytic enzymes derived from cells other than neutrophils have to be considered, as well as the effects of lung antiproteases other than  $\alpha_1$ -AT. Finally, there is the additional effect on retardation of elastin resynthesis by cigarette smoke, which has received much less research attention than that paid to the protease–antiprotease imbalance.



Since only 15–20% of cigarette smokers develop COPD, the question of susceptibility has to be considered. There are several pathogenic variables in the development of COPD, which may be genetically determined and may therefore play a significant role in the ultimate clinical course of patients who develop COPD. Such factors include the cellular response to tobacco, bronchial hyper-reactivity, variations in neutrophil and macrophage protease activity, protease inhibitor function and lung matrix injury and repair. Further understanding of the genetic determination of these factors may allow us to understand why some patients who smoke do not develop COPD, and why a significant portion of individuals who have homozygous  $\alpha_1$ -AT deficiency have not yet developed significant evidence of airways obstruction or pulmonary emphysema.

The mechanisms for the development of pulmonary emphysema can be conveniently described under three major headings: (i) increased protease burden; (ii) decreased antiprotease function; and (iii) decreased synthesis of elastin.

#### **Increase in protease burden**

An accumulating body of evidence supports a role for neutrophil elastase in the development of emphysema [81,264]. There are several processes by which the elastase burden could be increased in cigarette smokers:

- 1 increased sequestration and migration of neutrophils into the lungs in smokers;
- 2 neutrophils from susceptible smokers may contain increased amounts of elastase compared with non-susceptible smokers or control subjects;
- 3 neutrophils, once recruited, may show enhanced degranulation, leading to more connective tissue injury.

Under normal circumstances a proportion of the neutrophils are delayed or sequester while in transit in the pulmonary microvasculature [265]. This intravascular pool of neutrophils, which appears to be slow-moving within the pulmonary capillary segments or transiently adherent to the alveolar capillary endothelium, represents a source of cells that can migrate from the capillaries into the alveolar spaces in response to chemotactic stimuli. A small proportion of neutrophils migrate normally into the airspaces in response to inhaled allergens and toxins. The number of neutrophils in the airspaces is considerably increased in smokers [266]. In some studies a 10-fold increase in the number of neutrophils in BAL was demonstrated in smokers, although macrophages still remain the most predominant cell [267]. It appears that in some smokers an increased number of neutrophils become sequestered in the pulmonary microcirculation *during* smoking [182] via a mechanism that involves a decrease in the deformability of the neutrophils [184], so decreasing their ability to change their shape and pass through the

smaller diameter pulmonary capillary segments [104]. Once sequestered, the cells may be acted upon by cytokines to increase their adhesion to the endothelium and can migrate into the lung along chemotactic gradients. Although little is known of the details of this process in the lungs, there are several pieces of evidence that indicate enhanced chemotaxis in cigarette smokers.

Nicotine itself is chemotactic [268] and lung lavage fluids from smoke-exposed animals show increased chemotactic activity [269]. Chemotactic factors may also be released from bronchial epithelium [270]. There is some evidence suggesting a deficiency of a chemotactic factor inactivator in the serum of patients with  $\alpha_1$ -AT deficiency [271], which could lead to uncontrolled recruitment of neutrophils to the airspaces in these patients. It is possible that similar mechanisms play a role in patients without  $\alpha_1$ -AT deficiency. There is also evidence that circulating neutrophils are sensitized to chemotactic signals, even in passive smokers [272], and that neutrophils from patients with COPD show an enhanced response to standard chemotactic agents compared with non-smoking matched controls [273].

Some investigators have reported an association between blood leucocyte elastase concentrations and airflow obstruction in patients with  $\alpha_1$ -AT deficiency [274,275] while others have not [276,277]. Conflicting results also come from studies of patients with normal levels of  $\alpha_1$ -AT, some studies supporting the concept [276] while others do not [278]. The elastase content of neutrophils has a wide range in healthy subjects [273]. It may be that those subjects who develop COPD have neutrophils that, when activated, release more elastase. However, there is controversy over whether the elastase content of neutrophils in subjects with or without emphysema is increased [273,279]. Some support for this concept comes from studies which show that neutrophils harvested from peripheral blood from patients with emphysema degrade more fibronectin *in vitro* than cells from control subjects matched for age and smoking [273], an effect largely due to neutrophil elastase [280]. Other studies have shown that immunoreactive leucocyte elastase concentrations in the serum of patients with COPD are double those in age-matched controls [281]. However, the same is true in patients with other lung diseases, such as bronchiectasis. Thus although there is support for an increased protease burden from circulating leucocytes in patients with COPD, this association is not necessarily causal.

Studies that have sought evidence for increased elastolytic activity in the airspaces, as measured in BAL, have shown only a small increase in elastase-like activity in smokers compared with non-smokers [282,283]. Much of this activity appears to be due to metalloproteases [283]. There is a fourfold increase in macrophages in BAL in cigarette smokers [267]. These cells can secrete

cytokines, which cause neutrophil activation and degranulation and can also ingest and later release neutrophil elastase.

Enzymes other than neutrophil elastase have been identified in the lungs, including two present in neutrophils, cathepsin G and protease 3. Cathepsin G is a relatively weak elastolytic enzyme compared with neutrophil elastase [284] but can act synergistically with neutrophil elastase to degrade elastin [285]. Studies to date have failed to demonstrate that this protease can produce emphysema [286]. It is therefore unlikely that cathepsin G has a major role in elastin degradation alone and hence the development of emphysema. Protease 3 is another human neutrophil serine protease that has been shown to induce experimental emphysema [287]. It is more potent at degrading elastase than neutrophil elastase in acid pH (7.5) but is less potent at neutral pH [276]. This enzyme is also bactericidal [288]. The role of protease 3 in the development of pulmonary emphysema in humans has yet to be elucidated.

As mentioned above, macrophages have the ability to internalize and subsequently release elastase [289]. This fact has complicated the interpretation of earlier studies which showed that macrophages are capable of releasing elastolytic enzymes [290]. However, subsequent studies confirmed that human macrophages produce a metalloelastase [291] and other studies have shown that these cells also produce a cysteine protease (cathepsin L), which also degrades elastin at acidic pH [292]. Other studies have shown that cathepsin B is also present in macrophages [293]. Although several enzymes have the potential to degrade elastin, studies of BAL have not, as yet, provided any clear evidence to support a role for these other elastolytic enzymes in the pathogenesis of emphysema.

Studies measuring neutrophil elastase-like activity in BAL have been generally disappointing. Although values of elastolytic activity in BAL are higher in smokers than non-smokers [294,295], this may be a transient effect of acute smoking [296]. Others have demonstrated low elastase-like activity, which was increased in BAL in patients with emphysema [297]. However, this elastolytic activity does not appear to be due to neutrophil elastase, suggesting that either protease 3 or cathepsin G may be responsible.

### Decreased antiprotease function

A critical event in the protease–antiprotease theory of the pathogenesis of emphysema is the concept of a functional deficiency of  $\alpha_1$ -AT in the airspaces produced by smoking due to oxidation of the methionine-358 residue at the active site of the  $\alpha_1$ -AT molecule. This can occur by a direct oxidative effect of cigarette smoke or by oxidants released

from activated airspace leucocytes [298,299]. A decrease in  $\alpha_1$ -AT function has been confirmed in the lungs in animal models [300] and in at least one study in the lungs of healthy smokers [301]. In addition to the direct oxidant effect of cigarette smoke, both macrophages [302] and neutrophils [303] from cigarette smokers release more reactive oxygen species than cells obtained from non-smokers, and can inactivate  $\alpha_1$ -AT *in vitro* [302]. However, measurements of  $\alpha_1$ -AT in BAL from cigarette smokers indicate that  $\alpha_1$ -AT remains active in smokers [304]; indeed most studies comparing  $\alpha_1$ -AT function in BAL from healthy smokers and non-smokers have failed to find any difference [305,306], although it has been hypothesized that this may be due to mixing of the protein over wide areas in the lungs. Thus there is controversy as to whether the antielastase inhibitory activity of BAL is decreased in smokers, some workers finding it to be fully functional [307,308] and others finding it to be inactivated [305,306,309]. Although Gadek *et al.*'s original study in 1979 [310] showed a reduction in antitrypsin function by 40% in cigarette smokers and later studies revealed the presence of oxidized  $\alpha_1$ -AT in lungs of healthy smokers [301], more recent studies using specific monoclonal antibodies have failed to detect significant amounts of oxidized  $\alpha_1$ -AT in BAL fluid from smokers [311].

Thus studies on the elastase–antielastase imbalance in BAL have failed to produce clear supportive evidence in humans for the protease–antiprotease theory; in particular there is no strong evidence for an imbalance between elastase and  $\alpha_1$ -AT in cigarette smokers. Furthermore, the question of susceptibility of some cigarette smokers to the development of emphysema has not been fully addressed. Several explanations have been proffered to explain this somewhat unclear picture:

- 1 other antielastases may contribute to the antiprotease shield in the lungs, in addition to  $\alpha_1$ -AT;
- 2 more subtle mechanisms may reduce the inhibitory activity of  $\alpha_1$ -AT;
- 3 the protease–antiprotease imbalance occurs in a microenvironment or the lung interstitium, which is not sampled by BAL.

### Other antiproteases

There is considerable controversy regarding the role of other antiproteases in the pathogenesis of emphysema. This controversy is probably related to the techniques that have been used to address this problem. The simplest technique to assess the relative importance of different antiproteases is to compare the inhibitory ability of lung lavage fluid in the presence of known inhibitors. However, several antiproteases inhibit the same enzymes and thus the profile of individual antiproteases has to be assessed against a panel of enzymes in order to distin-

guish the extent of antiprotease activity related to a single antiprotease. This has led to the suggestion by some workers that less than 50% of the inhibition of neutrophil elastase in BAL fluid can be attributed to  $\alpha_1$ -AT [309,312], whereas others using different techniques suggest that  $\alpha_1$ -AT accounts for 90% of the antielastolytic activity in BAL [262].

Antileucoprotease (ALP) is an 11–12 kDa non-glycosylated protein present in lung and a variety of other body secretions. It is an important reversible inhibitor of several serine proteases [313] and is found in mucus, including that in the nose, lung and reproductive tract [314,315]. It is present in high concentrations in bronchial secretions, where it exceeds the concentration of  $\alpha_1$ -AT [316], and has also been shown to be present in Clara cells and peripheral airways [317], although it is present in lesser concentrations than  $\alpha_1$ -AT in BAL fluid [318]. At the bronchial level, ALP has been localized in the non-ciliated cells of the epithelium and the serous cells of the submucosal glands. In bronchioles ALP-producing cells have been identified as Clara and goblet cells [319]. Immunochemical quantification of ALP relative to  $\alpha_1$ -AT shows that the ALP/ $\alpha_1$ -AT molar ratio is approximately 0.1 in the peripheral airspaces [312,318]. In contrast the concentration of ALP in tracheobronchial secretions is three times greater than that of  $\alpha_1$ -AT. This suggests that ALP is a major inhibitor of neutrophil elastase in the large conducting airways. Immunohistological techniques indicate that ALP is present in the alveolar wall of human lungs and, interestingly, is localized in association with elastin fibres [320]. Thus although there is a lower concentration of ALP than  $\alpha_1$ -AT in the peripheral airspaces, its localization in association with elastin, the fact that it is more effective than  $\alpha_1$ -AT at inhibiting neutrophil elastase already bound to elastin [321], that it has been shown to limit connective tissue destruction by adherent neutrophils [322] and that it may be more effective *in vivo* at inhibiting elastase locally in lung tissue all suggest that a major physiological role of ALP may be to inhibit elastin-bound elastase. This is in contrast to  $\alpha_1$ -AT, which inhibits elastase in solutions. Although these immunohistological studies suggest that ALP is an important inhibitor of neutrophil elastase, there is no evidence of a quantitative, functional or absolute deficiency of ALP in patients with emphysema. However, patients with  $\alpha_1$ -AT deficiency and emphysema have low concentrations in the sputum compared with patients with normal  $\alpha_1$ -AT levels [316].

The role of other antiproteases in the pathogenesis of emphysema in smokers is also unclear. An elastase-specific inhibitor called elafin has recently been isolated from bronchial secretions [323] and a low-affinity inhibitor of neutrophil elastase of similar size to ALP has also been demonstrated [316]. The role of these and other inhibitors, such as metalloprotease inhibitors [324] and cysteine

protease inhibitors (cystatins) [325], remain to be elucidated.

#### *Other mechanisms that reduce the effectiveness of antiproteases*

The inhibitory activity of  $\alpha_1$ -AT, as described above, is affected by oxidation. Additional mechanisms that reduce the activity of  $\alpha_1$ -AT include cleavage of the active site and complex formation with the enzyme. Both of these mechanisms produce a change in the molecular size of  $\alpha_1$ -AT; molecules of  $\alpha_1$ -AT with different molecular weights have been shown to be present in BAL from both normal subjects [309] and patients with emphysema [326]. Other subtle changes can occur in the activity of  $\alpha_1$ -AT in smokers, such as a reduction in the association rate constant of  $\alpha_1$ -AT from BAL for neutrophil elastase [327]. Similar changes in association rate constants are found in PiZZ individuals [328].

Although BAL studies do not indicate an absolute or a relative functional deficiency in  $\alpha_1$ -AT in cigarette smokers, it has been suggested that susceptible smokers do not increase their  $\alpha_1$ -AT levels appropriately during the acute-phase response to infection. Recent studies have shown a polymorphism in the  $\alpha_1$ -AT gene [329]. This polymorphism is due to a single change in the nucleotide sequence of the gene, which alters the recognition sequence for the restriction enzyme *TaqI*, thus producing failure of the enzyme to cleave DNA at this site. The area involved in this polymorphism has recently been shown to be an enhancer sequence that can amplify gene expression [330]. Thus the hypothesis is that patients with this polymorphism may not be able to mount an acute-phase response because of the failure of the enhancer sequence to increase gene expression.

#### *Protease–antiprotease imbalance in a microenvironment in the lungs*

A further explanation for the failure to conclusively demonstrate a protease–antiprotease imbalance in the BAL of smokers is that this imbalance occurs in a microenvironment in the lungs not sampled adequately by BAL. Support for this theory comes from studies which show that neutrophils have the ability to degrade connective tissue matrices even in the presence of active enzyme inhibitors [331]. This is thought to result from tight cell adherence to connective tissue substrates and release of the enzyme at the interface between the two, thus excluding surrounding inhibitors. This mechanism clearly cannot be absolute, since it should result in connective tissue degradation in all subjects who have neutrophil recruitment to the lungs. Although there is no direct evidence for this mechanism *in vivo*, neutrophil elastase can

degrade connective tissue *in vitro*, even in the presence of  $\alpha_1$ -AT [321]. Thus the neutrophil has the potential to degrade elastin in a microenvironment, both when sequestered in the microcirculation, during migration through the lung interstitium, or in the airspaces. It has been suggested that the proteolytic imbalance responsible for emphysema may even be derived from neutrophils delayed in the microvasculature by cigarette smoke [332]. These neutrophils may be triggered to release reactive oxygen species that inactivate  $\alpha_1$ -Pi and allow proteolytic enzymes to diffuse the short distance from the neutrophil to elastin and collagen in the alveolar wall. Some support for this hypothesis comes from the marked decrease in the antioxidant capacity of the plasma that occurs during acute cigarette smoking [333]. This increased oxidant stress in the intravascular space could increase the sequestration and adhesion of neutrophils in the pulmonary microvasculature and in addition enhance the inactivation of  $\alpha_1$ -AT.

### Decreased elastin resynthesis

Immunologically reactive elastase, which can be measured in plasma and BAL fluid, is usually in an inactive form complexed with inhibitors. In order to determine the activity of the released enzyme rather than its amount, techniques have been developed to measure functional elastolytic activity in body fluids and to use these measurements to determine susceptibility in populations of smokers or patients with COPD.

Several studies have attempted to measure products of elastin degradation as a reflection of the excess proteolytic activity which is thought to occur in emphysema. The concentrations of the elastin cross-linking peptide desmosine and elastin peptides are elevated in experimental emphysema [334], in smokers and in patients with COPD [335]. The impact of these results is diminished by the fact that elevation of these degradation products is not specific for elastin degradation in the lungs, particularly as the turnover of lung elastin is likely to be very slow [336], and therefore measurements of the levels of these products should be minimal in normal individuals. In fact there is a high background level for the excretion of desmosine in normal non-smokers and this may mask the small changes that may be observed in smokers [337]. Thus no difference has been detected between urinary desmosine measurements in normal adults and those with  $\alpha_1$ -AT deficiency and emphysema or in asymptomatic adults with the PiZZ phenotype [338]. However, a recent study in a small group of smokers demonstrated that urinary desmosine levels were 36% greater in those smokers with a rapid decline in FEV<sub>1</sub> (91±27 mL/year) compared to those with a slow decline in FEV<sub>1</sub> (7±25 mL/year) [339].

Fibrinogen degradation products can be measured as an assessment of the activity of released elastase. The assay is

based on the fact that neutrophil elastase cleaves fibrinogen at the 21–22 amino-terminal sequence of the A $\alpha$  chain to generate an A $\alpha$  1–21 peptide, which would therefore be a specific indicator of elastase activity. Although early studies suggested that this peptide was elevated in both smokers [340] and patients with  $\alpha_1$ -AT deficiency [341], doubts over the suitability of A $\alpha$  1–21 as a marker of elastase activity have been voiced since the peptide is very labile and rapidly degrades to A $\alpha$  1–19 [342]. Furthermore, studies of the relationship between plasma or serum elastin-derived peptides and emphysema, as measured by CT, has produced conflicting results [343,344].

It has been suggested that a further factor leading to the development of emphysema is a defect in elastin resynthesis. Lysyl oxidase is an enzyme required for the cross-linking of elastin fibres and so is necessary for the formation of normal tissue elastin. Emphysema has been described in the connective tissue disorder cutis laxa, which may be partly due to a defect in lysyl oxidase activity [345]. Lathyrogens, which prevent elastin cross-linking, can be used to produce experimental emphysema [346]. There is some evidence to suggest that lysyl oxidase activity is reduced by cigarette smoking and this may contribute to emphysema by preventing elastase repair [347].

## Pathophysiology

### Lung mechanics

The characteristic physiological abnormality in COPD is a decrease in maximum expiratory flow. The concept of the 'equal pressure point' was developed by Mead and colleagues [348], who suggested that during forced expiration an equal pressure point develops in the airways, where the airway pressure becomes equal to the pleural pressure. The pressure driving flow from the alveoli to these equal pressure points is approximately the same as the static recoil pressure of the lungs. Thus three major factors can reduce forced expiratory flow: (i) loss of lung elasticity; (ii) an increase in airways resistance upstream from the equal pressure points; and (iii) an increase in the compliance of the airways downstream from the equal pressure points. When discussing lung mechanics it is useful to relate changes in patients with stable COPD to the stages of the disease, whether mild, moderate or severe. A review of the changes in lung mechanics in acute-on-chronic respiratory failure are described in detail elsewhere [349].

### Mild COPD

The enormous total cross-sectional area of the peripheral airways available for airflow means that the small peripheral airways, which are 2–3 mm or less in diameter, contribute relatively little to the total airways resistance in healthy subjects [171]. Amongst the earliest pathological

changes in cigarette smokers are those in the small bronchi and bronchioles and thus tests have been developed to study function in these peripheral airways. In advanced COPD, peripheral airways are the major site of the increase in total airways resistance. However, in the early stages of the disease, considerable obstructive changes can occur in the peripheral airways without causing significant changes in total airways resistance or maximum expiratory flow [350]. In its early stages the airspace enlargement characteristic of emphysema also has little effect on lung function.

In healthy young subjects, significant airway closure only occurs below functional residual capacity (FRC) [351]. However, enhanced airway closure occurs in the early stage of COPD and this can be measured by plotting nitrogen concentrations against expired volume following a single vital capacity (VC) breath of 100% oxygen. The 'closing volume' measures the lung volume at which expired nitrogen concentrations increase abruptly during slow deflation from total lung capacity (TLC). The closing volume is determined by the lung volume at which some lung units close their airways and hence stop emptying. In healthy young non-smokers, closing volume is about 5–10% of VC. This rises to 25–35% of VC in old age. Compared with non-smokers, young asymptomatic adult smokers have an increase in closing volume. As airways disease progresses the ability to define a closing volume decreases and therefore the test is not useful in established disease. However, follow-up studies of asymptomatic smokers over 10 years indicate that those who eventually develop a reduced  $FEV_1$  initially had an abnormal single-breath nitrogen test. Conversely, many subjects who had an abnormal single-breath nitrogen test did not develop an abnormal  $FEV_1$  over that period [352–354]. The slope of the plot of expired nitrogen concentration against expired volume is also a reflection of early disease, the greater the slope the more uneven being the distribution of ventilation and the more asynchronous the emptying of the lungs.

In comparison to healthy non-smokers, asymptomatic smokers also show frequency dependence of lung compliance, implying increased inequality of time constants in the lungs, resulting from changes in the compliance and resistance of parallel lung compartments [355]. Since the earliest pathological changes in COPD occur in the peripheral airways, it has been suggested that this might be reflected in changes in maximum flow at low lung volumes, below 50% of VC. The normal density dependence of maximum flow at 50% of VC ( $\dot{V}_{max_{50}}$ ) is decreased in some asymptomatic smokers, suggesting a greater contribution of density-independent flow regimes due to laminar flow, presumably in peripheral airways. However, some patients with established COPD retain a normal  $\dot{V}_{max_{50}}$ , possibly because the site of flow limitation remains in the large airways [356]. In addition the lack of a

relation between change in  $\dot{V}_{max_{50}}$  breathing air and helium and pathological changes in the peripheral airway [218,357] has meant that these tests are not in widespread use as a method of detecting mild COPD.

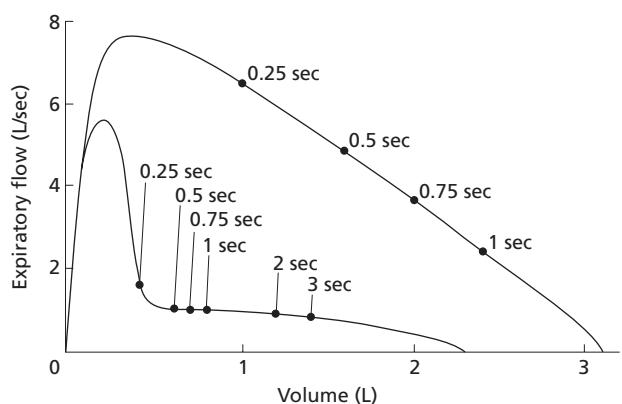
Asymptomatic smokers may show a small reduction in  $K_{co}$  [141]. There is a relationship between measurements of microscopic emphysema and  $K_{co}$ , although emphysema does not explain all the variation in  $K_{co}$  in this relationship [154].

### Moderate to severe COPD

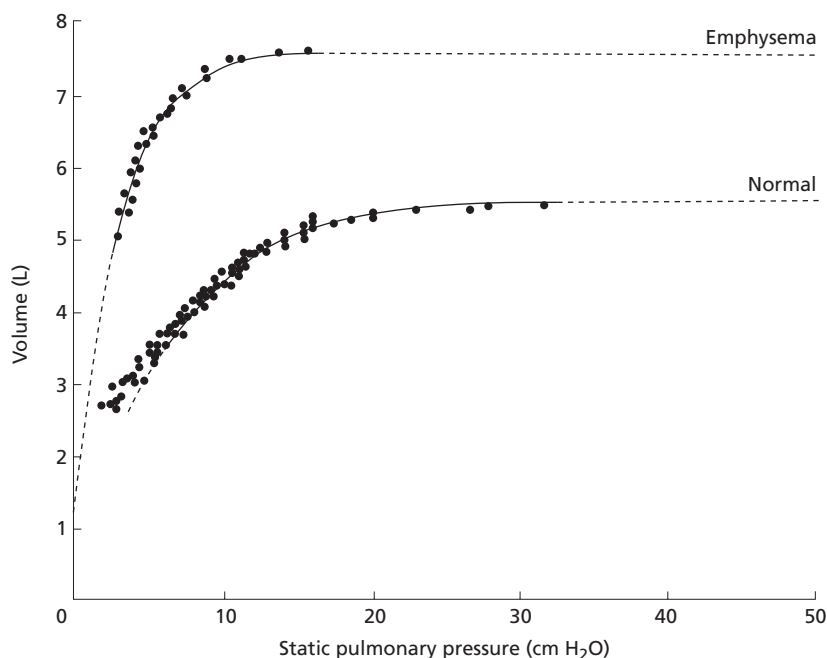
With the development of symptoms of breathlessness, tests of overall lung mechanics such as  $FEV_1$  and airways resistance become abnormal in patients with COPD. These are usually associated with an increase in residual volume (RV) and FRC and in some cases an increase in TLC. Maximum expiratory flow–volume curves show a characteristic convexity towards the volume axis, with (initially) preservation of peak expiratory flow (PEF) and the greatest reductions in expiratory flow at lower lung volumes close to RV (Fig. 23.11).

The uneven distribution of ventilation in advanced COPD causes a reduction in 'ventilated' lung volume and thus  $TLCO$  is almost always reduced, although  $K_{co}$  may remain relatively well preserved in those without emphysema.

The characteristic changes in the static pressure–volume curve of the lungs in COPD are an increase in static compliance and a reduction in static transpulmonary pressure ( $P_L$ ) at a standard lung volume (Fig. 23.12). These changes are generally thought to indicate emphysema. The lung pressure–volume curve can be fitted to a single exponential according to the equation:



**Fig. 23.11** Maximum flow–volume curves in a healthy subject (forced expiratory volume in 1 s,  $FEV_1$ , 2.4 L) and a subject with chronic obstructive pulmonary disease (COPD) and airways obstruction ( $FEV_1$  0.8 L). The development of convexity of the expiratory curve in mild obstruction is characteristic, as is the relative preservation of peak expiratory flow in the patient with COPD.



**Fig. 23.12** Static expiratory pressure–volume curves of lungs in a subject with severe emphysema compared with a normal subject. The broken lines represent extrapolation of the curve to infinite pressure and to the volume axis at zero pressure. (From Gibson *et al.* [359] with permission.)

$$V = V_{\max} - Ae^{-kp}$$

where  $V_{\max}$  represents the theoretical ‘maximal lung volume’ at infinite pressure,  $A$  is the volume difference between  $V_{\max}$  and the volume at zero  $P_L$ , and  $k$  the shape factor that describes the curve and has the dimension  $\text{cm} \cdot \text{H}_2\text{O}^{-1}$ . The constant  $k$  is useful since it describes the shape of the curve independent of the absolute volume of the lung. The shape factor  $k$  rises with increasing age [358,359]. Colebatch and coworkers [358] found a good relationship between an increase in  $k$  and the presence of relatively severe emphysema, measured in postmortem lungs. Similar, but rather weak relationships have been shown between  $k$  or  $P_L$  at 90% of TLC ( $P_{L_{90}}$ ) and macroscopic emphysema in surgical or postmortem lungs [360], and between abnormalities in the pressure–volume curve and the mean number of alveolar attachments to small airways [217,233].

It appears that areas of the lung affected by severe macroscopic emphysema, such as bullae, may not change lung volume at all during a VC manoeuvre and therefore contribute to the static pressure–volume curve only by displacing it to larger absolute volumes. An extension of this hypothesis is that changes in the pressure–volume curve in emphysema are less influenced by localized macroscopic emphysematous changes than by changes in the overall microscopic airspace enlargement, which accompanies and may precede the macroscopic changes. Kim and coworkers [199] used a microscopic scoring system to characterize emphysema into its centriacinar and panacinar forms. In the centriacinar form the distal airspace enlargement occurs around the respiratory bron-

chioles and in the alveolar ducts of the primary lobule, whereas in the panacinar form all the airspaces are enlarged. When they assessed microscopic emphysema as  $L_m$  (p. 631), the mean value for both types of emphysema was not different; however, those with centriacinar emphysema had a significantly increased SD, whereas those with the panacinar type had a narrow SD, indicating uniformly increased alveolar size. However, despite similar mean values of  $L_m$ , those with panacinar emphysema had a greater loss of lung elastic recoil (increased lung compliance, increased  $k$  and decreased  $P_{L_{90}}$ ) than those with centriacinar emphysema. They concluded that the pressure–volume curve in the lung was influenced more by the distribution of alveolar destruction, i.e. using the Swiss cheese analogy, by the ‘cheese’, rather than by the ‘holes’. Support for this contention comes from a study showing a correlation between pressure–volume variables and CT-derived measurements of lung density as an assessment of distal airspace size [361]. In established COPD the evolution of the changes in the pressure–volume curves are not known; however, studies in patients with homozygous  $\alpha_1$ -AT deficiency confirm that considerable change in the pressure–volume curve can occur at an early stage in the absence of airflow limitation.

The results of studies of pulmonary mechanics seem to indicate that the major site of the fixed airway narrowing in COPD is in the peripheral airways less than 2–3 mm in diameter. In addition, loss of lung elastic recoil pressure is also important in terms of airways obstruction, particularly in those with severe emphysema, as a result of a reduction in the distending force on all of the intrathoracic airways. Dynamic expiratory compression of the airways



is enhanced by loss of lung recoil and by atrophic changes in the airways and loss of support from the surrounding alveolar walls, allowing flow limitation at lower driving pressures and flows.

### Pulmonary gas exchange

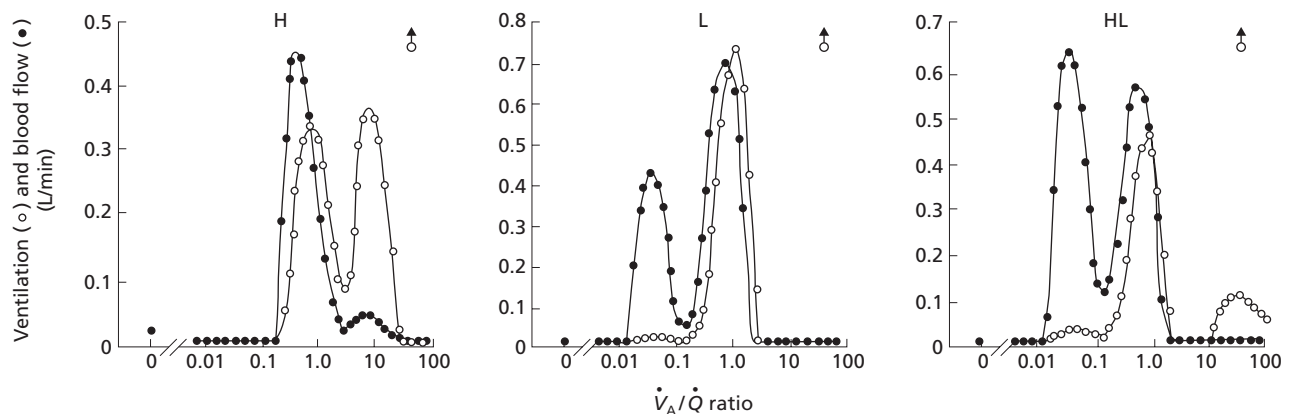
The underlying structural abnormalities in COPD result in disturbance of pulmonary gas exchange. Ventilation-perfusion ( $\dot{V}_A/\dot{Q}$ ) mismatching is the most important cause of impaired pulmonary gas exchange in COPD. Other causes, such as alveolar hypoventilation, impaired alveolar-capillary diffusion of oxygen and increased shunt, are of much less importance. The distribution of ventilation is very uneven in patients with COPD. A reduction of blood flow is produced by several mechanisms, including local destruction of vessels in alveolar walls as a result of emphysema, hypoxic vasoconstriction in areas of severe alveolar hypoxaemia and passive vascular obstruction as a result of increased alveolar pressure and distension.

The use of the multiple inert gas technique has shown various abnormalities in  $\dot{V}_A/\dot{Q}$  in patients with moderately severe COPD. In most patients the normal unimodal distribution of ventilation-perfusion is disturbed and a bimodal distribution is present. This bimodal distribution takes the form of distinct patterns [362] (Fig. 23.13). In the first pattern a substantial amount of ventilation is distributed to regions of high  $\dot{V}_A/\dot{Q}$  ratios, thus enlarging the physiological dead space. The second pattern is characterized by lung units where a large proportion of blood flow is diverted to areas with low  $\dot{V}_A/\dot{Q}$  ratios [362,363], although a true increase in anatomical shunt is unusual except in severe exacerbations of COPD, particularly those requiring assisted ventilation [364]. Thus in spite of severe unevenness of ventilation and even occlusion of many

peripheral airways, significant ventilation is still present in most areas of perfused lung, suggesting that collateral ventilation occurs. This is enhanced by lung distension in the presence of emphysema, where collateral channels are an important pathway for ventilation [365]. The third pattern is a combination of the first two.

Although a reduced  $TLCO$  is almost universal in advanced cases of COPD, analysis by the multiple gas technique does not suggest any significant alveolar-end-capillary limitation for oxygen at rest or during exercise, and that  $\dot{V}_A/\dot{Q}$  mismatching accounts for all of the hypoxia observed in these patients [362].

Patients with COPD have been divided on clinical grounds and blood gas abnormalities into two extreme presentations. Type A patients or 'pink puffers' have severe dyspnoea, a normal or low  $Paco_2$ , only a mild decrease in  $Pao_2$  at rest, and a low  $DLCO$ . These patients are hypoxaemic only at a late stage in the disease and therefore do not develop pulmonary hypertension, cor pulmonale and consequently fluid retention and secondary polycythaemia. In contrast, 'blue bloaters' or type B patients present with cough and sputum production and are likely to develop hypoxaemia and hypercapnia earlier in the course of their disease, and hence cor pulmonale, fluid retention and polycythaemia. The 'pink puffers' were thought to have predominantly emphysema and the 'blue bloaters' were the bronchitic type as described by Burrows and colleagues [366]. These types of presentation appear to represent two ends of a clinical spectrum in which most patients cannot be distinguished so clearly. However, Wagner and coworkers [367] in the late 1970s showed in 23 stable patients with advanced COPD that the majority of patients classified as 'pink puffers' had high  $\dot{V}_A/\dot{Q}$  patterns, whereas those characterized as 'blue bloaters' had no consistent pattern of  $\dot{V}_A/\dot{Q}$  ratios. They also found no



**Fig. 23.13**  $\dot{V}_A/\dot{Q}$  distributions in patients with advanced chronic obstructive pulmonary disease. Type H (high) represents a pattern where a substantial amount of ventilation is distributed to high  $\dot{V}_A/\dot{Q}$  regions; type L (low) depicts a profile where a marked amount of blood flow is diverted to low  $\dot{V}_A/\dot{Q}$  regions;

type HL is a mixture of both abnormal  $\dot{V}_A/\dot{Q}$  patterns. Shunt (left closed symbol) is trivial in all cases, whereas dead space (open symbol with arrow) is always moderately increased in all three patterns. (From Rodriguez-Roisin *et al.* [369] with permission.)



correlation between spirometry and the respiratory blood gases or  $\dot{V}_A/\dot{Q}$  ratio distributions in these patients [367]. These findings have been confirmed by others [368].

The blood gas abnormalities that occur during exacerbations of COPD may take several weeks to improve after treatment [369]. A study of sequential measurements in patients presenting with acute hypercapnic respiratory failure and COPD, but not requiring mechanical ventilation, showed that the severity of all the gas-exchange indices had improved after 1 month, with an increase in  $P_{aO_2}$  and a decrease in  $P_{aCO_2}$ . Indeed some of the distributions of  $\dot{V}_A/\dot{Q}$  inequalities had become unimodal [369]. These data suggest that some of the  $\dot{V}_A/\dot{Q}$  abnormalities occurring during exacerbations of COPD are due to partially reversible pathophysiological changes such as inflammation, producing airway narrowing and mucous plugging. Studies in patients with COPD requiring mechanical ventilation show that the patterns of  $\dot{V}_A/\dot{Q}$  abnormalities are more severe than those in patients breathing spontaneously [364]. The main difference between the stable group and the severe exacerbation/ventilated group is the presence of an intrapulmonary shunt of around 4–10% of cardiac output. This suggests that there is complete occlusion of some airways, possibly by bronchial secretions.

In severe but stable COPD, the patterns of  $\dot{V}_A/\dot{Q}$  distributions do not change on exercise [367] and may show a modest improvement in less severely disabled patients [368]. Barbera and coworkers [368] studied a group of 23 patients with a mild obstructive ventilatory pattern ( $FEV_1$  76% of predicted). The majority of these patients had a normal  $TLCO$ . The  $P_{aO_2}$  and  $P_{aCO_2}$  were also normal and the mean alveolar–arterial  $P_{O_2}$  gradient was moderately increased ( $>2$  kPa, 15 mmHg). These patients had only mild abnormalities in the dispersion of ventilation and blood flow, there was no evidence of an increase in shunt and the dead space was normal. Blood flow distributions were unimodal in two-thirds of patients and bimodal in the remaining one-third. In contrast, the ventilation distributions were never bimodal and therefore there were no areas of very high  $\dot{V}_A/\dot{Q}$  ratios. Preliminary studies suggest that functional abnormalities in small airways can produce maldistributions of ventilation and hence  $\dot{V}_A/\dot{Q}$  mismatching in the face of a normal  $P_{aO_2}$  [370].

There is a broad relationship between spirometry and blood gases in patients with COPD, where  $P_{aCO_2}$  rises when the  $FEV_1$  falls below 1.5 L [371]. This relationship also shows that although most patients whose  $FEV_1$  is less than 1 L have some degree of hypercapnia, many patients have normal  $P_{aCO_2}$  with very severe degrees of airways obstruction.

## Respiratory muscles

In patients with severe COPD a combination of pul-

monary overinflation and malnutrition, resulting in muscle weakness, reduces the capacity of the respiratory muscles to generate pressure over the range of tidal breathing. In addition, the load against which the respiratory muscles need to act is increased because of the increase in airways resistance. Overinflation of the lungs leads to shortening and flattening of the diaphragm, thus impairing its ability to generate pressure in order to lower pleural pressure. During quiet tidal breathing in normal subjects, inspiration is achieved predominantly by contraction of the diaphragm and expiration is largely passive, and depends on the elastic recoil of the lungs and the chest wall. As a result, patients with COPD need increasingly to use their rib cage muscles and inspiratory accessory muscles, such as the sternomastoid, even during quiet breathing. During exercise, this pattern may be even more distorted and on occasions results in paradoxical motion of the rib cage. Surprisingly, although the airway narrowing worsens on expiration in COPD, the respiratory muscles have most problems on inspiration.

The respiratory muscles show some morphological abnormalities in patients with COPD that could theoretically contribute to muscular weakness. Although the proportions of type I fibres (slow-contracting) and type II fibres (fast-contracting: type IIA fatigue resistant; type IIB fatiguable) are similar in normal subjects and in patients with COPD, subtle changes are present in these patients, such as a decrease in the diameter of individual fibres, variations in fibre size and splitting of fibres [372]. In addition, in autopsy studies of patients with severe COPD, the diaphragm, the main inspiratory muscle, is reduced in weight greater than would be expected for the reduction in overall body weight in these patients [373]. The metabolic activity of the diaphragm in patients with COPD is less than in normal subjects [374]. This argues against any training effect in response to the chronic increased work in patients with COPD. In addition the respiratory muscles in patients with COPD show decreased levels of ATP, which is necessary for muscle contraction [375]. This, together with the effects of hypercapnia, hypoxaemia, electrolyte and mineral deficiencies and infection, may contribute to the generalized muscle weakness in patients with severe COPD.

Weight loss is a common feature in patients with advanced COPD, in spite of a normal or increased dietary intake. Together with the increased metabolic requirements of the respiratory muscles as a result of the increased work of breathing, this produces an abnormally high resting energy expenditure in these patients [376]. The presence of these abnormalities has led to attempts to improve nutrition and hence respiratory muscle function in patients with COPD.

Clinical assessment of the global function of the respiratory muscles is often performed by measuring maximum inspiratory and expiratory mouth pressures ( $P_{imax}$ ,

$P_{Emax}$ ). Patients with COPD have impaired values of  $P_{imax}$  [377], although these measurements are very effort dependent. Diaphragmatic function can be assessed during inspiration by measurement of transdiaphragmatic pressure ( $P_{di}$ ) using balloon-tipped catheters or small transducers placed in the oesophagus and stomach. Measurements of  $P_{di}$  are also reduced in patients with COPD [378]. However, there is evidence that diaphragmatic function remains well preserved, at least in well-nourished patients with COPD [379], probably as a result of adaptation to overinflation via a mechanism that has not as yet been fully elucidated [379].

In patients with COPD and severe airways obstruction, expiratory airflow limitation occurs even during tidal breathing. This has led to the concept of 'dynamic hyperinflation' where expiration ends at a lung volume above FRC; as a consequence, inspiratory muscle contraction for the next inspiration occurs before expiratory flow ceases. This increases the burden on the inspiratory muscles as a result of an increase in elastic load associated with tidal breathing over a higher volume range. Thus the inspiratory muscles have to overcome what has been termed 'intrinsic positive end-expiratory pressure' before inspiration and hence lung inflation can commence.

### Respiratory muscle fatigue

Respiratory muscle fatigue is defined as a loss of the capacity of the muscles to develop force and/or velocity, resulting from muscle activity under load, that is reversible by rest [380]. The fact that it is reversible by rest distinguishes fatigue from muscle weakness. Numerous studies have explored the hypothesis that respiratory failure in patients with COPD is due to respiratory muscle fatigue [381]. Despite extensive investigation using various methods of assessment, including response to electrical stimulation, analysis of electromyographic spectra and analysis of the relaxation rate of the diaphragm, the evidence for respiratory muscle fatigue in experimental studies in patients with COPD during normal breathing is still a matter of debate [382,383].

The principle of the fatigue threshold for a muscle that contracts intermittently, such as the diaphragm, depends on the tension developed and the duration of each contraction. Thus diaphragmatic fatigue has been assessed by calculation of the tension–time index, which is the product of the mean  $P_{di}$  (as a fraction of  $P_{dimax}$ ) and the proportion of each breathing cycle spent on inspiration, i.e. the time during which the diaphragm is contracting (the so-called 'duty cycle') [384]. At rest, fatigue is considered to occur when the tension–time index is in the range 0.15–0.20. Since the mean  $P_{di}$  during a breath is increased in patients with COPD whereas the  $P_{dimax}$  decreases, this means that a threefold increase in  $P_{di}$  would be sufficient to push the tension–time index into the range at which

fatigue is likely to occur, in comparison to the eightfold increase that would be necessary in a normal subject [385]. Although patients with COPD have a higher tension–time index than normal subjects, the value does not lie within the fatiguing range [385]. Although hypercapnic patients with COPD have a higher tension–time index than those who are normocapnic [386], the tension–time index does not exceed the fatigue threshold, even in those who have severe hypercapnia [387].

### Breathing adaptations in patients with COPD

As a result of the respiratory muscle dysfunction in patients with COPD, patients with severe disease adopt a characteristic breathing pattern during tidal breathing, consisting of rapid frequency and a small tidal volume. This pattern helps to avoid the development of respiratory muscle fatigue but predisposes patients to the development of hypercapnia [386]. In contrast to normal subjects, who during quiet tidal breathing have predominantly abdominal breathing, patients with COPD, due to the presence of overinflation, demonstrate a relative increase in the motion of the rib cage and a decrease in diaphragmatic movement [388].

The increase in anteroposterior diameter of the rib cage, the classical clinical sign of overinflation, does not appear to be due to an absolute increase in the anteroposterior diameter of the chest, since radiographic measurements in patients with COPD have shown that both the anteroposterior diameter and the angulation of the ribs in patients with COPD are similar, at the same absolute lung volumes, to those in normal subjects of a similar age [389]. This clinical sign is therefore probably due to the increased resting lung volume of such patients. Indrawing of the lateral rib-cage margin occurs in some patients with COPD on inspiration (Hoover's sign) and paradoxical inspiratory motion of the abdomen and lower sternum also occurs as a result of overinflation [386]. The characteristic posture that many patients with severe airway obstruction adopt, leaning forward with outstretched arms in support, is a further adaptation which improves the maximum inspiratory pressure ( $P_{imax}$ ) [390], probably by improving the length–tension characteristics of the diaphragm and thereby allowing it to generate more force more effectively, accompanied by a reduction in the activity of the inspiratory accessory muscles.

### Therapeutic interventions

#### Respiratory muscle training

Benefits in specific respiratory muscle function tests can be achieved with respiratory muscle training. Although improvements in respiratory muscle function tests can be demonstrated, there is no consistent improvement in

exercise performance in these studies. Indeed a meta-analysis of 17 randomized trials of respiratory muscle training in patients with COPD showed that although training, using either resistance breathing or isocapnic hyperventilation, improved respiratory muscle strength and endurance, there was no overall improvement in exercise tolerance [391].

### Drug therapy

Numerous *in vitro* studies have shown that methylxanthines such as theophyllines (in doses not possible in humans) potentiate the response of fresh and fatigued muscle strips to an electrical stimulus. The results *in vivo* in humans have been less convincing and have either reported small or no improvements in the  $P_{di}$  generated during maximal voluntary effort [392,393].

### Ventilatory support

Some uncontrolled studies have suggested that resting the respiratory muscles, by long-term nocturnal use of either negative pressure applied to the chest wall or intermittent positive pressure ventilation (IPPV) using a nasal mask, results in some improvement in respiratory muscle function. However, a large controlled study failed to show any benefit on respiratory muscle function in patients with COPD [394]. Indeed the increase in negative intra-airway pressures generated by negative pressure ventilation may result in obstructive sleep apnoea in a few patients [395]. The use of nasal IPPV has been supported by uncontrolled studies that suggest benefit [396,397], but larger controlled studies are required before this form of treatment can be recommended in patients with chronic stable COPD.

### Nutritional supplementation

The results of controlled trials on the effects of nutritional supplementation on respiratory muscle function in malnourished patients with COPD have shown no consistent benefit [398–402]. Those studies that have achieved positive results have done so in association with an increase in weight. However, the cost-effectiveness of these studies has to be questioned.

### Control of ventilation

There are three major factors that influence the motor output of the respiratory system: inputs from the chemoreceptors, mechanoreceptor input and cortical factors. These factors all have an influence on ventilation in patients with COPD and their influence can vary depending on the situation. The control of ventilation has always been considered to be deranged in patients with

COPD. However, the techniques for assessing ventilatory control in these patients are fraught with methodological problems. The classical techniques of the steady-state carbon dioxide response during progressive isocapnic hypoxia or hyperoxia and the carbon dioxide rebreathing test are difficult both to perform and interpret in patients with COPD, particularly those who are already hypoxaemic. A simple assessment of minute ventilation indicates that most patients in the stable state, even with severe COPD, have a normal or slightly increased minute ventilation compared with normal subjects [403,404]. Even in those in whom ventilation–perfusion mismatching or an increase in the physiological dead space results in a rise in  $P_{aCO_2}$ , minute ventilation remains in the normal range [403,405]. However, the use of ventilation as a measure of the ventilatory output in COPD is influenced by abnormal lung mechanics.

Measurement of mouth pressure in the first 0.1 s of an occluded inspiration ( $P_{0.1}$ ) is a non-invasive technique that gives an indication of the central drive to breathing [406]. However, in severe airways obstruction, with large swings in intrathoracic pressure, transmission of these swings may be delayed, which therefore reduces the  $P_{0.1}$  measured at the mouth [406]. However, allowing for these limitations, this is probably the best test of ventilatory control in COPD and has been used most often. The only test of ventilatory control not influenced by respiratory mechanics is electromyography of the diaphragm, which is a technically difficult test to perform. However, limited studies using this method suggest that diaphragmatic activity in patients with COPD, particularly in response to hypercapnia, is greater than in normal subjects [407].

Many studies have measured the ventilatory or  $P_{0.1}$  response to breathing carbon dioxide and have demonstrated that the chemoreceptor control of breathing is abnormal in patients with severe COPD [408–410]. There is agreement between these studies that there is a reduced ventilatory response to hypoxia and hypercapnia, which is usually associated with increased neural output compared with normal subjects. It is not clear whether the increased neural output can be explained by the increase in the mechanical load imposed on the respiratory system in COPD or whether this represents an intrinsic reduction in respiratory chemosensitivity. The data available suggest that an increase in the mechanical load on the respiratory system is responsible for the impaired ventilatory response to changes in blood gas tensions [411].

Another controversial issue relates to whether those patients with COPD who develop hypoxia and hypercapnia ('blue bloaters') differ in their responses from those who maintain their blood gases but have similar impairment in  $FEV_1$  ('pink puffers'). Some studies, using various techniques, suggest that hypercapnic patients have a lower respiratory drive to breathing than eucapnic patients [412,413], although this has not been confirmed in

other studies [414]. Methodological problems may have resulted in the apparent discrepancies between these studies. In addition, compensatory changes in cerebrospinal fluid acid–base status, as a result of chronic hypercapnia, may mask any acute changes that stimulate peripheral chemoreceptors and thus makes interpretation of these data difficult [415]. In patients with acute exacerbations of COPD and acute respiratory failure,  $P_{0.1}$  is five times greater than in normal subjects [404].

Support for the hypothesis that differences in hypoxic and hypercapnic drives to breathing account for the different clinical patterns of COPD comes from studies of healthy family members of patients afflicted by COPD. These studies avoid the problems inherent in studying respiratory drive in a patients with lung disease [416,417] and have shown that reduced hypercapnic and hypoxic drives to breathing occur more frequently in individuals whose relatives have developed hypercapnic COPD compared with relatives of those patients with similar degrees of airways obstruction who have not developed hypercapnia. However, larger studies are required to confirm these results.

### **Pulmonary hypertension, cardiac function and fluid balance**

Pulmonary arterial hypertension develops late in the course of COPD, with the development of hypoxaemia ( $P_{aO_2} < 8 \text{ kPa}$ , 60 mmHg) and usually hypercapnia. It is the major cardiovascular complication of COPD and is associated with the development of right ventricular hypertrophy (cor pulmonale) [418] and with a poor prognosis [419].

### **Pulmonary circulation**

Changes in the pulmonary circulation occur characteristically in the peripheral arteries in patients with COPD [228,420]. Among the earliest changes in the pulmonary vasculature that develop as airflow limitation worsens is thickening of the intima of the small pulmonary arteries [420,421]. Medial hypertrophy then develops in the muscular pulmonary arteries in those patients who develop pulmonary arterial hypertension [422]. Peripheral airway inflammation in patients with COPD may be associated with pulmonary arterial thrombosis [223].

When chronic hypoxaemia develops, the consequent pulmonary arterial hypertension is associated with right ventricular hypertrophy. Indeed a relationship has been shown between the usual  $P_{aO_2}$  in a group of patients receiving long-term oxygen therapy and the degree of right ventricular hypertrophy [223]. However, there is no relationship between right ventricular weight and the extent of emphysema in postmortem lungs [423]. Furthermore, the extent of emphysema, as measured by CT, does

**Table 23.4** Factors contributing to the development of pulmonary arterial hypertension in patients with COPD.

Destruction of the pulmonary vascular bed
Abnormal blood gas tensions
Abnormal pulmonary mechanics
Increased cardiac output
Blood volume changes
Increased blood velocity
Endothelial abnormalities

not correlate with the pulmonary arterial pressure in patients with COPD [424].

Several factors contribute to the development of pulmonary arterial hypertension in patients with COPD (Table 23.4). The most important of these factors is alveolar hypoxaemia. Hypoxia is a potent pulmonary vasoconstrictor in normal subjects [425]. Many studies have shown a negative correlation between oxygen saturation and pulmonary arterial pressure in patients with COPD [426]. However, supplemental oxygen therapy produces only a trivial fall in pulmonary arterial pressure, which seldom falls to normal values in these patients due to the presence of structural abnormalities in the pulmonary arteries. A positive correlation has also been shown between  $P_{aCO_2}$  and pulmonary arterial pressure [427].

Although the factors listed in Table 23.4 contribute to its development, the fundamental mechanisms resulting in pulmonary hypertension in patients with hypoxic COPD remain unclear [428]. There is increasing evidence that endothelial dysfunction is an underlying factor. This may result in a reduction in nitric oxide synthesis or release in response to hypoxaemia [429]. Thus the putative role of nitric oxide in preventing an excessive rise in pulmonary vascular tone, as a result of stimuli such as hypoxaemia, may be lost in COPD. Support for this contention comes from studies showing that isolated pulmonary arterial rings from patients undergoing lung transplantation for end-stage COPD have impaired endothelium-dependent vasodilatation [430]. It has also been suggested that nitric oxide may have an inhibitory effect on cell proliferation in the pulmonary vessel walls and therefore has a role in preventing the vascular remodelling that occurs in hypoxic COPD [429].

### **Pulmonary haemodynamics**

Pulmonary haemodynamics in patients with COPD depend on the stage of the disease. In patients with mild COPD, without severe hypoxaemia or hypercapnia, pulmonary arterial pressure is usually normal or only slightly elevated when measured at rest but may rise abnormally during exercise [431–434]. Cardiac output is normal, as are right atrial and right ventricular end-diastolic pressures. The vascular resistance is therefore normal or only slightly

**Table 23.5** Haemodynamics and blood gases in 74 patients with COPD and 32 normal subjects. (From Naeije [436].)

	COPD		Normal	
	Mean	Range	Mean	Range
$P_{aO_2}$ (mmHg)	43	23–67	91	75–105
$P_{aCO_2}$ (mmHg)	51	33–68	38	32–43
Cardiac output (L/min/m <sup>2</sup> )	3.8	2.3–5.8	3.6	2.6–4.5
Right atrial pressure (mmHg)	3	0–21	5	2–9
Mean pulmonary arterial pressure (mmHg)	35	15–78	13	8–20
Pulmonary artery wedge pressure (mmHg)	6	0–19	9	5–14
Pulmonary vascular resistance index (dyne/s/cm <sup>5</sup> /m <sup>2</sup> )	660	231–1377	58	40–200
Right ventricular stroke work index (g/m)	16	5–29	6	3–18

elevated when measured at rest but may rise markedly during exercise [431,433].

As airflow limitation and arterial blood gas abnormalities worsen, particularly when chronic hypoxaemia and hypercapnia are present, pulmonary hypertension develops at rest and worsens on exercise. However, even in patients with severe COPD when measurements are made in a clinically stable state, the pulmonary arterial pressure is only modestly elevated [435] (Table 23.5).

### Effects of pulmonary hypertension

The natural history of untreated pulmonary hypertension in patients with COPD is of slow progression. Weitzenblum and coworkers [436] found a change of greater than 5 mmHg in the mean pulmonary arterial pressure in only 33% of patients with established pulmonary hypertension, measured over a 5-year period. In these patients, hypoxaemia and hypercapnia also progressed. In spite of the slow progression, the presence of pulmonary arterial hypertension implies a poor prognosis. In one study, those who had a normal pulmonary arterial pressure had a 72% 4-year survival compared with a 49% survival in those whose pulmonary arterial pressure was elevated [437]. However, many other factors such as FEV<sub>1</sub> and arterial blood gas values also affect survival in COPD [437–439]. The presence of pulmonary arterial hypertension may therefore simply be a reflection of the severity of the disease and may not have a direct effect on mortality.

Mixed venous  $P_{O_2}$  also correlates with survival in patients with COPD [440]. It has been proposed that patients with COPD who have decreased oxygen carriage maintain a higher cardiac output as an adaptive mechanism to sustain normal tissue oxygenation. Thus failure to maintain an adequate cardiac output may worsen survival [435].

Cor pulmonale was defined by a WHO expert committee [441] as ‘hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of

the heart, as in congenital heart disease’. This is a pathological definition of limited clinical value since the diagnosis of right ventricular hypertrophy in life is imprecise. The definition was revised by Behnke and colleagues [442] who replaced the term ‘hypertrophy’ by ‘alteration in structure and function of the right ventricle’. However, the definition remains imprecise as it covers a spectrum of dysfunction from mild abnormality to frank right ventricular failure. Indeed the term ‘cor pulmonale’ is often misused as a synonym for right ventricular failure or to indicate the presence of pulmonary hypertension in patients with COPD [443].

The prevalence of right ventricular hypertrophy in a large European study of patients with ‘lung disease’ was 8.9% [444] and increased as airflow limitation worsened in patients with COPD, being present in 70% when the FEV<sub>1</sub> had fallen to 0.6 L [445]. The development of oedema in patients with hypoxic COPD is usually a late feature, often occurring during acute exacerbations of the condition [446]. However, a proportion of patients who develop pulmonary hypertension or indeed right ventricular hypertrophy never develop peripheral oedema [447]. Patients who are free of oedema at first presentation have developed oedema for the first time at a rate of 6% per annum in studies over a 3–4 year follow-up period [448].

### Clinical assessment of pulmonary haemodynamics

The presence of pulmonary hypertension produces accentuation of the pulmonary component of the second heart sound, and a systolic parasternal heave indicates right ventricular hypertrophy. However, these clinical signs are often difficult to detect in patients with COPD because of overinflation of the chest and posterior rotation of the heart [449]. Extra heart sounds and the murmur of tricuspid regurgitation, which are best heard on inspiration, all suggest right ventricular dysfunction but again may be obscured by overinflation; the jugular venous pressure is often difficult to assess due to large swings in intrathoracic pressure. Peripheral oedema may be due to other causes

such as hypoalbuminaemia. These signs develop late in the clinical course in patients with COPD and are not sensitive indicators of pulmonary hypertension or right ventricular hypertrophy.

The presence of pulmonary hypertension can be assumed on a plain chest radiograph if the right descending main pulmonary artery has a width greater than 16 mm [450]. However, in one study the sensitivity for detecting a mean pulmonary arterial pressure of greater than 20 mmHg was only 43%, with a specificity of 63% [451]. In a subgroup of patients with mild pulmonary hypertension (mean pulmonary arterial pressure 20–30 mmHg), the sensitivity was only 38%. Right ventricular hypertrophy or dilatation is not easily recognized on a plain chest radiograph, although encroachment into the retrosternal space on a lateral chest film can be a helpful sign [452].

ECG criteria for detecting right ventricular hypertrophy have a reasonably high specificity of 86 and 96% in two studies but have a relatively low sensitivity (38 and 63% respectively) [451,453].

Detectable tricuspid regurgitation by echo Doppler is probably the best technique to measure pulmonary arterial pressure non-invasively. In this technique the transtricuspid pressure gradient (DP) is calculated from the maximum velocity ( $v$ ) of the tricuspid regurgitant jet, using a simplified form of the Bernoulli equation: DP (mmHg) =  $4 \times v^2$ . Adding the transtricuspid gradient to the mean right atrial pressure (estimated clinically from the jugular veins) allows calculation of the right ventricular systolic pressure. In patients with a wide range of cardiac diseases and hence pulmonary arterial pressures, correlation coefficients between Doppler and cardiac catheter measurements have ranged between 0.89 and 0.97 [454]. A tricuspid regurgitant signal can be recorded in 90–100% of patients with clinical signs of right heart failure and is almost invariably present in those with a pulmonary arterial pressure of greater than 50 mmHg [455]. This falls to 72% in the absence of right heart failure [456] and can be as low as 24% in patients with COPD [457], although the detection rate improves with the use of saline contrast enhancement [458]. The pulsed Doppler technique can be used to record pulmonary artery flow velocity. Measurement from the Doppler pulmonary flow velocity curves of the time to peak flow velocity (or acceleration time), which is reduced in the presence of pulmonary hypertension, correlates significantly but variably with the pulmonary arterial pressure or pulmonary vascular resistance ( $r=0.65-0.96$ ); recovery rates for pulmonary flow velocity curves are high, ranging from 81 to 98% [456,457,459–461].

Two-dimensional and M-mode echocardiography have been used to assess right ventricular dimensions and function [462]. Quantitative techniques are available to assess right ventricular volume by echocardiography but are cumbersome and not used clinically. M-mode echocardiography can be used semi-quantitatively to assess right

ventricular dimensions from a parasternal view. A right ventricular end-diastolic dimension of greater than 25 mm is reasonably predictive of right ventricular enlargement, and a right ventricular wall thickness of more than 6 mm is associated with right ventricular pressure overload in patients with COPD [451]. Pressure overload on the right ventricle also produces right ventricular wall motion abnormalities, which can be qualitatively assessed but accuracy is heavily dependent on the experience of the operator. A characteristic abnormality associated with right ventricular pressure overload on two-dimensional echocardiography is systolic bowing of the interventricular septum towards the left ventricle [463].

There are problems with obtaining a good echocardiographic signal in patients with COPD [454,464], particularly related to overinflation of the lungs, which reduces the window available for the examination. Most studies report that an adequate examination can be obtained in more than 70% of patients, although the range of examinations from which clinically useful information can be obtained varies from 24 to 98% in published studies [451,457].

Right ventricular dimensions are more accurately assessed by magnetic resonance imaging (MRI) [465,466]. Right ventricular wall volume has been shown to correlate with pulmonary arterial pressure [465]. An emerging technology that may prove useful in the evaluation of patients with COPD is ultrafast CT, which can be used to assess ventricular volumes and systolic function [467]. Its role in COPD remains to be established. However the high cost of CT and MRI have limited their availability.

One of the major indications for assessing cardiac function in COPD is to determine the potential role of other cardiovascular diseases that may coexist and may contribute to the patient's symptoms. There is still some debate about whether left ventricular dysfunction contributes to the syndrome of cor pulmonale [468]. Measuring the pulmonary arterial pressure is not a routine test in the assessment of patients with COPD but may become more important if new therapeutic options become available for the treatment of pulmonary hypertension.

### Right ventricular function

The question of whether the right ventricle truly fails in patients with COPD is the subject of much debate [469,470]. The classical view of the development of 'heart failure' in patients with COPD is that hypoxia leads to pulmonary hypertension, which imposes increased work on the right ventricle, leading to right ventricular hypertrophy and eventually right ventricular dilatation and the development of peripheral oedema [471]. Thus the definition of right heart failure in this context is an inability of one or more of the chambers of the heart (the right ventricle in this case) to accept and expel venous return

throughout the range of physiological activity, without alteration of normal circulatory haemodynamics [472]. In such patients, however, the cardiac output remains normal or may even be slightly elevated [433,473].

The problem of assessing right ventricular function is the lack of a good non-invasive method of assessment, because of the wide variability of right ventricular geometry [474]. Radionuclide ventriculography overcomes this problem but may produce a falsely high value for right ventricular ejection fraction in the presence of tricuspid regurgitation. Right ventricular ejection fraction measured using this technique has a wide range of values in a population of patients with COPD but are on average lower than those in a normal population (<40%), particularly in patients who have developed peripheral oedema [475]. Studies using a combination of invasive pulmonary haemodynamics, measured by cardiac catheterization, and radionuclide ventriculography suggest that right ventricular contractility is maintained in patients with COPD when their condition is clinically stable, even in the presence of increased pulmonary arterial pressure [476].

In patients who have developed respiratory failure and peripheral oedema, pulmonary arterial pressure is greater than those studied in a stable state but decreases with treatment [433,473]. However, cardiac output remains normal in these patients compared with the low-output state that occurs in congestive cardiac failure [477]. In patients with oedema, right ventricular contractility is decreased [473], in association with an increase in right ventricular end-diastolic pressure and volume [473,478]. Although this decrease in right ventricular contractility may be related to the level of pulmonary arterial pressure in some patients [478], this has not been confirmed in all studies [473].

### Cause of the oedema

There is increasing evidence that the oedema which develops late in the course of the disease in patients with COPD may not be entirely due to right ventricular failure [479]. A complex balance exists between factors that promote salt and water retention and those that promote natriuresis in patients with COPD. The key factor leading to changes in salt and water balance in patients with COPD is the development of hypoxaemia in association with hypercapnia.

The most consistent change in renal function in patients with hypoxic COPD, particularly those with oedema, is a reduction in renal blood flow [480]. This fall in renal blood flow has recently been confirmed non-invasively by Doppler ultrasound [481]. Hypoxia and hypercapnia may interact to reduce renal blood flow. Hypercapnia reduces renal blood flow through catecholamine release and via a neurally mediated action [482].

In addition, arginine vasopressin (AVP) levels may be inappropriately high in patients with COPD who have

developed both hypoxia and hypercapnia, particularly those who have also developed oedema, and this may also contribute to increased water retention [483]. The mechanism of this increase in AVP is poorly understood but may relate to stimulation of AVP release as a consequence of activation of the renin-angiotensin system [484].

Several studies have now demonstrated changes in hormonal balance in patients with COPD and chronic respiratory failure, including activation of the renin-angiotensin-aldosterone system [483-485] and elevation of circulating catecholamines [484], particularly in those patients who have developed oedema [486,487]. Thus a decrease in renal blood flow, activation of the renin-angiotensin system and increase in AVP as a result of changes in blood gases lead to salt and water retention in patients with COPD. There is also some evidence that sub-clinical autonomic nerve dysfunction, which is relatively common in patients with severe COPD [488], may affect hormonal levels [489] and renal blood flow [490], and may also contribute to the salt and water retention in these patients [491].

However, several compensatory mechanisms that promote natriuresis are also activated in patients with hypoxic COPD [468]. The levels of atrial natriuretic peptide (ANP) are elevated in patients with COPD [492,493], particularly in those with oedema [494]. Increased release of ANP results from increased atrial stretch as a result of the presence of pulmonary hypertension [495]. ANP has a number of potential beneficial effects that could act to prevent the development of oedema in patients with COPD, including the promotion of natriuresis [496], decrease in plasma renin activity [497] and inhibition of angiotensin II-mediated aldosterone production [498]. Moreover, ANP produces pulmonary vasodilatation [496]. A number of other factors, including renal dopamine [499] and digoxin-like immunoreactive factor [500], may also be activated and promote natriuresis.

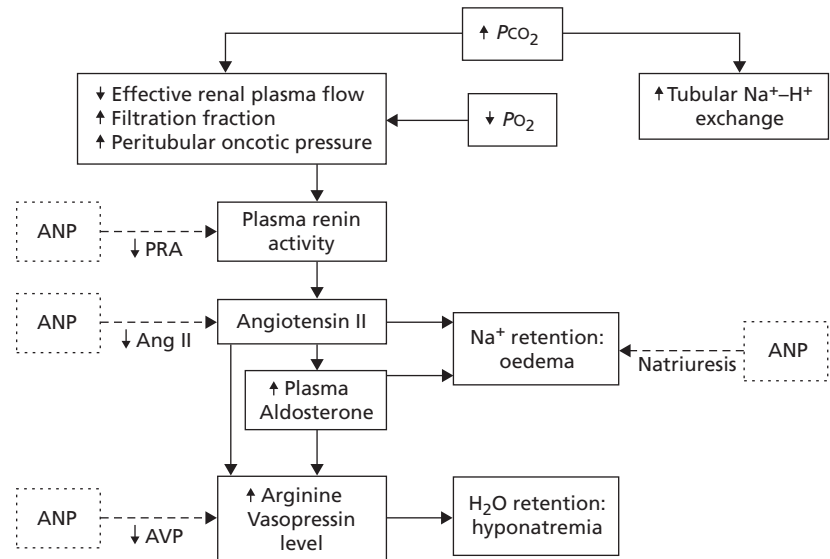
Thus a complex interaction between pulmonary haemodynamics and changes in salt, water and hormonal homeostasis occurs in patients with hypoxic and hypercapnic COPD. The influence of the protective diuretic and natriuretic factors probably prevents the formation of oedema in most patients. However, in some patients these protective mechanisms are overwhelmed by the oedema-promoting factors, such as activation of the renin-angiotensin system, leading to the development of oedema (Fig. 23.14).

## Clinical features

### Symptoms

The characteristic symptoms of COPD are breathlessness on exertion, sometimes accompanied by wheeze and cough, which is often but not invariably productive [501].





**Fig. 23.14** Mechanisms of sodium, water and hormonal disturbance in patients with chronic obstructive pulmonary disease. ANP, atrial natriuretic compound. (Modified from MacNee [468].)

Breathlessness is the symptom that commonly causes the patient to seek medical attention and is usually the most disabling of these symptoms. Patients often date the onset of their illness to an acute exacerbation of cough with sputum production, which leaves them with a degree of chronic breathlessness. However, close questioning usually reveals the presence of a 'smoker's cough', with the production of small amounts (usually  $<60\text{mL}$ ) of mucoid sputum, often occurring predominantly in the morning for many years [24].

Most patients have a smoking history of at least 20 pack-years before symptoms develop, commonly in the fifth decade, although dyspnoea on effort often does not occur until the sixth or seventh decades. It is characteristic of COPD that patients progress through the clinical stages of mild, moderate and severe disease. Symptoms and signs therefore vary in any individual depending on the stage of the disease.

Breathlessness is the symptom that causes most disability and is associated with loss of lung function over time [28]. It is usually first noticed on climbing hills or stairs, while carrying heavy loads or hurrying on level ground. The appearance of breathlessness indicates moderate to severe impairment of airway function. By the time the patient seeks medical advice the  $\text{FEV}_1$  has usually fallen to 1–1.5 L in an average man. Patients with COPD may adapt their breathing pattern and their behaviour to minimize the sensation of breathlessness. However, it is noticeable that the perception of breathlessness, as assessed using the 10-point Borg scale, varies greatly for individuals with the same degree of ventilatory capacity [502]. Mood is an important determinant of the perception of breathlessness in patients with COPD [502]. However, when the  $\text{FEV}_1$  has fallen to 30% or less of the predicted values (equivalent in an average man to an  $\text{FEV}_1$  of around 1 L), breathlessness

is usually present on minimal exertion [503]. Severe breathlessness is often affected by changes in temperature and occupational exposure to dust and fumes. Position has a variable effect on breathlessness. Some patients have severe orthopnoea that is relieved by leaning forward, whereas others find greatest ease when lying flat [504]. Breathlessness can be assessed on the MRC scale [505], which has been used extensively in epidemiological studies. The Borg scale and visual analogue scales have also been used to monitor the progress of specific symptoms and other questionnaires, such as the baseline dyspnoea index and the transitional dyspnoea index, have also been used [506].

A productive cough occurs in up to 50% of cigarette smokers [507]. In most patients with COPD, cough precedes the onset of breathlessness or appears with it and many patients may dismiss this symptom as a 'smoker's cough'. The MRC symptom questionnaire uses cough as a defining symptom of chronic bronchitis, i.e. a cough productive of sputum on most days for three consecutive months over two consecutive years [505]. Previous studies have shown no association between the presence of cough and sputum production and mortality [28] (see Fig. 23.3). However, a more recent study did indicate an association between cough and the development of airflow limitation [29].

Cessation of cigarette smoking produces resolution of the cough in 94% of smokers [159]; however, the airflow limitation often persists. The frequency of nocturnal cough does not appear to be increased in stable COPD [508]. In the presence of severe airway obstruction, with the generation of high intrathoracic pressures, paroxysms of cough may produce syncope [509] and cough fractures of the ribs [510].

Wheeze is common but not specific to COPD, since it is

due to turbulent airflow in large airways from any cause. The presence of wheeze was a pointer to a positive bronchodilator response in one study [511], although these data require confirmation.

Chest pain is common in patients with COPD but is often unrelated to the disease itself, and may be due to underlying ischaemic heart disease or gastro-oesophageal reflux [512]. Patients with COPD often complain of chest tightness during exacerbations of breathlessness, particularly during exercise, and this is sometimes difficult to distinguish from ischaemic cardiac pain. Pleuritic chest pain may suggest an intercurrent pneumothorax, pneumonia or pulmonary infarction.

Haemoptysis in association with purulent sputum may be due to inflammation or infection. However, this symptom should be treated seriously and the need for investigations for bronchial carcinoma should be considered.

Weight loss and anorexia are features of severe COPD and are thought to result from both a decrease in calorie intake and hypermetabolism [513].

Psychiatric morbidity, particularly depression, is common in patients with severe COPD, reflecting the social isolation and the chronicity of the disease [514]. Sleep quality is impaired in advanced COPD [515], which may contribute to the impaired neuropsychiatric performance.

### Occupation/smoking history

It is important to obtain a detailed smoking history in patients with COPD since the disease is rare in lifelong non-smokers. Although in general there is a negative relationship between the number of cigarettes smoked and the level of FEV<sub>1</sub>, there are huge individual variations that reflect differences in susceptibility to cigarette smoke [30,40]. In general symptomatic COPD develops after 20 pack-years of smoking.

Occupational exposure to dusts has an additive effect on the decline in lung function, as has been shown in coal-miners, where both smoking and years of dust exposure contribute to the decline in FEV<sub>1</sub>, although the contribution of smoking was three times as great as that of the average dust exposure in one particular study [85].

### Physical signs

The physical signs in patients with COPD are not specific to the disease and depend on the degree of airflow limitation and pulmonary overinflation. However, the sensitivity of physical signs for detecting or excluding moderately severe COPD is poor [516]. Variable degrees of tachypnoea may be present in patients with severe COPD and this is dependent on the type of clinical presentation of the disease (see below). Prolonged forced expiratory time (>5

s) can be a useful indicator of airway obstruction. Tar-stained fingers emphasize the smoking habit. In advanced disease cyanosis may be present, indicating hypoxaemia, but may be influenced by the background lighting or accentuated by polycythaemia, and therefore this sign is fairly subjective. The flapping tremor associated with hypercapnia is neither sensitive nor specific, and the often-reported papilloedema associated with severe hypercapnia is rarely seen.

Weight loss may also be apparent in advanced disease, as well as a reduction in muscle mass. Finger clubbing is not a manifestation of the disease and should suggest the possibility of complicating bronchial neoplasm or bronchiectasis. The breathing pattern is often characteristic, with a prolonged expiratory phase, some patients adopting pursed-lip breathing on expiration, which may reduce expiratory airway collapse [517] and may even improve oxygenation [518].

The use of the accessory muscles of respiration, particularly the sternomastoids, is often seen in advanced disease and these patients may adopt the position of leaning forward, supporting themselves with their arms to fix the shoulder girdle and allowing the use of the pectorals and latissimus dorsi to increase chest wall movement [519].

In the later stages of COPD the chest is often barrel-shaped, with kyphosis and an apparent increased antero-posterior diameter, horizontal ribs, prominence of the sternal angle and a wide subcostal angle. These are all signs of overinflation rather than anatomical changes. As a result of the elevation of the sternum, the distance between the suprasternal notch and the cricoid cartilage (normally three finger breadths) may be reduced, and an inspiratory tracheal tug may be detected, which has been attributed to the contraction of the low flat diaphragm [520]. The horizontal position of the diaphragm also acts to pull in the lower ribs during inspiration (Hoover's sign) [521]. Widening of the xiphisternal angle and abdominal protuberance occur, the latter due to forward displacement of the abdominal contents, giving the appearance of apparent weight gain. Increased intrathoracic pressure swings may result in indrawing of the suprasternal and supraclavicular fossae and of the intercostal muscles. A rise in jugular venous pressure may be seen on expiration.

On percussion of the chest there is decreased hepatic and cardiac dullness, indicating overinflation. A useful sign of gross overinflation is the absence of a dull percussion note, normally due to the underlying heart, over the lower end of the sternum.

Breath sounds may have a prolonged expiratory phase or may be uniformly diminished, particularly in the advanced stages of the disease. However, in a comparison of recorded breath sounds at comparable airflows, no difference was found between the intensity of the breath sounds in patients with COPD and normal subjects [522].

Wheeze, heard by the unaided ear or at the patient's mouth, is common in COPD [523]. Wheeze may be variably present on both inspiration and expiration but is not an invariable clinical sign [524]. Crackles may be present particularly at the lung bases, but are usually scanty, vary with coughing and cannot be distinguished from the persistent coarse crackles of bronchiectasis or the fine respiratory crackles of fibrosis or left ventricular failure [525].

### Cardiovascular examination

The presence of emphysema or overinflation of the chest produces difficulty in localizing the apex beat and reduces the cardiac dullness. The characteristic signs indicating the presence or consequences of pulmonary arterial hypertension may be detected in advanced cases. The heave of right ventricular hypertrophy may be palpable at the lower left sternal edge or in the subcostal angle. Heart sounds are generally soft, although the second heart sound may be exaggerated in the second left intercostal space. There may be a right ventricular gallop rhythm, with a third sound audible in the fourth intercostal space to the left of the sternum or in the epigastrium. The jugular venous pressure can be difficult to estimate in patients with COPD as it varies widely with respiration and is difficult to discern because of the prominent accessory muscle activity. When the fluid retention of cor pulmonale occurs there may be evidence of functional tricuspid incompetence, producing a pansystolic murmur at the left sternal edge. The liver may be tender and pulsatile, and a prominent *v* wave may be visible in the jugular venous pulse. The liver may also be palpable below the right costal margin as a result of the low diaphragm, due to the overinflation of the lungs.

Peripheral vasodilatation accompanies hypercapnia, producing warm peripheries with a high-volume pulse. Pitting peripheral oedema may also be present as a result of fluid retention. However, other causes of oedema, such as deep venous thrombosis, venous stasis and low serum albumin, should be considered.

### Types of clinical presentation

Many smokers are content to accept the development of cough with sputum production and exertional dyspnoea as an inevitable consequence of the smoking habit, and therefore often present to their doctor when the disease is at a fairly advanced stage. Relatively few patients are detected early in the disease process as a result of screening by spirometry. The BTS guidelines [4] encourage the use of spirometry in cigarette smokers in order to identify susceptible smokers with established airflow limitation. Repeated measurements over the course of several years will identify smokers with a rapid decline in FEV<sub>1</sub> who

could be targeted for smoking cessation and early intervention with treatment. Not all patients fulfil the criteria for the MRC definition of chronic bronchitis; breathlessness is the most common presenting symptom in patients with COPD. A description of symptoms that vary throughout the day and which are particularly worse in the morning is not a good discriminatory sign for those patients who show a response to bronchodilator or steroid therapy [526]. Some patients present initially to hospital during an exacerbation of the disease and claim that they have had no significant symptoms until that time. However, close questioning usually reveals the presence of progressive symptoms in most.

Two clinical patterns of the disease have been described, the so-called 'pink puffers' and 'blue bloaters'. The pink and puffing patient is thin, breathless and preserves blood gas values until late in the course of the disease and therefore does not develop pulmonary hypertension until the disease is very advanced. In contrast, the blue and bloated patient develops hypoxaemia and hypercapnia earlier and thus the complications of oedema and secondary polycythaemia. These represent the extreme ends of a spectrum, with most patients lying between these extremes. Although the presentation of these two extreme clinical patterns seems to be diminishing, it is important to recognize them since 'blue bloaters' have almost double the mortality rate of 'pink puffers' with similar degrees of airflow obstruction [419].

### Physiological assessment

The most important disturbance of respiratory function in COPD is obstruction to forced expiratory airflow. The degree of airflow obstruction cannot be predicted from the symptoms and signs [527] and therefore its assessment should be encouraged both in primary and secondary care. At an early stage of the disease conventional spirometry may reveal no abnormality. This results from the fact that the earliest changes in COPD affect the alveolar walls and small airways, so that a modest increase in peripheral airways resistance is not reflected in these conventional spirometric measurements [528]. Tests of small airway function, such as the frequency dependence of compliance, closing volume, flow-volume loops breathing air and helium/oxygen mixtures and flow rates at low lung volume, may be abnormal [355,529,530]. However, these tests are difficult to perform and have high coefficients of variation. Although they can distinguish smokers from non-smokers, they are only valid when elastic recoil is normal and there is no increase in large airways resistance, conditions seldom met even in mild COPD. They are therefore not recommended in normal clinical practice. By the time most patients present clinically, conventional spirometry is abnormal and the most useful and commonly employed test is the FEV<sub>1</sub>.

Spirometry

Spirometry is the most robust test of airflow limitation in patients with COPD. A low FEV<sub>1</sub> with an FEV<sub>1</sub>/forced vital capacity (FVC) ratio below the normal range is a diagnostic criterion for COPD [2–4]. The rate of decline of FEV<sub>1</sub> can be used to assess susceptibility in cigarette smokers, progression of the disease and reversibility of the airways obstruction. It is important that a volume plateau is reached when performing the FVC; this can take 15 s or more in patients with severe airways obstruction. If this manoeuvre is not carried out, the FVC can be underestimated. Since the FEV<sub>1</sub> is effort dependent, the traces must be checked to ensure maximum effort has been achieved [531] and in addition that full expiration has been performed [532]. It has been suggested that the standard ATS criteria [533] should be modified to encourage a maximum expiratory effort during the first part of the manoeuvre and then a ‘relaxed’ expiration when expiratory airflow falls to less than 200 mL/s [532]. The BTS guidelines [4] have equated the FEV<sub>1</sub> to disability and hence can be used as a guide to therapy (Table 23.6).

Flow–volume loops

Expiratory flows at 75% or 50% of VC have been used as a measure of airflow limitation and provide complementary information to the usual volume–time plot. There are problems with the reproducibility of these measurements, so that abnormal values must fall to below 50% of the predicted values. Flows at lung volumes less than 50% of VC were previously considered to be an indicator of small airways function but probably provide no more clinically useful information than measurements of FEV<sub>1</sub> [533]. Measurements of flow at fixed lung volumes are very variable in patients with COPD since volume calculated from flow at the mouth does not take account of thoracic gas compression during expiration. The flow–volume loop in

severe COPD shows a relatively preserved PEF followed by a rapid decrease in flow after the first 200–300 mL as airways collapse (see Fig. 23.11).

Peak expiratory flow

PEF can either be read directly from the flow–volume loop or measured with a hand-held peak flow meter. The hand-held instruments are relatively easy to use and are particularly useful for repeated measurements in asthmatics, since serial measurements during exacerbations or at home can reveal variations in response to therapy or spontaneous diurnal variability [534]. However, in COPD there is little daily change in PEF and many variations are often within the error of the measurement [535]. Although repeated measurements of PEF can be used in place of FEV<sub>1</sub>, single measurements are not useful as the variation is so high [536]. There are several theoretical reasons why FEV<sub>1</sub> is a better test than PEF in the diagnosis and assessment of COPD (Table 23.7), so that PEF is an inferior measurement of airways obstruction in COPD.

Lung volumes

Measurements of static lung volumes, such as TLC, RV and FRC, are used in patients with COPD to assess the degree of overinflation and gas trapping that results from loss of elastic recoil and collapse of the airways. Dynamic overinflation is recognized to occur particularly during exercise and may be an important determinant of symptoms such as breathlessness [349].

The standard method to measure static lung volumes using the helium dilution technique during rebreathing may underestimate lung volumes in COPD, particularly in those patients with bullous disease, where the inspired helium does not have time to equilibrate properly in the airspaces. The body plethysmograph uses Boyle’s law to calculate lung volumes from measurements of changes in

Table 23.6 BTS scheme for assessing patients with COPD.

	Clinical state	Results of measurements	Use of healthcare resources
Mild	Smoker’s cough, but little or no breathlessness. No abnormal signs	FEV <sub>1</sub> 60–79% of predicted. FEV <sub>1</sub> /VC and other indices of expiratory flow mildly reduced	Unknown: presymptomatic within the community
Moderate	Breathlessness (± wheeze) on exertion, cough (± sputum) and some abnormal signs	FEV <sub>1</sub> 40–59% of predicted often with increased FRC and reduced DLco. Some patients are hypoxaemic but not hypercapnic	Known to GP with intermittent complaints
Severe	Breathlessness on any exertion. Wheeze, cough prominent. Clinical overinflation usual, plus cyanosis, peripheral oedema and polycythaemia in some patients	FEV <sub>1</sub> <40% of predicted with marked overinflation. DLco variable, but often low. Hypoxaemia usual and hypercapnia in some patients	Likely to be known to hospital and by GP, with frequent problems and hospital admissions

FEV<sub>1</sub>, forced expiratory volume in 1 s; FRC, functional residual capacity; VC, vital capacity; DLco, diffusing capacity for carbon monoxide.

**Table 23.7** The reasons why FEV<sub>1</sub> is recommended as the measurement of choice in COPD.

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The FEV <sub>1</sub> is a reproducible and objective measurement. There are well-defined normal ranges that allow for the effects of age, race and sex
It is relatively simple and quick to measure and can be measured at all stages of disease
The forced expiratory manoeuvre records not only FEV <sub>1</sub> but also FVC. An FEV <sub>1</sub> /FVC ratio less than 70% is diagnostic of airways obstruction. If the ratio is normal (>70%) and the test was performed well, the pattern is not obstructive and the diagnosis is not COPD.
PEF measurements cannot determine whether values are low because of obstruction or restriction
The variance of repeated measurements in the same person is well documented and is low
Studies of mortality and disability have shown that the FEV <sub>1</sub> predicts future mortality
Serial measurements provide evidence of disease progression
In COPD the relationship between PEF and FEV <sub>1</sub> is poor
PEF may underestimate the degree of airways obstruction in COPD

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FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

mouth and box pressures during gentle panting against a closed shutter. This technique measures trapped air within the thorax, thus including poorly ventilated areas and therefore giving higher readings than the helium dilution technique. Estimation of FRC by whole-body plethysmography may reveal values as much as 1–2 L greater than those found with the helium dilution technique in patients with COPD [537]. However, delayed equilibration of pressure between the alveoli and mouth can result in an error that leads to overestimation of lung volumes [538].

X-ray planimetry has also been used in COPD to measure lung volumes [539] and this method can now be computerized. However, the accuracy of this measurement in COPD has been questioned [540].

### Reversibility to bronchodilators

The American, European and British Thoracic Societies (ATS, ERS and BTS) recognize that assessment of reversibility to bronchodilators is an essential part of the investigation and management of patients with COPD [2–4]. Reversibility tests are important in COPD for several reasons: (i) to help distinguish those patients with marked reversibility who have underlying asthma; (ii) to aid with future management; and (iii) because the FEV<sub>1</sub> after bronchodilator is the best predictor of survival. However, there is no agreement on a standardized method of assessing reversibility [541]. Reversibility is usually assessed by measuring changes in FEV<sub>1</sub> or PEF but could also be determined as a change in static lung volumes after bronchodilators, which may explain why some patients have improvement in symptoms with little spirometric change following a bronchodilator [542].

The use of bronchodilator testing in patients with COPD is limited by the variability of the FEV<sub>1</sub> measurement itself, which is reported to be less than 5% in normal subjects [543]. However, Tweeddale and colleagues [543] in a study of repeated measurements of FEV<sub>1</sub> on the same day found an SD of 102 mL that was independent of base-

line FEV<sub>1</sub>. Thus if the change in FEV<sub>1</sub> exceeds 170 mL it can be considered not to have arisen by chance. The ERS and BTS guidelines both recommend that changes should only be considered significant if they exceed 200 mL, which is supported by a recent study [544]. In addition to this absolute change in FEV<sub>1</sub>, a percentage change of 12% over baseline as a percentage of the predicted normal value has been suggested as a significant bronchodilator response by the ATS [2]; an improvement of 15% over baseline FEV<sub>1</sub> and a 200-mL absolute change has been suggested by ERS and BTS guidelines [3,4,545]. A third approach that has received less support is to express the change in FEV<sub>1</sub> as a percentage of the potential possible change, which is the predicted value minus the baseline value [535].

It is important when comparing studies of reversibility that the methodology of assessing bronchodilator response is similar. Unfortunately daily variations in airway smooth muscle tone may affect the response to bronchodilators in patients with COPD. Thus when airway smooth muscle tone is higher, and thus FEV<sub>1</sub> is lower, a response to bronchodilators may be more likely than when muscle tone is lower and FEV<sub>1</sub> is higher. In addition, airway calibre may alter drug deposition, adding further to the variability in the response [546]. Thus as many as one-third of those patients initially shown to have a response to a bronchodilator may on retesting on a different day have no response [511]. For this reason it has been suggested that measurement of the FEV<sub>1</sub> after bronchodilator is a better estimate of progression of airway obstruction.

It is usually recommended that the response to a bronchodilator be assessed with a large dose, either using repeated doses from a metered-dose inhaler or via the nebulized route, since this produces a larger number of patients with a significant response than if a small dose is given by metered-dose inhaler [547]. In some cases the addition of a second drug, such as an anticholinergic, to a  $\beta$ -agonist produces a further increase in FEV<sub>1</sub> [548]. Thus it is worth while assessing the bronchodilator response to both  $\beta$ -agonist and anticholinergic drugs in patients with COPD.

### Reversibility to corticosteroids

Whether all patients with symptomatic COPD should have a formal assessment of steroid reversibility remains controversial [2,4]. However, this is the recommendation of the BTS guidelines [4]. The most common regimen is the administration of 30 mg of prednisolone for a period of 2 weeks. Those patients who have previously shown a response to nebulized bronchodilators are more likely to show a response to steroids [526]. However, it is not possible to predict the response to corticosteroids in any individual patient and therefore to avoid the need for a trial of steroids in all patients. There is also no relationship between the response to oral steroids and  $DLCO$ , as a surrogate measurement of emphysema, or atopic status [549].

An alternative approach is to assess the response to inhaled steroids. Weir and coworkers [550,551] suggested a 6-week trial of inhaled steroids, measuring the  $FEV_1$  before and after and/or the average PEF of the first 5 days and the last 5 days. Whether a trial of oral or inhaled steroids is the best way to assess steroid reversibility is still a matter of debate; however, one small placebo-controlled study showed improvement following inhaled beclomethasone (beclomethasone) that was not increased by subsequent oral prednisolone [552].

However, an acute response in the  $FEV_1$  in a bronchodilator reversibility test does not necessarily predict a symptomatic response [553]. For example the improved exercise tolerance in patients with COPD in response to ipratropium bromide was not dependent on whether the patient had previously shown a significant bronchodilator response to this drug [554]. Similarly, improvements in exercise tolerance have been shown with  $\beta_2$  agonists [555] and corticosteroids [556] in patients who show no significant  $FEV_1$  response.

### Gas transfer for carbon monoxide

$DLCO$  values are below normal in many patients with COPD and although there is a relationship between  $DLCO$  and the presence of microscopic emphysema [207,208], the severity of the emphysema in an individual patient cannot be predicted from the  $DLCO$ . Neither is a low  $DLCO$  specific for emphysema. Thus a low  $DLCO$  is suggestive of a significant degree of alveolar destruction, probably as a result of emphysema, although a normal  $DLCO$  does not exclude a diagnosis of COPD. The methodology to assess  $DLCO$  may also influence the result in patients with COPD. The method of Ogilvie and colleagues [557] measures the rate of carbon monoxide uptake during a 10-s breath-hold and relates this to the alveolar volume, derived by adding the inspired volume to the RV measured in a separate helium dilution test. A now more widely used method is the single-breath technique [558], which uses alveolar volume calculated from helium dilution during the single-breath

test. This underestimates alveolar volume in patients with severe COPD, producing a lower value for  $DLCO$ .

### Arterial blood gases

Measurement of arterial blood gases is essential in patients with COPD to confirm the degree of hypoxaemia and hypercapnia and, in acute exacerbations particularly, to determine the hydrogen ion concentration. It is recommended in patients with an  $FEV_1$  <40% of their predicted value [4]. It is essential to record the inspired oxygen concentration when reporting blood gases, and it is also important to note that it may take at least 30 min for a change in inspired oxygen concentration to have its full effect on the  $PaO_2$  because of long time constants for alveolar gas equilibration in COPD.

Pulse oximetry and transcutaneous oxygen tension measurements are increasingly used in intensive care units. They can be useful in measuring changes in oxygenation during an acute exacerbation of COPD. However, they should not replace an assessment of blood gas tensions, since measurements of  $Paco_2$  are often required.

Acid–base status can also be assessed from the arterial pH (hydrogen ion concentration) and bicarbonate concentration. From the modified Henderson–Hasselbalch equation,  $[H^+] = k \times Paco_2 / [HCO_3^-]$ , where  $[H^+]$  is the hydrogen ion concentration,  $k$  a constant and  $[HCO_3^-]$  the bicarbonate concentration, increases in  $Paco_2$ , which can occur rapidly, can be compensated by renal conservation of bicarbonate, a relatively slow process. Acid–base status, particularly mixed respiratory and metabolic disturbances, can be characterized by plotting values on an acid–base diagram [559]. Such a diagram is useful in apportioning the relative contributions of primary respiratory and metabolic causes of the acid–base disturbance and, when serial values are plotted, the response to treatment.

### Exercise tests

Exercise produces an increase in oxygen consumption and carbon dioxide production from skeletal muscle. Patients with COPD have the same oxygen consumption for a given workload as normal subjects; however, their dead space ventilation is higher and so a larger minute ventilation is needed to maintain carbon dioxide constant. Since in many patients expiratory airflow is limited within the tidal volume range, the only way to increase minute ventilation is to increase inspiratory flow and/or shift the end-expiratory position [560]. Both of these manoeuvres are problematic in patients with COPD, requiring more work from already compromised inspiratory muscles or resulting in progressive overinflation, which increases both the work of breathing and symptoms. There is still debate about whether under these circumstances exercise is

limited by the development of inspiratory muscle fatigue [561].

The cardiovascular responses to exercise are, in general, considered to be appropriate [562], although the increase in stroke volume is less than normal in severe COPD, perhaps due to a combination of overinflation and pulmonary hypertension. However, metabolic acidosis develops at lower work rates in patients with severe COPD [563]. In a study of 97 patients with COPD during progressive cycle exercise, exercise was limited by dyspnoea in 40% and by leg fatigue in 25% [564], probably reflecting the general debility present in patients with COPD [565].

Three forms of exercise test can be performed that provide useful information.

#### **Progressive symptom-limited exercise**

In this test the patient is encouraged to maintain exercise, on a treadmill or a cycle, until symptoms prevent them from continuing. The usual criteria for defining a maximum test are a heart rate of greater than 85% of predicted or a ventilation greater than 90% predicted. The reproducibility of the test from day to day is good [566] and the results are useful, particularly when simultaneous ECG and blood pressure monitoring are performed in order to assess whether coexisting cardiac or psychological factors contribute to exercise limitation.

#### **Self-paced exercise**

These tests are easy to perform and give information on more sustained exercise, which may be more relevant to performance in everyday life. The 6-min walk is the most commonly used test [567] and has a similar reproducibility to the previously described 12-min walk [568], with a coefficient of variation of around 8%. Shortening the walk to 2 min reduces the reproducibility [569]. It has been suggested that a learning effect may affect the result of repeated tests, although this view is debated [569]. In addition the test is only useful in patients with moderately severe COPD ( $FEV_1 < 1.5L$ ) who would be expected to have an exercise tolerance of less than 600 m in 6 min. There is only a weak relationship between walking distance and  $FEV_1$  [570].

#### **Steady-state exercise**

In this test patients exercise at a sustainable percentage of maximum capacity for 3–6 min and blood gases are measured, enabling calculation of the dead space–tidal volume ratio and shunt. This assessment is seldom required in patients with COPD.

Other more complex tests, such as assessment of the lung pressure–volume curve, are difficult to undertake, requiring measurement of oesophageal pressure with a

balloon, and are not part of the routine assessment but may be necessary in special circumstances.

#### **Sleep studies**

Patients with COPD become more hypoxaemic during sleep, particularly REM sleep [571]. There is no evidence that measurement of nocturnal hypoxaemia provides any further prognostic or clinically useful information in the assessment of patients with COPD unless coexisting sleep apnoea syndrome is suspected [572].

#### **Non-physiological assessments**

In patients with severe COPD, identifying polycythaemia is important since it predisposes to vascular events, and there is some evidence that venesection may improve exercise tolerance [573,574]. Polycythaemia should be suspected when the haematocrit is greater than 47% in women and more than 52% in men and/or the haemoglobin is greater than 16 g/dL in women and more than 18 g/dL in men, provided other causes of spurious polycythaemia, such as decreased plasma volume due to dehydration, can be excluded.

There is no indication for measuring blood biochemistry routinely in patients with clinically stable COPD [4]. The levels and phenotype of  $\alpha_1$ -AT should be measured in all patients under the age of 40 years and in those with a family history of emphysema at an early age.

Routine ECG is not required in the assessment of patients with COPD [4], and is an insensitive technique in the diagnosis of cor pulmonale.

#### **Radiology**

There are no features on a plain posteroanterior chest radiograph specific for COPD. The features that are usually described are those of severe emphysema. However, there may be no abnormalities, even in patients with very appreciable disability [575]. Recently improvements in imaging techniques, particularly the advent of high-resolution CT (HRCT), have provided a more sensitive means of diagnosing macroscopic emphysema in life [576–578].

#### **Plain chest radiography**

On both plain chest radiography [579] and CT [580] the trachea may be seen rarely to be narrowed in its coronal section, the so-called ‘sabre-sheath’ trachea, in patients with COPD. This unusual association occurs in patients over the age of 50. Its pathogenesis is unclear but may be related to abnormal thoracic pressure gradients generated in these patients; it is unlikely to contribute significantly to the airflow obstruction.



Bronchial wall thickening, shown as parallel line opacities on plain chest radiography, has been described in clinico-radiological series of patients with COPD [581], although this is not a universal finding in all studies [582]. Bronchial wall thickening has also been observed on HRCT in smokers and ex-smokers, many of whom had chronic bronchitis [583]. However, many of these findings may relate to coincidental bronchiectasis.

The most reliable radiographic signs of emphysema can be divided into those due to hyperinflation, those due to vascular changes and those due to bullae. Overinflation of the lungs results in the following.

1 Low flattened diaphragms (Fig. 23.15). Abnormally low diaphragms are present when the border of the diaphragm in the mid-clavicular line is at or below the anterior end of the sixth [584] or seventh [585] rib. Flattened diaphragms are present when the maximum perpendicular height from a line drawn between the costal and cardiophrenic angles to the border of the diaphragm is less than 1.5 cm.

2 Increase in the retrosternal airspace (Fig. 23.15b), which can be demonstrated on the lateral film at a point 3 cm below the manubrium, occurs when the horizontal distance from the posterior surface of the aorta to the sternum exceeds 4.5 cm [575].

3 An obtuse costophrenic angle on the posteroanterior or lateral chest radiograph.

**Fig. 23.15** Plain chest radiographs of generalized emphysema particularly affecting the lower zones. (a) PA radiograph showing low, flat diaphragms (below anterior ends of seventh ribs); obtuse costophrenic angles; reduced vessel markings in lower zones which are transradiant. (b) Lateral radiograph; low, flat and inverted diaphragm and widened retrosternal transradiancy (white arrows) which approaches the diaphragm inferiorly (black arrows).

4 The inferior margin of the retrosternal airspace is 3 cm or less from the anterior aspect of the diaphragm (Fig. 23.15b).

The vascular changes associated with emphysema result from loss of alveolar walls and are shown on the plain chest radiograph by the following.

1 A reduction in size and number of pulmonary vessels, particularly at the periphery of the lung.

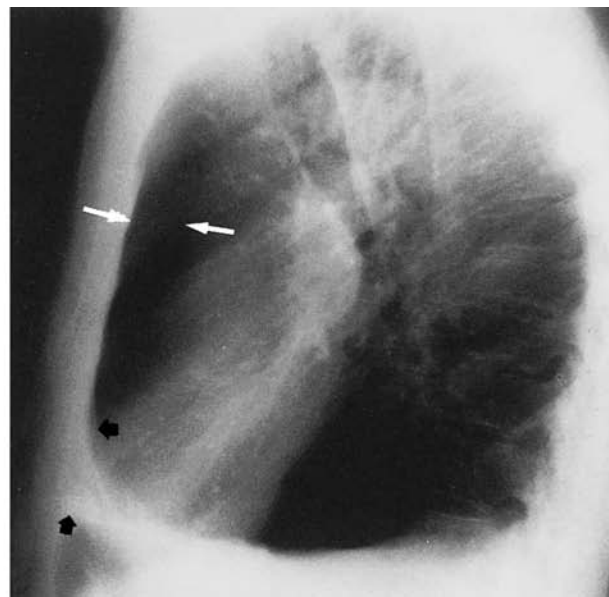
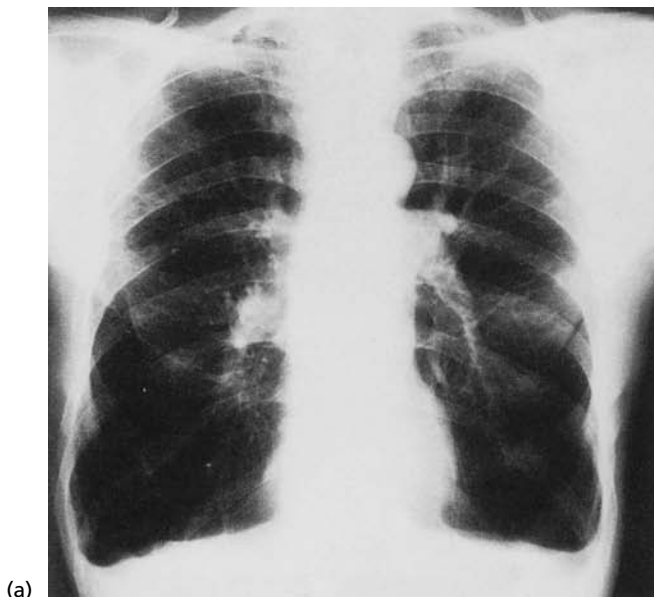
2 Vessel distortion, producing increased branching angles, excess straightening or bowing of vessels.

3 Areas of transradiancy.

On fluoroscopy the range of diaphragmatic movement, normally 6–8 cm and always greater than 3 cm, is often only 1 cm in severe COPD. Occasionally the flattened diaphragms may be drawn upwards in parallel in inspiration, a motion different from true paradoxical movement due to paralysis of the phrenic nerve. In the latter, inspiratory sniffing gives rise to a sharp upward movement of the convex diaphragm, quite different from the slight upward movement of a flattened diaphragm in COPD.

Assessment of the vascular loss in emphysema clearly depends on the quality of the X-ray film. A general increased transradiancy may be due to an overexposed chest film. Focal areas of transradiancy surrounded by hair-line walls represent bullae [586]. These may be multiple, as part of a generalized emphysematous process, or localized. An 'increase in lung markings' rather than areas of increased transradiancy has often been described in patients with COPD. The cause of these changes is unknown but may be at least contributed to by non-vascular linear opacities due to scarring.

In early studies it was considered that the radiographic changes of emphysema on a plain chest film did not correlate well with pathological findings of emphysema. However, the method of defining emphysema pathologi-



cally had not been standardized in many of these studies; in those where standardization had been employed, this was usually based on a semi-quantitative picture-grading technique to assess macroscopic emphysema [575,587–589]. The accuracy of diagnosing emphysema on the plain chest film increases with the severity of the disease and has been reported as being 50–80% accurate in patients with moderate to severe disease [590]. However, the sensitivity has been reported as being as low as 24% in patients with mild to moderate disease [588].

A recent study has revived interest in the diagnosis of emphysema by plain chest radiography and suggests that the careful application of standardized radiographic criteria produces results as accurate in the diagnosis of macroscopic emphysema as CT [591]. However, many of the criteria remain subjective.

### Computed tomography

CT has been used since the early 1980s to detect and quantify emphysema [592]. Studies using CT can be divided into those using visual assessment of low-density areas of the scan, which can be either semi-quantitative or quantitative, and those using CT lung density to quantify areas of low X-ray attenuation. These studies divide roughly into those measuring macroscopic and microscopic emphysema respectively.

A visual assessment of emphysema on CT (Fig. 23.16) reveals:

- 1 areas of low attenuation without obvious margins or walls;
- 2 attenuation and pruning of the vascular tree;
- 3 abnormal vascular configurations.

The sign that correlates best with areas of macroscopic emphysema is an area of low attenuation [593,594]. Several studies have shown that visual interrogation of the scan can locate areas of macroscopic emphysema subsequently assessed in postmortem or resected lungs [207,594–597]. The problem with these correlations is that the emphysema is often assessed by a picture-grading score, which does not measure emphysema on a linear scale [230,595,596].

However, visual assessment of the extent of macroscopic emphysema by CT is insensitive, subjective and has a high intraobserver and interobserver variability [593,598,599]. Thus in most of these studies CT tended to underestimate the severity of the disease; in particular centrilobular lesions smaller than 5 mm were missed [598]. Interestingly the use of high-resolution, thin-cut (1–5 mm) sections does not improve the detection of mild emphysema, for although it shows the parenchymal destruction well it is less good at showing the vascular changes [599].

It is possible using HRCT to distinguish the various types of emphysema, particularly when the changes are not severe [593,599,600]. The distinction between the types of emphysema depends on the distribution of the lesions,



(a)



(b)

**Fig. 23.16** CT HLTCT emphysema, showing diffuse panlobular emphysema (a), and more patchy centrilobular emphysema with bullae (b).

those of centrilobular emphysema being patchy and prominent in the upper zones, whereas those of panlobular emphysema are diffuse throughout the lung zones [599]. However, more recent pathological studies suggest that both the major types of emphysema can occur in the same patient [199,201].

A more quantitative approach for assessing macroscopic emphysema has been taken by Müller and colleagues [601] who described a more objective method of highlighting pixels within the lung fields in a predetermined low-density range, between –910 and –1000 Hounsfield units, the so-called ‘density mask’ technique. The choice of the density range is fairly arbitrary, although these workers were able to show a good correlation

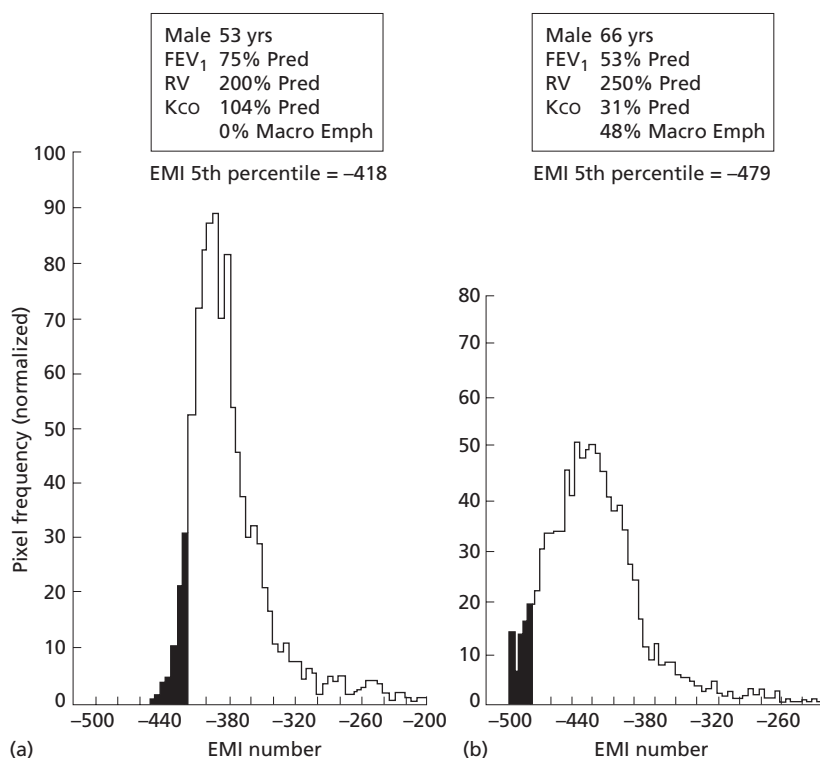
between pathological emphysema scores and CT 'density mask' score. However, they indicated that this technique may miss areas of mild emphysema. In addition no study has validated the comparison of horizontal slices obtained by CT or by section of fixed lung slices and the parasagittal lung slices used by Thurlbeck and coworkers [230] to obtain pathological scores for macroscopic emphysema.

A more quantitative way of measuring emphysema, particularly at the microscopic level, uses measurements of CT lung density. CT density is expressed as a linear scale in Hounsfield units (water = 0, air = -1000). In this range, CT lung density is a direct measure of physical density and is determined by the relative mix of air, blood and interstitial fluid in tissue. Thus as emphysema develops a decrease in alveolar surface area would occur as alveolar walls are lost, associated with an increase in distal airspace size, which would decrease lung CT density in association with a decrease in lung function. Several studies have assessed CT lung density in normal subjects [602,603]. However, the range of normality has yet to be standardized particularly with respect to lung volume, which changes CT lung density [604,605]. If CT is to be used to measure microscopic emphysema, then care should be taken to standardize the scanning conditions, particularly the lung volume [606], and to calibrate the CT scanner, since these factors affect CT lung density [603].

Frequency distributions of the CT lung density values from the matrix of picture elements (pixels) from a CT lung slice can be generated and are shown to be skewed, with a tail of high-density values produced by large

vessels and airways. In emphysema there is an increase in the numbers of low-density pixels and the whole curve is shifted to the left [8] (Fig. 23.17). The lowest 5th percentile of the CT density histogram was used to characterize the CT lung density in 28 patients undergoing lung resection for peripheral lung tumours. Respiratory function and CT (two slices) were performed 48h before thoracotomy [207]. Emphysema was measured in the resected lung as AWUV (see p. 631). There was a significant correlation between CT lung density and AWUV. In addition AWUV correlated with Kco. Since these patients were surgical candidates they had relatively mild, largely microscopic emphysema. Indeed only five individuals had greater than 5% of the surface area of the mid-sagittal slice showing macroscopic emphysema. Moreover, the correlation between AWUV and CT lung density appeared to be independent of the presence of macroscopic emphysema. This relationship was also found in a larger group of normal subjects and patients with emphysema, the latter with a wide range of functional impairment. In these studies CT lung density correlated with  $DL_{CO}/\dot{V}_A$  [607] and with the shape parameter  $k$  of the lung pressure-volume curve [361].

More studies are required before CT lung density can be used as a standardized technique to quantify microscopic emphysema. It is particularly important to define the range of normality and to correlate the measurements with normal values of distal airspace size, as a defining characteristic of emphysema [209]. In addition, standardizing the calibration of CT scanners and the lung volume



**Fig. 23.17** CT density histogram of (a) a subject with no emphysema and (b) a patient with severe emphysema. The shaded area represents the lowest 5% of the distribution.

at which scans should be performed [605] is required for multicentre studies. However, based on present knowledge, CT is the most sensitive and specific imaging technique for assessing emphysema in life and can detect mild emphysema in symptomatic patients with a normal chest radiograph [608]. Preliminary studies also suggest that CT may be able to detect the progression of emphysema [609].

### **Pulmonary hypertension/cor pulmonale**

The development of right ventricular hypertrophy or enlargement produces non-specific cardiac enlargement on the plain chest radiograph. The development of pulmonary hypertension can be assessed from the plain chest radiograph; however, in most studies measurements have been made in diverse conditions, including mitral stenosis, and the results have been extrapolated to patients with cor pulmonale, which may not be entirely valid. The most widely used measurement to assess the presence of pulmonary hypertension is the width of the right descending pulmonary artery, measured just below the right hilum, where the borders of the artery are delineated against air in the lungs laterally and the right main stem bronchus medially. The upper limit of the normal range of the width of the artery in this area is taken as 16 mm in males and 15 mm in females [610]. Other studies have suggested an upper limit of normal ranging between 16 and 20 mm, which gives a sensitivity of detecting a pulmonary arterial pressure greater than 20 mmHg of 68–95%, with a specificity of 65–88% [611–613]. Although these measurements can be used to detect the presence or absence of pulmonary arterial hypertension, they cannot accurately predict the level of the pulmonary arterial pressure and therefore can only be used as a screening test.

### **Emphysematous bullae**

A bulla has been defined arbitrarily as an emphysematous space greater than 1 cm in diameter [189]. Bullae may give rise to spontaneous pneumothorax, remain undetected on a chest radiograph or indicate the presence of more widespread pulmonary emphysema.

Whether a bulla is detected on a chest radiograph depends on its size and the degree to which it is obscured by overlying lung. Some bullae may only be seen on the lateral film. On the plain chest radiograph, bullae appear as localized avascular areas of transradiancy, usually separated from the rest of the lung by a curvilinear hair-line wall. In the absence of such a radiological sign, it is extremely difficult to detect and quantify the number of bullae [587]. Marked compression of the lung may be seen and bullae may also depress the diaphragm. Diaphragmatic depression is sometimes localized, the upper surface of the diaphragm showing a slight convexity downwards; the fine line of the bulla wall may be

detectable at the lateral edges of the convexity. Bullae rarely displace the heart or trachea, although sometimes they extend across the retrosternal space to produce a fine convex line in the opposite lung. Fluoroscopy of large bullae may show deviation of the mediastinum to the opposite side on expiration due to air trapping.

CT (Fig. 23.16) is much more sensitive than plain chest radiography and can be used to determine the number, size and position of the bullae [614]. Ventilation of the bullae can also be assessed using inspiratory–expiratory images [614,615]. It is also possible to estimate the volume of bullae by measuring the area of the bullae in each CT lung slice [586]. Many techniques used in the past to assess a patient's suitability for bullectomy, such as bronchography and pulmonary angiography, have now been replaced by CT [586,615].

### **Clinical features and physiology**

Exertional dyspnoea is the usual presenting feature in patients with bullous disease, although a single bulla of moderate size is unlikely to produce symptoms when the remaining lung is normal. Occasionally a bulla presents as a chance finding on a chest radiograph. Bullae may also present as a pneumothorax and occasionally a bulla may be misinterpreted as a pneumothorax (see Fig. 44.9) in a breathless patient and a chest drain inserted directly into the bullous cavity. Bullae occasionally become infected, in which case there may be a fluid level with, sometimes, surrounding consolidation. Infection may result in closure of the bronchial connection, shrinkage or even obliteration of the bulla [616]. Occasionally in a patient with a large bulla, clinical examination may show asymmetrical overinflation of the chest and reduction of chest wall expansion, but this is not a reliable sign.

Respiratory function tests may be non-specific and may simply be those of COPD [586,617,618]. Almost always some degree of airway obstruction is present, which may result from concomitant diffuse emphysema or airways disease, or as a result of the loss of lung elastic recoil that accompanies large bullae [620]. Overinflation is almost always present but is underestimated if measured by the helium dilution technique rather than by plethysmography [619]. Gas exchange is usually impaired as shown by a reduced  $TLCO$ . The  $Kco$  may reflect the quality of the non-bullous lung if the bulla is non-ventilating and may be helpful in making a decision concerning surgery [620].

### **Treatment**

The only treatment considered for large bullae is surgical obliteration [192,621,622]. The selection of patients suitable for surgery is critical. Surgery should not be offered to patients who are asymptomatic, since the operation does have an appreciable risk. The principal indication for

surgery is progressive dyspnoea. The best surgical results are in younger patients with large bullae, minimal airways obstruction and normal surrounding lung [617]. In those with airflow limitation it has been difficult to determine which patients benefit from bullectomy. A critical feature is the quality of the non-bullous lung. Studies using CT have shown that the airflow limitation is determined by the degree of emphysema in the non-bullous lung rather than the extent of the bullous disease [620]. Patients with bullae occupying one lung less than 50% of an FEV<sub>1</sub> of less than 1 L or hypercapnia carry a high risk of a poor response to surgery.

Pulmonary angiography can be used to demonstrate preserved vasculature in surrounding collapsed lung, which if present would suggest that removal of the bullae would improve function. Quantitative perfusion scanning may also demonstrate retained perfusion in the collapsed peri-bullous lung, which may improve after operation [621]. However, other techniques, such as bronchspirometry and bronchoscopic inert gas techniques, have not improved the ability to predict a successful operation. Thus there appears to be no technique that predicts whether bullectomy results in expansion and improved function in the surrounding lung, which is the object of the operation.

Several techniques have been described to remove bullae including excision, plication, marsupialization and intracavity drainage. The aims of surgery are to obliterate the bullous space and restore the elastic integrity of the lung. Improvement in FEV<sub>1</sub> after removal of a bulla of 500 mL or less, particularly in a patient with associated diffuse emphysema, is unlikely to be an effective treatment considering the risks of the surgical intervention. Most operations are performed by a conventional lateral thoracotomy, although bilateral bullae can be approached through a median sternotomy [623]. Superficial bullae have also been dealt with using thoracoscopic and laser techniques [624]. An alternative approach has been the use of intracavity drainage. This technique was originally described by Monaldi, and is often restricted to patients who are a poor risk for general anaesthesia, since the technique can be performed under local anaesthesia [625].

The results of surgery for bullous disease have been published by several authors [617,623–629] but in relatively small numbers of patients. The perioperative mortality in published series ranges from 0 to 20% in patients with a wide range of disability, and hence operative risk. The best functional results occur in patients with mild symptoms and relatively well-preserved pulmonary function. Those with small bullae (<1 L), poor overall lung function and diffuse emphysema have least functional improvement and in these the functional improvement has to be weighed against the risk of surgery. Studies of long-term follow-up of patients after surgery indicate that once removed, giant bullae do not recur [621,623]. The initial improvement following

surgery appears to be maintained, and the subsequent decline in lung function depends on the condition of the remaining lung. As with those patients with generalized COPD, those who continue to smoke show a more rapid decline in FEV<sub>1</sub> [192]. Lung volume reduction surgery is discussed separately on p. 679.

## Prevention (see also Chapter 10)

Tobacco smoking is the major aetiological factor in COPD, outweighing all other factors. In most patients the disease is theoretically preventable and thus cessation of cigarette smoking is the single most important way of affecting the outcome. Other important aetiological factors, such as atmospheric pollution, are also preventable. Unfortunately, in most developing countries the trends for both these factors are upwards. In the UK around 31% of men and 29% of women are current cigarette smokers, and around 80–90% of patients with COPD have been regular smokers at some time in their lives [630]. At least 90% of smokers are aware of the adverse health effects of cigarette smoking, 70% wish to give up smoking, and the majority of these have made a serious attempt to quit [631]. However, only 40% of regular smokers have succeeded in quitting cigarette smoking by age 60 [632]. Nicotine in tobacco smoke is addictive and regular smokers who reduce or cease their nicotine intake experience the characteristic withdrawal syndrome resulting from nicotine craving, in the form of anxiety, lack of concentration, irritability, restlessness and increased appetite. Nicotine addiction develops relatively rapidly and withdrawal symptoms can be shown to occur even in adolescent smokers [633]. Thus a critical preventive measure is to reduce the initiation rate of children starting smoking in the UK, which currently runs at 450 children per day [634]. This could be achieved by providing information to reduce the attractiveness and the peer pressure that causes children to start smoking, and by legislating against cigarette advertising and the availability of cigarettes to children. There is no doubt that tobacco advertising does increase tobacco consumption and therefore legislation against tobacco advertising is the single most important factor in trying to reduce the number of young people taking up the smoking habit.

## Smoking cessation

Since smoking cessation reduces the subsequent decline in lung function, particularly in those with an accelerated decline in FEV<sub>1</sub> [35], smoking cessation is the single most important step that can be taken to prevent the progression of the disease. This is particularly true during the early stages of COPD, when both symptoms and lung function may improve, whereas in older men smoking cessation only reduces the rate of decline in FEV<sub>1</sub> [36,635].

Although in advanced disease quitting smoking may not improve pulmonary function, symptoms such as cough may still improve [36].

All patients who smoke should have the implications for their future health discussed. Even the briefest of advice from health professionals can lead to smoking cessation in those who wish to quit. Asking about smoking habit in every patient may also have a positive reinforcing effect against starting smoking in non-smokers. The reported success rates of smoking cessation come mainly from studies conducted in a primary care setting and vary between 10 and 30% [636]. These figures cannot necessarily be extrapolated to other circumstances, such as an outpatient clinic. A BTS study [637] conducted in the setting of a respiratory outpatient clinic indicated that even brief advice by a physician on smoking-related diseases could produce a long-term success rate of 5.1%, which increased to 8.1% when the doctor sent brief letters to the patients encouraging abstinence. A recent review of the literature suggests that in those who request extra help to stop smoking, when given in the form of nicotine replacement or even contact with a support group, the success rate can be up to 25% [636].

Although it would seem logical, as in other addictions, to suggest a reduction in nicotine levels by a gradual reduction in the number of cigarettes smoked so as to reduce the severity of withdrawal symptoms [638], it has been shown that patients who gradually cut down the number of cigarettes tend to inhale more in order to maintain their usual blood nicotine levels [639]. In one randomized study comparing gradual reduction with abrupt quitting on a target date, the latter was more successful [640]. It has also been shown that those who are unable to quit abruptly are not successful in reducing their consumption of cigarettes over the long term [641,642].

The intensity of the strategy employed in a cessation programme should depend on the motivation of the patient to give up smoking. There is no difference in the success rates between regimens involving brief interven-

tion and those with more prolonged intervention in unselected smokers, whereas it is clear that those who are motivated to attend smoking cessation clinics have a better chance of long-term cessation than those who have a brief intervention by the general practitioner. Thus patient motivation influences all smoking cessation trials [636]. It is therefore better to put time and effort only into those patients who are motivated to give up and only a brief intervention in those with less motivation.

If any additional resources are employed in smoking cessation, it is important that patients are given clear instructions with a clear strategy and that success rates are corroborated with breath carbon monoxide measurements [643], although this technique can be slightly inaccurate in patients with COPD [644]. Support groups to help smokers quit are successful in patients with motivation [645]. Pharmacological aids are also available but, again, are particularly successful in those who are motivated. Meta-analysis of randomized controlled trials of nicotine gum found a clear benefit in terms of abstinence rates at 1 year (23% vs. 13%) in a smoking cessation clinic but no effect in a general practice setting (11% vs. 12%) [646]. Similar abstinence rates at 1 year have been quoted in a general hospital study in the UK [647]. In general poor compliance has been reported for the use of nicotine gum, which many find unpleasant to use [647,648].

The development of nicotine skin patches allows a slow infusion of nicotine that creates plasma nicotine levels up to half those produced by smoking. Trials have been carried out with nicotine patches and indicate that similar success rates to nicotine chewing gum can be achieved [649] and that these, unlike nicotine chewing gum, may be achievable in settings other than smoking cessation clinics [650,651]. An advantage in terms of sustained cessation rates has even been demonstrated in the primary care setting [652].

Based on a review of the literature, a strategy for smoking cessation has been suggested by Foulds and Jarvis and is shown in Table 23.8.

**Table 23.8** Smoking prevention and cessation strategy for medical outpatients. (Modified from Foulds & Jarvis [636].)

Intervention	To whom?	Time per patient	Success rate*
Ask about smoking, record in notes	All attenders	10s	Prevention?
Measure carbon monoxide, give advice plus leaflet	Smokers (no extra help requested)	4 min	4%
Prescribe nicotine replacement, arrange quit-date plus follow-up	Smokers who ask for extra help	15 min	10%
Group treatment with nicotine replacement (5×1 h per group)	Smokers who ask for more support	22.5 min	25%
Overall strategy	All patients	mean 2.3 min per patient	5.8% of smokers

\* A 'success' is a patient who stops smoking immediately following the intervention and maintains abstinence for at least 1 year.

### Atmospheric pollution (see also Chapter 11)

Although the traditional atmospheric air pollutants that resulted from the burning of fossil fuels, such as black smoke and sulphur dioxide, have decreased considerably in developed countries, recent evidence has implicated other pollutants derived increasingly from vehicle traffic, such as ozone and fine particulate air pollution, in the exacerbations and increased mortality in patients with COPD [62,63]. These effects occur at relatively low levels and have prompted the UK Government recently to introduce new air pollution standards for these pollutants. A biologically plausible hypothesis has been proposed to account for the harmful effects of particulate air pollution at such low levels that implicates the reactivity of the particles as a result of their ultrafine size and their oxidative properties, which create airway inflammation [65]. As a result it seems justified, if practical, for patients with COPD to stay indoors and certainly to sleep with closed windows during episodes of high air pollution.

## Long-term management

### Bronchodilators

Bronchodilator therapy is the cornerstone of treatment to reduce symptoms and increase exercise tolerance in patients with COPD. In contrast to bronchial asthma, where bronchodilator therapy can return ventilatory capacity to normal in mild to moderate disease, the effects are small in patients with COPD because of structural changes within the airways. Indeed the change with a bronchodilator, which often falls within the normal variability of the measurement of FEV<sub>1</sub>, may still have clinical relevance. Thus symptomatic relief is not always accompanied by significant functional improvement. The principal symptomatic bronchodilators ( $\beta_2$  agonists, anticholinergic drugs and theophylline derivatives) have as their primary action relaxation of airway smooth muscle and hence decrease airways resistance [653]. However, in addition, these drugs may reduce the overinflation of the lungs characteristic of COPD, allowing the lungs to empty more completely [654]. The  $\beta_2$ -agonist drugs have been shown to increase ciliary beat frequency and so accelerate mucociliary clearance, which is impaired in COPD [655]. Although anticholinergic drugs may be considered theoretically to have an adverse effect on mucociliary clearance, clinical studies suggests that this is not the case. There is still considerable controversy regarding the proposed property of theophyllines in increasing respiratory muscle endurance and strength [656,657]. The proposed anti-inflammatory actions of both  $\beta_2$  agonists and theophyllines have recently received considerable attention, particularly in the case of theophyllines [658]. However, the major effect of these drugs is on changes in airway calibre secondary to airway

smooth muscle relaxation. It should be emphasized that relatively small changes in airway dimensions can have major effects on respiratory mechanics, which may be translated into improvement in symptoms and exercise capacity [659]. Thus inhaled bronchodilators may reduce symptoms even when there is little demonstrable reversibility in terms of FEV<sub>1</sub>.

### $\beta$ -Agonists

Inhaled  $\beta_2$  agonists (see Chapter 9) are preferred to oral preparations, since they are as efficacious as oral preparations in much smaller doses and have fewer side-effects [660]. Oral and intravenous  $\beta_2$  agonists have vasodilator properties [661,662] but these effects are unlikely to have any clinical significance in patients with COPD. The  $\beta_2$  agonists have a relatively rapid onset of action and therefore are used for symptomatic relief and can also increase exercise tolerance in patients with COPD [511,555,556,663,664].

The IPPB trial group examined a group of 65 patients with COPD. The response to 250  $\mu$ g of inhaled isoprenaline was tested repeatedly over 3 years [511]. The majority of these patients showed significant bronchodilatation to the  $\beta$  agonist at one or more visits during this trial. There appears to be a very small dose-response relationship to  $\beta_2$  agonists in terms of the change in FEV<sub>1</sub> in patients with COPD [526,556,663]. Patients with the largest response to  $\beta_2$  agonists are more likely to respond to corticosteroid therapy [526,665]. Even in those who show no significant improvement in FEV<sub>1</sub>, treatment with  $\beta_2$  agonists may improve exercise tolerance [556,664]. The view that older patients with COPD are less likely to respond to a  $\beta_2$  agonist [548], perhaps as result of loss of  $\beta$  receptors [666], is not universally accepted [544]. Neither is there any evidence that the response to a  $\beta$  agonist diminishes with time [663]. Patients with COPD should be told to take their  $\beta_2$  agonists as required, although those with severe disease may prefer to take regular doses three to four times daily to obtain symptomatic relief. The concerns that have been expressed over the safety of  $\beta_2$  agonists in patients with bronchial asthma [667] have also been applied to patients with COPD [668]. In a study of 144 patients with obstructive airways disease, of whom 93 had 'chronic bronchitis', the decline in FEV<sub>1</sub> was more rapid in those patients who used continuous  $\beta_2$ -agonist (or anticholinergic) treatment than in those whose therapy was used on demand, the difference in FEV<sub>1</sub> decline between the groups being 52 mL/year [668]. This study from The Netherlands has been criticized because of the difficulty in differentiating this group from asthmatics. There is also recent evidence showing that the rebound airway responsiveness and bronchoconstriction that may occur after cessation of regular bronchodilator therapy in asthmatics does not occur in patients with COPD [669].



Very limited information is available on the effects of long-acting  $\beta_2$  agonists in patients with COPD [670–674]. In the studies that were randomized and placebo controlled there was an improvement in symptoms, quality of life and a small improvement in spirometry, without any significant change in exercise capacity [670,672,673]. Until further information is available these drugs should be restricted to those patients with a demonstrable bronchodilator response to  $\beta_2$  agonists and their use monitored in terms of symptoms. There is little evidence to support the use of sustained-release oral  $\beta_2$  agonists in patients with COPD.

### Anticholinergics

Anticholinergic drugs (see Chapter 9) have been used to treat airways obstruction for some time [675]. The side-effects from the older anticholinergic drugs such as atropine, which limited their use, was overcome by the development of an inhaled quaternary ammonium salt of atropine, ipratropium bromide, that was poorly absorbed [676]. A derivative of ipratropium bromide, oxitropium bromide, has become available in Europe and Japan [677]. Ipratropium bromide, like the  $\beta_2$  agonists, affects both central and peripheral airways [678,679] and also reduces FRC significantly [654]. Anticholinergics have a time to peak effect of 30–60 min in most COPD patients, which is slower than  $\beta_2$  agonists, but have a somewhat longer time of effectiveness (6–10 h) compared with  $\beta_2$  agonists [676]. Tiotropium bromide is a newly developed anticholinergic agent that appears to have a longer time course of action than ipratropium [680].

Optimal bronchodilatation appears to occur with 80  $\mu\text{g}$  of ipratropium and 200  $\mu\text{g}$  of oxitropium bromide [681,682]. Studies comparing 200  $\mu\text{g}$  of oxitropium bromide with 80  $\mu\text{g}$  of ipratropium bromide suggest no difference in the peak or duration of bronchodilatation [682]. Thus 80  $\mu\text{g}$  of ipratropium should be used in patients with COPD rather than the customary 40  $\mu\text{g}$  in order to produce maximum effect [683].

There is conflicting evidence regarding the effects of ipratropium bromide on exercise in patients with COPD. Some studies found an increase in maximum exercise, ventilation and a reduction in oxygen consumption at any given workload with both ipratropium bromide [684] and oxitropium bromide [685]. Studies of walking distance have also been variable. Other studies showed no improvement after ipratropium [664] or a significant improvement 45 min after 200  $\mu\text{g}$  of ipratropium in patients with COPD [686]. There is no evidence to suggest tachyphylaxis to either ipratropium or oxitropium [677,687]. The recently reported Lung Health Study in a large group of patients with COPD showed that treatment with ipratropium bromide produced a small but significant beneficial effect on  $\text{FEV}_1$  during treatment but had no

other effect on the decline in  $\text{FEV}_1$  over a 5-year period [37].

Clinical studies of anticholinergic drugs show that they are at least as efficacious as  $\beta_2$  agonists in patients with COPD [663]. Some studies report a more prolonged bronchodilator response than with the  $\beta_2$  agonists [657,688].

### Theophyllines

The bronchodilator effect of theophyllines (see Chapter 9), or methylxanthine derivatives, is modest in patients with COPD [689,690]. Their effect on symptoms and exercise tolerance is variable [691–693] and often occurs at the top of the therapeutic range. Long-term treatment with theophyllines is limited to the oral route, resulting in a slower onset of action compared with inhaled bronchodilators; thus theophyllines should only be used for maintenance therapy in oral form. There has been considerable improvement in the pharmacokinetics of oral theophyllines with the production of long-acting formulations with a half-life of 12–18 h [689,690].

The bronchodilator action of theophyllines is relatively limited in patients with COPD [689–693]. Changes in exercise tolerance in patients with COPD following theophylline treatment have been variable, either showing no improvement [691–694] or only a small improvement in either corridor or treadmill exercise [695,696]. Some of the improvement in exercise tolerance has been thought to result from the beneficial effect of theophyllines on respiratory muscles [692] or a fall in trapped gas volume [693,696], although these mechanisms are still the subject of debate. Other non-bronchodilator effects of theophylline, such as improving right ventricular performance [697] and their anti-inflammatory actions [658], are of questionable clinical significance.

Theophyllines have a narrow therapeutic index and patients often experience side-effects within the therapeutic range [698]. Other factors common in COPD, such as smoking, hypoxaemia and infection, all alter theophylline clearance and therefore make the control of dosage difficult, requiring measurement of plasma theophylline levels (Table 23.9). Thus, the possible beneficial effects of theophyllines have to be balanced against their potential side-effects in individual patients and the fact that similar benefit may be achievable with inhaled bronchodilators. This has resulted in theophyllines being reserved for patients in whom other treatments have failed to control symptoms adequately.

### Combination therapy

Studies of combination therapy are difficult to assess due to problems of suboptimal dosing. Some studies suggest that combining drugs, such as salbutamol and ipratropium [664] or salbutamol and aminophylline [695], pro-

**Table 23.9** Theophylline metabolism in COPD.

Increased by	Decreased by
Cigarette smoking**	Arterial hypoxaemia (<6.0 kPa, 45 mmHg)**
Anticonvulsant drugs	Respiratory acidosis*
Rifampicin	Congestive cardiac failure
	Liver cirrhosis
	Erythromycin/ other macrolides**
	Ciprofloxacin** (not ofloxacin)
	Cimetidine (not ranitidine)
	Viral infections
	Old age*

Many factors influence theophylline metabolism and those posing particular problems in COPD are indicated by asterisks, the number of these indicating the likely hazards.

duces improvement in exercise tolerance in the face of trivial changes in spirometry. It is unclear whether higher doses of salbutamol could have achieved a similar effect. Thus, combinations of bronchodilator drugs should only be used if single drugs have been tried and have failed to give adequate symptomatic relief. Combination therapy should only be continued if there is good subjective or objective benefit.

**Drug-delivery devices**

Compliance with inhaled treatment is poor. In the Lung Health Study the overall compliance with therapy was 65% [699]. Since many patients with COPD are elderly, the difficulties encountered with standard metered dose inhalers are exaggerated. These problems can often be overcome by dry powdered formulations or by a spacer device. Patients with severe COPD are only able to achieve low inspiratory flow rates; flow rates as low as 40 L/min may cause failure of the one-way valve in a spacer device to open.

**Home nebulizer therapy**

There is still controversy over the use of home nebulizer therapy in patients with COPD [700]. Using end-points such as spirometry and corridor walking exercise, it has been shown that nebulized salbutamol is no more effective in patients with COPD than lower doses of the same drug given through a spacer device [701]. However, patients appear to prefer nebulized bronchodilator therapy. This may be due to the fact that the total dose of the drug delivered by nebulizer therapy is higher, and because the facial cooling that occurs with the nebulized solution itself may have an effect on dyspnoea independent of any effect on airway calibre [702].

Although those patients who show a response in routine nebulized bronchodilator testing would seem to be the obvious candidates for this therapy, acute improve-

ment in spirometry does not necessarily predict a long-term response [702–705]. Only a minority of patients are likely to obtain benefit from high-dose bronchodilator therapy [692]. Since comparative clinical trials of metered dose inhaler and nebulized bronchodilators in COPD are inconsistent [706,707], the BTS guidelines recommend that patients should only be supplied with a nebulizer if they have been fully assessed by a respiratory physician able to assess the risk–cost benefit [708]. This assessment should include ensuring that optimal use is made of a simple metered dose inhaler or dry powdered device and that some assessment is made of the patient’s response to nebulizer therapy. It has been suggested that a formal assessment of efficacy should include a home trial with PEF measurements. It is essential that adequate technical support and follow-up is available whenever a home nebulizer is prescribed. Dosage regimens need to be tailored to individual patient needs and drug side-effects monitored. This is discussed in detail in the BTS guidelines for nebulizer therapy [708].

**Corticosteroids**

Chronic inflammation in the large and small airways is a characteristic feature of COPD. This inflammatory process provides a rationale for the use of corticosteroids in this condition. However, the use of corticosteroids (see Chapter 9) in patients with COPD remains contentious, particularly the prediction of which patients will respond to this treatment.

**Oral corticosteroids**

There are several short-term studies of the effect of oral corticosteroids on airways obstruction in patients with COPD [709–715]. However, relatively few controlled studies have been undertaken [711–715] and the results of these randomized controlled trials are conflicting. Clearly, a subgroup of patients do respond to corticosteroids, and the response may continue beyond the standard 14 days of treatment [550]. A meta-analysis of trials of oral corticosteroids indicates that a significant improvement in FEV<sub>1</sub> (>15% and >200 mL improvement in FEV<sub>1</sub>) occurs in 10–20% of patients with clinically stable COPD [710]. There are no reliable predictors of which patients will respond. Indeed, in one study the presence or absence of clinical features of emphysema did not affect the response rate [716]. In contrast to asthma, corticosteroids do not affect the bronchial hyperresponsiveness that occurs in patients with COPD [717]. Furthermore, the response to high doses of oral prednisolone in short-term studies does not necessarily predict continued FEV<sub>1</sub> response to long-term inhaled steroids, although the studies on this subject are limited [665,713]. In one double-blind study in 18 patients with COPD [717], the addition of 400 or 1600 µg of inhaled budesonide daily permitted a reduction of

approximately 6.5 mg of prednisolone per day without altering the FEV<sub>1</sub>. This suggests that 400 µg daily of an inhaled corticosteroid should be adequate in patients with COPD. The follow-up period of this study was only 7 months and extrapolation to long-term effects requires further study. Data from uncontrolled retrospective studies of oral corticosteroids suggest that long-term treatment may slow the decline in FEV<sub>1</sub> [718,719]. However, the relationship between the inflammatory changes in patients with COPD and the degree of airflow limitation or indeed their response to treatment is poor [712,713]. In general, long-term oral corticosteroid treatment in COPD cannot be recommended in view of adverse side-effects.

### Inhaled corticosteroids

Short-term studies of inhaled corticosteroids given over a period of 3–12 weeks [128,551,720–722] have in general been disappointing, and have shown no change in the level of airways obstruction as assessed by FEV<sub>1</sub> or peak flow or indeed in the degree of airway responsiveness to histamine. However, two studies [551,721] indicate that a subpopulation of patients with COPD do show a response and indeed in one study inhaled steroids had a significant effect on markers of inflammation, particularly on albumin levels in BAL, reflecting an improvement in epithelial permeability [721]. There is only one study of the long-term effects of inhaled corticosteroids [723] in a group of patients who had previously shown a rapid decline in respiratory function when they did not use inhaled steroids [668]. In this study, 800 µg of beclometasone daily improved the FEV<sub>1</sub> after bronchodilator significantly during the first 6 months of treatment. However, a fall in FEV<sub>1</sub> continued over the next 6 months, indicating to the authors that longer-term follow-up was required. These effects were shown in a group characterized as COPD and in another group characterized as asthmatics, although the overlap between the two groups was significant. A long-term follow-up study [724] over a period of 2.5 years in a group of patients with both asthma and COPD also showed a beneficial effect on the number of exacerbations in both groups of patients. The limited information available suggests that there is no modifying effect of corticosteroids on the action of bronchodilators [720].

On presently available evidence, inhaled corticosteroids in doses of 1000 µg of beclometasone, 800 µg of budesonide or 500 µg of fluticasone should be given to those patients who show a response to either oral or inhaled corticosteroids. Those who do not respond should *not* be given maintenance therapy. The effects of long-term inhaled corticosteroids in COPD is currently under examination. So far the results of one large trial imply that abstinence from tobacco is likely to be more effective in reducing the rate of decline in FEV<sub>1</sub> than regular budesonide 400 µg twice daily, which had no significant effect on

the overall rate of decline or indeed symptom scores or the number of exacerbations [725].

### Other therapeutic agents

There is no evidence to support a role for anti-inflammatory drugs such as sodium cromoglycate, nedocromil sodium or antihistamines in patients with COPD. Although used widely in continental Europe, mucolytic drugs are rarely used in the UK.

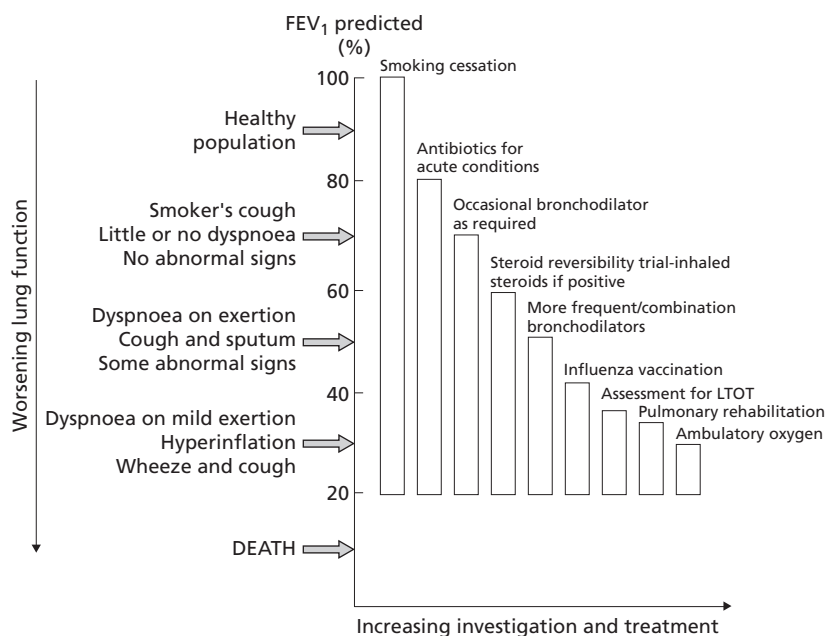
### An approach to the management of patients with COPD

The BTS guidelines suggest an approach to the management of patients with COPD based on severity of disease [4] (Fig. 23.18). COPD can be arbitrarily divided into patients with mild, moderate and severe disease based on the percentage predicted FEV<sub>1</sub>. In those with mild disease (FEV<sub>1</sub> 60–69% of predicted), stopping smoking and, in symptomatic patients, a trial of inhaled β<sub>2</sub> agonists or an anticholinergic, taken as required, may be useful. There is no convincing evidence at present that any other treatment, such as inhaled corticosteroids, affect the long-term progression of COPD. Exercise should be advocated and patients who are overweight encouraged to lose weight with the appropriate dietary advice.

In those with moderate disease (FEV<sub>1</sub> 40–59% of predicted), stopping smoking is the single most important way of affecting the outcome and this is particularly important in those who have already shown evidence of an accelerated decline in FEV<sub>1</sub>. These patients show some benefit from bronchodilator use and thus a reversibility test to a bronchodilator should be obtained, both to determine those patients who show a large degree of reversibility and therefore have asthma and because the FEV<sub>1</sub> after bronchodilator is a good predictor of survival. Unfortunately, single-dose reversibility tests do not predict which patients will have long-term symptomatic benefit from bronchodilator therapy. The effect of bronchodilator therapy should be monitored in terms of lung function or subjective symptomatic improvement.

In patients with severe disease, the severity of airflow obstruction cannot be predicted from symptoms or signs [516]. Measurement of the FEV<sub>1</sub> is the only reliable guide to severity. Reversibility tests to nebulized bronchodilators and corticosteroids should be assessed, since even patients with severe airflow obstruction can demonstrate reversibility. Those patients who show a bronchodilator response are more likely to respond to a trial of oral inhaled corticosteroids. Those who show a positive response to oral steroids should be continued on inhaled steroids.

More detailed measurements of respiratory function, such as lung volumes, transfer factor for carbon monoxide (Tl<sub>CO</sub>) or tests of pulmonary mechanics, are not routinely



**Fig. 23.18** The chronic obstructive pulmonary disease escalator: as lung function declines the treatments need to be increased. LTOT: long-term oxygen therapy.

indicated in these patients but may be useful in some cases. In these patients, hypoxaemia and hypercapnia are common and arterial blood gases should be considered in all patients with severe disease. Pulse oximetry may be useful in assessing arterial oxygenation and obviate the need for blood gas measurements if the  $SaO_2$  is greater than 92%. However blood gas measurements are obligatory for the measurement of  $Paco_2$  and in patients who are clinically deteriorating or who develop complications.

Even in the group of patients with severe disease smoking cessation should be encouraged, since it results in a more gradual deterioration in  $FEV_1$  and improves the chances of a beneficial effect of long-term oxygen therapy (LTOT) (see below). Bronchodilator therapy and corticosteroid therapy should be given as for patients with moderate disease. It is common for patients with severe COPD to receive nebulized therapy at the general practitioner's request. The prescription of nebulizers in this group remains controversial. Most patients can be managed using metered dose inhalers with spacer devices or dry powder devices. There is no evidence to support the use of continuous or intermittent prophylactic antibiotics in patients with COPD.

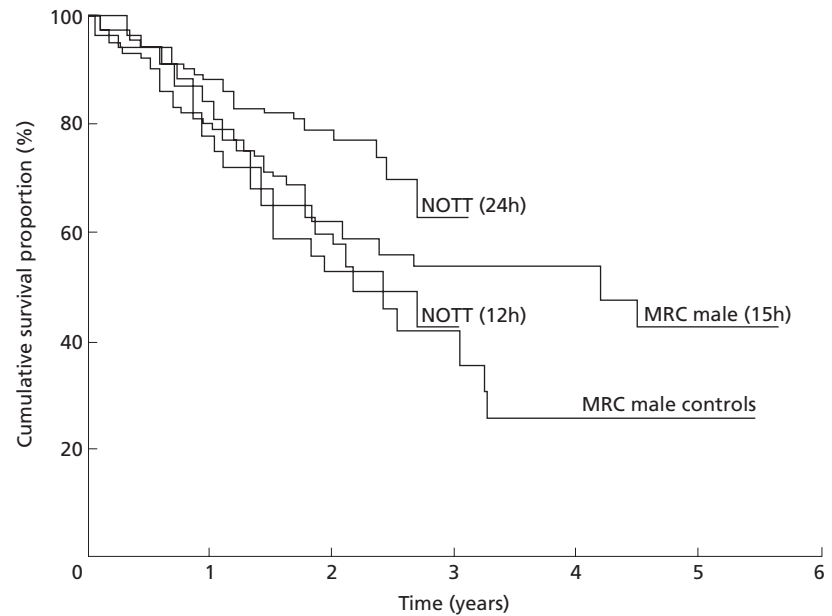
### Domiciliary oxygen therapy

Two landmark multicentre trials, the Medical Research Council (MRC) trial [150] and the nocturnal oxygen therapy trial (NOTT) [149], have shown improved survival with domiciliary oxygen therapy when given for at least 15 h daily (Fig. 23.19). The design of these two studies differed. The MRC study compared patients receiving 15 h

of oxygen daily with a control group who received no oxygen, whereas the NOTT compared continuous oxygen therapy (averaging 17.7 h of oxygen daily) with overnight oxygen therapy (12 h daily). Although the patients in the two studies had similar spirometry and  $PaO_2$ , the patients in the MRC study were hypercapnic (mean  $Paco_2$  7.3 kPa, 55 mmHg), whereas those in the NOTT trial were largely normocapnic ( $Paco_2$  5.7 kPa, 43 mmHg). The major outcome was an improved survival in patients receiving oxygen therapy for at least 15 h daily, although survival in the MRC group receiving 15 h daily was only significantly increased after 500 days had elapsed.

In addition to the improvement in survival, a number of studies have examined the effects of supplementary oxygen therapy and exercise tolerance. Several studies have shown an improvement in exercise endurance in patients with COPD breathing supplemental oxygen, associated with a reduction in ventilation at a given submaximal work rate and an improvement in walking distance and in ability to perform daily activities [726–729]. The effects of oxygen therapy on breathlessness remain unclear. Some studies have shown a reduction in dyspnoea scores during submaximal exercise in patients given oxygen therapy [726,728]. However, controlled trials using supplementary oxygen vs. compressed air have shown conflicting effects on breathlessness [727,729].

Assessment of patients taking part in the NOTT study showed that they had marked disturbances in mood and quality of life [514]. After 6 months of oxygen therapy, 42% of patients showed evidence of an improvement in cognitive function but little change in mood or quality of life [730]. Further studies are required to investigate the effects of oxygen therapy on quality of life.



**Fig. 23.19** Combined data from the Nocturnal Oxygen Therapy Trial (NOTT) and the Medical Research Council trial. (From Nocturnal Oxygen Therapy Trial Group [149] and Medical Research Council Working Party [150] with permission.)

The reasons for the improvement in survival with oxygen therapy in patients with COPD are still unclear. The NOTT reported a reduction in pulmonary arterial pressure on exercise after 6 months with either continuous or nocturnal oxygen therapy, and also a small improvement in pulmonary arterial pressure at rest in the group receiving continuous oxygen therapy [149]. These changes in pulmonary arterial pressure were also reflected in the measurements of pulmonary vascular resistance. The same group also showed that survival over a period of 8 years was related to a decrease in mean pulmonary arterial pressure during the first 6 months of treatment [731]. A report in a different group of patients showed that those patients who demonstrated an acute fall in pulmonary arterial pressure of more than 5 mmHg with oxygen therapy had a better survival on LTOT than those who did not show this response [732]. However, the patients in this study were unusual, since they showed a marked decrease in pulmonary arterial pressure when breathing controlled oxygen therapy.

In the MRC trial, there was no significant improvement in pulmonary arterial pressure following oxygen therapy; however, the increase of 3 mmHg per year in pulmonary arterial pressure in the control group did not occur in the treated group [150]. From these studies, it has been suggested that an improvement in pulmonary haemodynamics may account for the improved survival with LTOT. In a group of 16 patients with COPD, Weitzenblum and coworkers [733] showed that the annual increase in pulmonary arterial pressure of around 2 mmHg per year over a period of nearly 4 years before LTOT was instituted changed to an annual reduction in pulmonary arterial pressure of 2 mmHg over a period of 31 months after the

commencement of LTOT. It has also been shown that overnight oxygen therapy, which abolishes nocturnal desaturation, also decreases pulmonary arterial pressure [734]. Although some studies have shown a relationship between the fall in pulmonary arterial pressure with oxygen, given over 24 h, and long-term survival on subsequent LTOT [732,733], this has not been confirmed in one other study [735].

Thus it is still a matter of debate whether the changes in pulmonary haemodynamics relate to the improvement in survival of patients treated with LTOT [736]. However since the changes in pulmonary haemodynamics produced by LTOT are small, it seems unlikely that these changes have a major influence on survival. Indeed Wilkinson and coworkers [228] showed continued evidence of pulmonary vascular changes in patients with respiratory failure who died despite having received LTOT.

As in all studies of patients with COPD, Cooper and colleagues [737] showed that the  $FEV_1$  was the strongest predictor of survival in patients receiving LTOT, and that LTOT did not influence the decline in  $FEV_1$  [738]. However, as in general studies in patients with COPD, the level of pulmonary arterial hypertension is also related to survival in patients who receive LTOT [739].

LTOT has also been shown to affect the polycythaemia that occurs in patients with chronic hypoxaemia, by reducing both the haematocrit and the red cell mass [150]. The clinical relevance of these haematological changes produced by LTOT remains unclear. However, continued cigarette smoking, and hence chronic elevation of carboxyhaemoglobin, decreases the effectiveness of LTOT in correcting polycythaemia [740]. The red cell mass formed

part of a complex equation for the prediction of improved survival in patients treated with LTOT in the MRC trial, and this has been used as evidence to support the contention that those who continue to smoke are less likely to have a survival benefit from LTOT [150]. Thus continued cigarette smoking should be a relative contraindication to LTOT.

### Criteria for the prescription of domiciliary oxygen therapy

There are three forms of domiciliary supplemental oxygen therapy:

- 1 long-term controlled oxygen therapy for at least 15 h daily in patients with chronic respiratory failure, conventionally called LTOT;
- 2 portable oxygen therapy for exercise-related hypoxaemia;
- 3 short-burst oxygen therapy as a palliative treatment for the temporary relief of symptoms.

It is important to realize that the criteria for the prescription of LTOT are based on the clinical parameters of those patients with COPD who showed an improved survival in the two controlled trials of LTOT [149,150]. The same criteria have been applied to other forms of chronic hypoxaemic lung disease, although the rationale for the

prescription of LTOT in these patients is not based on evidence from controlled trials. Furthermore, central to the prescription criteria is the demonstration of significant hypoxaemia in a patient with COPD breathing room air, measured when clinically stable (Table 23.10).

In the UK, the absolute indications for LTOT refer to the criteria in the patient group who have been clearly shown to have improved survival with LTOT. The relative indications are the same as the absolute indications, without the need for oedema or hypercapnia. In the USA, LTOT can be prescribed based on pulse oximetry and in patients whose  $P_{aO_2}$  lies between 7.3 and 7.9 kPa (55–59 mmHg), provided there is evidence of cor pulmonale or polycythaemia. In Australia, patients who show desaturation on exercise to a level below 90% can also be prescribed LTOT.

A community survey in the Sheffield area by Williams and Nicol [741] found that 0.3% of patients randomly sampled from general practitioners' lists had a  $P_{aO_2}$  less than 7.3 kPa (55 mmHg). From these data they suggested that around 60 000 people in England and Wales could be eligible for LTOT; the comparable figure in the USA would be 750 000. However the majority of patients receiving home oxygen therapy do not receive 15 h oxygen daily but will be receiving cylinder oxygen [742].

LTOT is usually prescribed in the UK in the form of oxygen concentrators, although a recent survey from Scot-

**Table 23.10** Prescribing criteria for long-term oxygen therapy.

#### *UK: DHSS Drug Tariff (1985)*

- 1 Absolute indications: COPD, hypoxaemia, oedema  
 $FEV_1 < 1.5$  L;  $FVC < 2.0$  L  
 $P_{aO_2} < 7.3$  kPa (55 mmHg);  $P_{aCO_2} > 6.0$  kPa (45 mmHg)  
 Stability demonstrated over 3 weeks
- 2 Relative indications: as above but without oedema or  $P_{aCO_2} > 6.0$  kPa (45 mmHg)
- 3 Palliative

#### *Europe: Report of a SEP Task Group (1989)*

- 1  $P_{aO_2} < 7.3$  kPa (55 mmHg), 'Steady-state COPD'
- 2  $P_{aO_2}$  7.3–8.7 kPa (55–65 mmHg) with additional features as in the USA (Group 2)
- 3 Restrictive disease with  $P_{aO_2} < 7.3$  kPa (55 mmHg)

#### *USA*

- 1  $P_{aO_2} \leq 7.3$  kPa (55 mmHg) (room air)  
 $SpO_2 \leq 88\%$
- 2  $P_{aO_2} \leq 7.85$  kPa (59 mmHg) with evidence of at least one of the following:  
 P pulmonale 9 > 3 mm in leads II, III or a VF  
 (pulmonary hypertension? right ventricular hypertrophy?)  
 Dependent oedema (cor pulmonale?)  
 Erythrocytosis (haematocrit > 56%)  
 Certificate of medical necessity (CMN)  
 For Group 1: annual update of CMN required  
 For Group 2: revised CMN required after 3 months

#### *Australia: Thoracic Society of Australia (1985)*

- 1  $P_{aO_2} < 7.5$  kPa (56 mmHg), COPD, right ventricular hypertrophy, polycythaemia, oedema
- 2 Desaturation < 90% on exercise
- 3 Refractory dyspnoea associated with cardiac failure

land [743] confirmed previous regional data from England and Wales that the majority of home oxygen therapy is given to patients with COPD in the form of cylinder oxygen therapy for the relief of breathlessness. In England and Wales, general practitioners can prescribe LTOT, which contrasts with Scotland, where only respiratory physicians can prescribe this treatment [744]. Data from the Liverpool area [745] indicate that adherence to the criteria for the prescription of LTOT and patient compliance is better in those patients who were prescribed LTOT by respiratory physicians. However, it is clear that even among respiratory physicians, strict adherence to the criteria in the prescription of LTOT is less than optimal, with studies reporting adherence to the criteria for domiciliary oxygen in around 40% of patients [745–747] and a mean duration of oxygen usage of around 12 h daily [742,745]. A study from Scotland by Morrison and colleagues [742], where LTOT is prescribed exclusively by respiratory physicians, showed that the majority of patients had an assessment of arterial blood gases and had established hypoxaemia. However, a major diversion from the criteria for the prescription of LTOT was that these measurements were often made when the patients were in an unstable state, often at the end of a hospital admission for an exacerbation of COPD. This raises the concern that some patients may be receiving LTOT inappropriately, since data from the NOTT study showed that 43% of patients who were initially screened and shown to fit the criteria for LTOT were no longer eligible when reassessed 4 weeks later [748], data that have been confirmed by others workers [749]. It is therefore essential that clinical stability is demonstrated, with no exacerbation of COPD for at least 4 weeks before a decision is made to prescribe LTOT, and that other treatment such as bronchodilators and inhaled steroids are optimized before the prescription of LTOT. Furthermore, reassessment is recommended to ensure that the patient remains significantly hypoxaemic and still fits the criteria for LTOT. It has been suggested that such reassessment in these very disabled patients is best done by domiciliary nursing visits and measurements of pulse oximetry [750]. Arterial blood gases are required at the follow-up clinic to ensure that adequate oxygenation is achieved while breathing oxygen. A  $P_{aO_2}$  of 8 kPa (60 mmHg) is desirable, and this can usually be achieved by nasal prongs at flow rates between 1 and 3 L/min. Precipitating an increase in hypercapnia with LTOT is seldom a problem in clinically stable patients.

### Portable oxygen therapy

In the UK, there are no established criteria for the prescription of portable oxygen/liquid oxygen therapy, although the latter is not currently available on the NHS tariff. It has been suggested that patients who desaturate during exercise by 5% or more would be suitable for portable oxygen therapy [751], although it has been shown previously that

exercise capability may improve irrespective of the arterial oxygen desaturation [728]. Portable oxygen therapy is now well established in the USA [752]. The use of portable oxygen therapy to enhance mobility should be encouraged in patients in order to help prevent the downward spiral of immobility and physical deconditioning.

Surveys have also indicated that between 10 and 20% of patients restart the tobacco smoking habit after commencing LTOT, having quit at the time of prescription [742,753]. Not only is there the theoretical problem of loss of the survival benefit of LTOT in patients who continue to smoke, but the combination of cigarette smoking and oxygen is clearly a fire hazard.

LTOT should be prescribed continuously during sleeping hours, which should reduce the rise in pulmonary arterial pressure by preventing episodes of oxygen desaturation at night [754] and also improves sleep quality [515].

### Travel

Commercial air cabins are pressurized to the equivalent of an altitude of no more than 2600 m, producing an oxygen tension of around 13 kPa (100 mmHg). Increasing hypoxaemia may worsen the symptoms of breathlessness, particularly in patients who are already hypoxaemic with a  $P_{aO_2}$  less than 9.6 kPa (72 mmHg) [755]. The airline should be contacted by letter by the patient's respiratory physician recommending the use of oxygen and most will provide oxygen throughout the flight.

### Oxygen delivery systems

In the UK, home oxygen therapy can only be supplied in the form of compressed gas cylinders or oxygen concentrators on the NHS tariff. Liquid oxygen is used in the USA and continental Europe.

The cylinders that UK pharmacists ordinarily dispense for home use are aluminium (A) F-size, containing 1360 L so that they will last approximately 11.3 h at a 2 L/min flow rate. Various other sizes of cylinder are available for purchase outside the UK NHS drug tariff, the oxygen itself being prescribable. Aluminium lightweight E-size cylinders, weighing about 6 Kg and providing about 5 h at 2 L/min, can be made portable by the provision of a purpose built cart. Smaller PD-size cylinders, containing 300 L of oxygen and providing a little over 2 h supply at 2 L/min, are much thinner and can be carried by the patient for short trips by using a shoulder strap. Oxygen concentrators are the mainstay and most convenient and cost-effective method of supplying home oxygen therapy [756]. The device contains a molecular sieve incorporating zeolite, a synthetic aluminium silicate that entraps gas molecules according to their size and polarity, and is capable of producing 96% oxygen since argon is also concentrated to about 4%. The systems are



not generally portable, although lighter versions have been developed that can produce up to 90% oxygen at 3 L/min. It is important when developing an oxygen service that there is sufficient patient education, technical support and frequent maintenance to ensure adequate oxygen delivery [757]. Oxygen concentrators become less efficient at delivering oxygen at higher flow rates [758], for example at a flow rate of 5 L/min many systems produce only 70% oxygen, although technology has improved this recently.

Generally, oxygen is delivered by means of nasal prongs, since controlled oxygen therapy is usually required. Higher flow oxygen (>35%) requires a facial mask. Inspired oxygen concentrations with nasal cannulae appear to be independent of whether the patient breathes through the nose or mouth [759], although there is clearly variability in the inspired oxygen concentration in different patients and also in the same patient from time to time [760]. Some patients are intolerant of nasal cannulae, since they complain of local irritation and dermatitis. Humidification can be supplied by the addition of a humidifier to an oxygen concentrator, although this is not normally recommended in view of the possibility of bacterial contamination. Patient compliance with masks is generally considered to be less than that with nasal prongs. In those intolerant of nasal prongs, or in whom there is refractory hypoxaemia, oxygen can be delivered tracheally in an acceptable form to patients [761,762]. Several groups have now reported their experience with transtracheal oxygen therapy [763–765] using various techniques, including a totally implanted system with tubing tunnelled beneath the skin [766]. Transtracheal oxygen can reduce the resting flow rate requirements by 25–50% compared with nasal cannulae [761,763,765] and this can result in considerable savings, particularly if liquid oxygen is the supply mode. There are complications, including the formation of mucous balls in some 25% of cases, cough, infection and catheter dislodgement [765]. In general, this form of oxygen delivery has not been very popular in the UK.

Other reservoir devices have been developed to reduce the total oxygen requirement and therefore cost, particularly if cylinder liquid oxygen is required. These systems work on the basis of a reservoir that fills during the patient's exhalation and supplies oxygen only during inspiration. These systems can reduce oxygen flow requirements by around 50% [767–769]. Other devices, including respiratory-phased, demand or pulsed oxygen delivery systems, have also been developed [770].

There is evidence that LTOT is being prescribed too late in the treatment of the disease [742] since as many as 50% of patients die in the first 3 months of LTOT. Based on this evidence, early referral to pulmonary specialists to identify the need for oxygen is appropriate.

In the UK, oxygen therapy at 15 h per day in the form

of cylinders currently costs about £6500 per annum per patient, whereas supplying an oxygen concentrator service can usually be arranged for around £1000 per annum.

## Pulmonary rehabilitation

Rehabilitation has been defined as 'the restoration of the individual to the medical, mental, emotional, social and vocational potential of which he/she is capable' [771]. An important aim of pulmonary rehabilitation is to prevent the deconditioning that occurs with lack of exercise and immobility due to dyspnoea and allow the patient to cope with the disease [772]. Before considering rehabilitation, it is vital that investigations and therapy are directed towards any reversible component of the airflow limitation and that this treatment is optimized. Patients with moderate to severe COPD should be considered for pulmonary rehabilitation programmes and each rehabilitation programme should be tailored to fit individual patients' needs, depending on the factors deemed to limit exercise [773].

### Pulmonary rehabilitation programme

Establishing a pulmonary rehabilitation programme requires a multidisciplinary approach [772] and appropriate healthcare resources. Exercise training programmes have taken two approaches. The first is to attempt to improve cardiorespiratory fitness by aerobic exercises of 20–30 min duration at least three times per week [773]. It has been suggested that this may not be the correct approach in patients with COPD, since they may be unable to achieve the required increase in oxygen uptake in order to produce the required 'training effect' because of breathlessness [774]. This approach is therefore usually restricted to those patients with mild to moderate exercise limitation. In selected groups of patients, this form of training can result in a substantial reduction in minute ventilation at equivalent submaximal workloads [775,776].

The second approach is used in those patients who are unable, because of breathlessness, to sustain sufficient exercise to improve their anaerobic fitness. In this group the target should be to improve mobility [777]. This can be achieved by providing regular exercise sessions so that patients work to their maximum tolerable ventilatory limit or, alternatively, perform exercises aimed at specific muscle training [778]. In patients with very severe COPD, there are no established guidelines for pulmonary rehabilitation programmes, but carefully supervised exercise conditioning in the hospital setting, with oxygen supplementation, should be considered in those who develop hypoxaemia during exercise. Exercise desaturation cannot be predicted from measurement of pulmonary function

[779]. There are no published data showing the effects of supplemental oxygen on exercise rehabilitation outcomes. The presence of resting hypercapnia is not a contraindication to pulmonary rehabilitation and, in one study at least, improvements in exercise tolerance following rehabilitation were similar in those with normocapnia or hypercapnia [780].

Respiratory muscle training and ventilatory-assist devices have been used to attempt to reduce ventilatory limitation during exercise [781]. Proponents of inspiratory muscle training, achieved by breathing through a resistance, suggest that it improves respiratory muscle endurance as well as exercise performance [782]. Research in this area has recently shifted away from attempts to train the inspiratory muscles using overload techniques, in order to improve exercise tolerance in COPD [781], towards investigating the role of periodic rest in the reduction of incipient muscle fatigue [783]. Meta-analysis of studies of respiratory muscle training in patients with COPD have failed to show definite evidence of benefit, probably as a result of differences in patient selection, variations in the methods of respiratory training and doubt over the role of respiratory muscle fatigue and ventilatory limitation in COPD [391,784]. Some studies have shown positive results for the use of resistive inspiratory loading during pulmonary rehabilitation, resulting in a reduction in breathlessness [785,786]. However, the changes were small and of doubtful clinical significance. However, measurements such as maximum inspiratory and expiratory pressure ( $P_{\text{imax}}$ ,  $P_{\text{emax}}$ ) have been included in pulmonary rehabilitation programmes.

It is important to evaluate the effect of a pulmonary rehabilitation programme. The outcome is usually assessed by measuring improvement in lung function or exercise tolerance. However, benefit may not always be apparent in these variables [777,787]. In general, the results of studies of pulmonary rehabilitation show a favourable effect on exercise tolerance [788,789] and a reduction in symptoms such as breathlessness during exercise [790]. Since social factors contribute to the disability in COPD [791], assessment of quality of life should be included in a rehabilitation programme and can be measured by a health profile questionnaire [787]. It is important also to assess compliance and the longevity and cost-benefit of any pulmonary rehabilitation programme.

Education of patients to enable them to understand the various components of their disease seems intuitively valid [792]. However, studies have failed to show any significant impact of an education programme alone on symptoms, daily activity or quality of life [793,794]. Nevertheless, a controlled trial of education plus pulmonary rehabilitation has shown very encouraging effects on exercise tolerance [795].

Mood disturbances, particularly depression, are very

common in patients with advanced disease [796] and often contribute to an enhanced perception of symptoms, particularly breathlessness, and to social isolation. Antidepressant drugs can often produce encouraging results in these patients [797].

### Exercise training

Expiratory flow rates during tidal breathing in patients with severe COPD are close to the maximum expiratory flow-volume relationships [798]. Thus an increase in expiratory flow rate can occur during exercise in patients with COPD through dynamic hyperinflation [799] but at the expense of an increase in inspiratory work, since tidal volume operates in a less compliant range of the pressure-volume relationship and hence initiation of inspiration requires additional inspiratory pressure to overcome the increased elastic recoil of the respiratory system [800]. Continuous positive airway pressure (CPAP) overcomes the increased recoil pressure at the end of expiration, thus reducing dyspnoea and work of breathing. One study has shown that application of CPAP (at approximately 10 cmH<sub>2</sub>O) during exercise improved breathlessness in a small group of patients [801]. Further work is required to determine the role of this form of treatment in pulmonary rehabilitation.

### Controlled breathing techniques

This form of pulmonary rehabilitation attempts to diminish breathlessness by training patients to breathe efficiently [802]. This treatment aims to:

- 1 restore the diaphragm to a more normal position and function;
- 2 decrease the respiratory rate by using a breathing pattern that diminishes air trapping and improves the respiratory duty cycle;
- 3 diminish the work of breathing;
- 4 reduce dyspnoea and allay patient anxiety.

Techniques such as pursed lip breathing have been employed and some studies have shown an improvement in blood gases [517,803]. The effects of different postures on respiratory muscle function have also been assessed [804,805]. Diaphragmatic breathing exercises have been used to improve diaphragm function and are thought to be most helpful in patients with hyperventilation [806,807].

### Nutrition

Weight loss is common in patients with COPD, particularly in those with severe airways obstruction [791]. Those patients who are less than 90% of their ideal body weight are generally considered to be malnourished. Weight loss has been associated with a higher mortality in these

patients [808]. It would therefore seem logical to give nutritional support to patients with COPD. However, studies that have addressed this issue have produced variable results. The weight gain is lost soon after cessation of nutritional support and any improvements in peripheral muscle performance and exercise capacity are also small and of short duration [397,400,401]. However, if sustained weight gain can be achieved this may improve survival [809]. The theoretical complication of carbohydrate-based diets increasing carbon dioxide production and hence hypercapnia in patients with COPD does not appear to be a problem [810]. Further studies are required before nutritional supplementation can be recommended in patients with COPD.

Obesity should be discouraged in patients with COPD in order to avoid additional strain on the cardiorespiratory system, and appropriate dietary advice should be given.

### Vaccination

Influenza vaccination is recommended for patients with COPD, although the specific evidence for this in COPD patients is lacking. The rationale relates to other studies in elderly patients, not specifically with COPD, where a 70% reduction in mortality from influenza can be demonstrated [811].

## Management of acute exacerbations

Acute exacerbations of COPD vary from a mild increase in cough, sputum and dyspnoea to a severe illness resulting in respiratory failure and often fluid retention. Although some exacerbations may be initiated by an increase in atmospheric pollution, infection is usually an important precipitating feature. Exacerbations of COPD occur on a background of established disease and are among the most common acute respiratory problems presenting to either general practitioners or hospitals. It has been estimated that in an average UK health district serving 250 000 people, exacerbations of COPD account for 340 hospital admissions per annum and 8100 general practice consultations per annum [10]. Many patients can be managed in the community. A decision whether a patient requires inpatient support is often difficult.

### Antibiotics

Infection is a common precipitating factor, although only 50% of patients with severe exacerbations with associated respiratory failure have a positive sputum culture for a bacterium [812,813]. The commonest organisms are *Haemophilus influenzae* and *Streptococcus pneumoniae* [812,814], although more recently *Moraxella catarrhalis* has also been shown to be a common pathogen [815]. However, patients with COPD are often chronically colo-

nized with common bacterial pathogens and therefore culture of one of these organisms during an acute exacerbation does not imply that this organism is responsible for the exacerbation. Some studies have demonstrated an increased antibody titre to *H. influenzae* following the exacerbation, suggesting that this organism is causally involved [816]. Viral infections have been shown to be responsible for up to 30% of all exacerbations of COPD [817]. This may well be an underestimate due to the difficulties in viral isolation. In view of the relatively limited number of pathogens, it has been considered that bacteriological examination of the sputum may not influence the management in an acute exacerbation of COPD [819], although this is controversial [819].

There is very limited information from controlled trials on the effects of antibiotics in exacerbations of COPD [820,821]. In a small study of 40 patients requiring hospitalization for an exacerbation for COPD, there was no difference in outcome between placebo and tetracycline given for 1 week [821]. In a much larger trial of 362 exacerbations of COPD in 173 patients, the patients received a 10-day course of sulfamethoxazole (sulphamethoxazole), amoxicillin (amoxycillin), doxycycline or placebo [820]. Relief of symptoms within 21 days was achieved in 68% of the antibiotic-treated group and in 55% of the placebo-treated exacerbations. Peak expiratory flow recovered faster in the antibiotic-treated group, although the differences were small. Treatment failures were twice as common in the placebo group compared with the antibiotic-treated group. The difference in successful outcome between the antibiotic and placebo was significant if two of the following were present: increase in dyspnoea, increase in sputum volume, increase in sputum purulence. Therefore, antibiotics are recommended when these symptoms are present.

In view of the limited range of bacteria present in the sputum of these patients, broad-spectrum antibiotics such as amoxicillin 250 mg three times daily or tetracycline 250 mg four times daily are usually employed. Prescription of antibiotics should take into account local bacteriological sensitivity patterns, particularly the prevalence of  $\beta$ -lactamase-positive *H. influenzae* (around 20% in most areas in the UK) and *Moraxella catarrhalis*, of which 90% are  $\beta$ -lactamase positive. If the patient is known to have previous  $\beta$ -lactamase-positive organisms in the sputum or fails to respond to amoxicillin, then co-amoxiclav should be considered. There is no justification for expensive new antibiotics, although clarithromycin is a useful first-line drug in patients with exacerbations of COPD who are hypersensitive to penicillins, and it has better activity against *H. influenzae* than erythromycin. Antibiotics should be given orally unless there is a specific indication for intravenous administration. The presence of a pneumonia on the chest film in patients with exacerbations of COPD clearly requires antibiotic therapy and should be based on guide-

lines for community-acquired pneumonia, taking into account that *H. influenzae* and *Moraxella catarrhalis* can be aetiological organisms in patients with COPD.

### Bronchodilators

Since many studies have shown that a proportion of patients with COPD have a bronchodilator response, the use of nebulized bronchodilators in acute exacerbations of COPD is always justified. Large doses of bronchodilators inhaled in nebulized form produce greater bronchodilatation and fewer side-effects than comparable oral doses [660,822]. Nebulized bronchodilators should be given as soon as possible on admission and at intervals of 4–6 h thereafter, or more frequently if required. In patients with COPD, particularly in those with an elevated  $P_{aCO_2}$ , the nebulizer should be driven by compressed air and not oxygen in order to avoid a further rise in  $P_{aCO_2}$ . Oxygen can be given by nasal prongs at 1–2 L/min during nebulization. A  $\beta$  agonist (salbutamol 2.5–5 mg or terbutaline 5–10 mg) or an anticholinergic drug (ipratropium bromide 0.5 mg) are usually given by nebulizer in severe exacerbations. When the response to either treatment alone is poor, both can be given. However, a response to a nebulized bronchodilator in an acute exacerbation does not justify long-term treatment and assessment for a home nebulizer should be made when the patient is in a stable condition as an outpatient. Several studies have shown no difference in the degree of bronchodilatation achieved when the same dose of bronchodilator is given by metered dose inhaler, with or without a spacer device, or via a nebulizer [823,824] even in patients with an acute exacerbation of airways obstruction [825]. Patients with respiratory failure have been excluded in these studies. Thus, nebulized bronchodilators are still recommended but perhaps a switch to metered dose inhaler could be considered earlier; this would have a considerable cost benefit [826].

Several studies suggest that ipratropium bromide produces the same or greater bronchodilatation in patients with COPD than  $\beta_2$  agonists [827,828]. In acute exacerbations of COPD, no difference has been shown between the two drugs given alone or in combination in nebulized form [829,830]. In most cases nebulized bronchodilators should only be necessary for 24–48 h and a change to a metered dose inhaler or a dry powder device should be made 24–48 h before discharge.

If a patient is not responding to nebulized bronchodilators during an exacerbation, intravenous methylxanthines (e.g. aminophylline 0.5 mg/kg/h) should be considered. Although the use of methylxanthines in obstructive airways diseases is under scrutiny [831], there is relatively little information on the role of theophyllines in acute exacerbations of COPD. Rice and colleagues [832] studied 28 patients who received intravenous aminophylline or placebo in a randomized double-blind trial. Over a period

of 72 h following initial hospitalization, there were no differences in spirometry, arterial blood gases or the sensation of dyspnoea between the aminophylline-treated and the placebo-treated groups. Thus, the prescription of theophyllines has no clear role in management of acute exacerbations of COPD and the possible benefits should be weighed against the side-effects, particularly in patients with COPD who have hypoxaemia and infection, are receiving antibiotics and who may smoke, all of which can affect theophylline clearance. Thus the dose must be carefully individualized (see Chapter 9) and the serum level maintained within a narrow therapeutic range (10–20 mg/L) [833]. The usual loading dose is 6 mg/kg of aminophylline with maintenance dosage of 0.5 mg/kg/h.

There is a paucity of data on the use of corticosteroids in patients with acute exacerbations of COPD and therefore the role of these drugs remains unclear. In one single randomized, double-blind, placebo-controlled study, methylprednisolone has been shown to be efficacious in patients with an acute exacerbation of COPD [834]. In this study of 44 patients, methylprednisolone (0.5 mg/kg every 6 h) produced a significant improvement in  $FEV_1$  compared with placebo over the course of 72 h. However, only percentage changes in  $FEV_1$  were given in this study and it has been criticized in view of this. More recently, Emerman and coworkers [835] studied 96 patients presenting with acute exacerbations of COPD. This study showed that there was no difference between the effects of methylprednisolone 100 mg or placebo given in addition to other treatments in patients followed up only over the first 7 h, which may have been insufficient time to detect any improvement. However, further studies of exacerbations treated with corticosteroids in the community [836] and in hospitalized patients [836a] show a positive result.

The BTS guidelines [4] suggest that, in the absence of any further data, a 7–14 day course of steroids (e.g. 30 mg prednisolone daily or 100 mg hydrocortisone i.v. if the oral route is not possible) is clinically justified in an exacerbation of COPD if:

- 1 the patient is already on oral steroids;
- 2 there is a previously documented response to oral steroids;
- 3 the airflow obstruction fails to respond to an increase in bronchodilator;
- 4 this is the first presentation of an acute exacerbation of COPD.

However, after the acute episode, it is critical that oral steroids are discontinued, unless there has been a previously demonstrable long-term effect. The effects of steroids during an acute exacerbation do not necessarily predict a later response to chronic treatment with inhaled steroids.

### Diuretics

In patients who show fluid retention as a result of respira-

tory failure and cor pulmonale, diuretics should be used with care, as they have the potential to reduce right ventricular end-diastolic volume considerably and hence cardiac output.

Anticoagulants

Pulmonary emboli are probably more common than are recognized in severe COPD. Prophylactic use of anticoagulants has not been properly assessed in exacerbations of COPD and it is difficult to diagnose pulmonary emboli where ventilation–perfusion abnormalities are often present and can lead to false-positive reports of pulmonary thromboembolic disease. Prophylactic subcutaneous heparin is often given to patients with exacerbations of COPD, particularly those who have respiratory failure.

Physiotherapy

There is very little evidence to support the use of physiotherapy to improve expectoration of secretions in patients with acute exacerbations of COPD [837,838], although some studies suggest that there is some benefit in patients producing large amounts of sputum [839,840]. Employing physiotherapy may cause worsening of blood gases [840,841]. Chest physiotherapy is a relative contraindication in patients with respiratory failure and although some patients with large volumes of sputum may benefit, it is important to monitor oxygen saturation during physiotherapy and increase inspired oxygen concentrations if there is any evidence of desaturation.

Assessment of recovery from acute exacerbations

The FEV<sub>1</sub> should be recorded prior to discharge and arterial blood gases should be checked with the patient breathing air, which gives a guide to the need for later formal reassessment for LTOT therapy. Antibiotics need not usually be given for more than 7 days.

Lung transplantation (see also Chapter 59)

Lung transplantation developed from heart–lung transplantation, which was initially indicated for pulmonary vascular diseases [842] but was subsequently extended to other pulmonary conditions [843]. However, it became apparent that many patients undergoing heart–lung transplant had received a new heart unnecessarily. With careful patient selection, improved surgical techniques to restore a viable blood supply to the bronchial anastomosis and the introduction of cyclosporin as the principal immunosuppressant, single lung transplantation, initially for patients with fibrosing lung diseases, became possible

in 1986 [844]. In 1988 double lung transplantation, with a tracheal anastomosis, was introduced [845]. However, this procedure was accompanied by more frequent problems with airway healing and was more surgically complex than heart–lung transplantation [846]. The problem of airway healing was overcome by performing two separate bronchial anastomoses [847].

It was previously considered that patients with end-stage COPD were not suitable for single lung transplantation since perfusion would be preferentially directed towards the transplanted lung because of its lower pulmonary vascular resistance, producing profound ventilation–perfusion mismatch [848]. The success of single lung transplantation, despite the presence of abnormal mechanics in the native lung, is due in part to improved patient selection, lung preservation and anaesthetic management. There are problems if residual infection is present in the native lung [849]. In addition, large bullae may still show evidence of gross overinflation in the native lung in the early postoperative period and subsequent mediastinal shift and compression of the transplanted lung. Therefore, those patients with recurrent pulmonary infection or bilateral large bullae are considered for heart–lung transplantation or bilateral sequential lung transplantation. Criteria to be considered before lung transplantation are shown in Table 23.11.

The results of single lung transplantation and bilateral sequential single lung transplantation are good [850–853]. Only 10–15% of all recipients die within the first few weeks following transplantation. This is generally due to problems with poor lung preservation, which produces alveolar damage, sepsis or both. The 1-year survival in the UK is 60–75%, with a 3-year survival of 55–60%.

The important complications leading to death are opportunistic infections and the development of oblitera-

Table 23.11 Indications and contraindications for lung transplantation.

Indications

- Age < 50 years for heart–lung transplantation or double lung transplantation
- Age < 60 years for single lung transplantation
- Patients with an estimated life expectancy of less than 18 months

Contraindications

- Malnutrition is a relative contraindication; ideally, recipients should be within 15 kg of their ideal body weight
- Recurrent or persistent pulmonary infections are a contraindication to single lung transplantation

Other considerations

- Previous thoracic surgery increases the risk of haemorrhage
- Cor pulmonale is not a contraindication to single lung transplantation
- Psychological stability is necessary
- Absence of other major organ dysfunction should be demonstrated

tive bronchiolitis. Approximately 30% of patients surviving the perioperative period subsequently develop obliterative bronchiolitis in the first 5 years after transplantation. The development of obliterative bronchiolitis leads to progressive deterioration and ultimately respiratory failure or consideration for retransplantation after 6–12 months.

## Other forms of emphysema

### Infantile lobar emphysema

Infantile lobar emphysema is obstruction and distension of one lobe in an infant and often gives rise to severe dyspnoea necessitating surgical removal. There is a strong female preponderance and about half of the cases also have congenital cardiac abnormalities [158].

### Pathology and pathogenesis

The upper lobe, especially on the left, or the middle lobe are most often affected. The lobe, or occasionally part of it, is grossly distended with thin atrophic alveoli and impinges on the neighbouring lung, often causing collapse [158]. It is thought that in some patients there is atresia of bronchial cartilage causing a ball-valve obstruction. In others, the obstruction may be inflammatory or due to mucus or a flap of mucous membrane. One study reported an increase in the deposition of collagenous tissue in the alveolar walls but no bronchial lesions in any of the seven cases studied [854]. A few cases have been described with similar clinical and radiological features in whom the pathological finding was a gross increase in the number of alveoli with or without emphysema [855]. In most patients the cause of the abnormality is obscure.

### Clinical features

Most patients with this condition develop symptoms when less than 6 weeks old, the chief manifestation being dyspnoea. The condition may prove fatal. The rest of the lung, heart, mediastinum, diaphragm and even the chest wall may be displaced or bulged out by the distended lobe. Cough and stridor may occur. A few patients have less distension and milder symptoms, which allows surgery to be withheld for several years at least.

### Treatment

Most of the acute cases require surgery. As the cause of the obstruction can seldom be identified, the lobe has to be removed. CPAP has been used in distressed patients pending surgery [856]. Follow-up of surgically and medically treated patients suggests that asymptomatic or mildly symptomatic infants do not require surgery [857].

### Lobar emphysema with bronchial atresia

This appears to be a rare variant of infantile lobar emphysema [158]. There is complete atresia of the proximal bronchus, which is blind on its hilar side but may be patent peripherally. The left upper lobe is transradiant and hypoplastic, being aerated by collateral ventilation. Most patients have been diagnosed in young adult life and are symptom free, a transradiant left upper zone on the radiograph having drawn attention to the anomaly [858].

### Unilateral emphysema of a lung or lobe due to localized bronchiolitis or bronchitis (McLeod's syndrome)

McLeod [859] was the first to draw attention to patients with a chest film showing unilateral hypertransradiancy. In these cases the pulmonary artery on the affected side is often small and pulmonary angiography shows a poor blood supply. Bronchography reveals irregular dilatation of the bronchi of about the fifth order, with failure to fill the peripheral airways, an appearance characteristic of bronchiolar obliteration [860]. Study of a number of resected lung specimens have shown evidence of previous widespread patchy bronchitis or bronchiolitis [861]. It is presumed that this dates from childhood. In some children, the condition has been shown to develop 6 months to 5 years after a viral bronchiolitis and, indeed, there is a history of such an event in more than half of the cases [862].

### Pathology

The affected lung is usually normal or subnormal in size. If an operation is performed to resect the lung, when the chest is opened the lung does not deflate. There is panacinar emphysema but also evidence that there are fewer alveoli than normal. The bronchi appear to have a full complement of branches and therefore it is thought that the causal condition must occur between birth and the age of 8 years. There is usually evidence of patchy destruction or obstruction of small bronchi and bronchioles and occasionally the larger bronchi. The pulmonary arteries often appear less hypoplastic than might be expected from the pulmonary angiogram, suggesting that there may be additional hypoxic vasoconstriction to cause the appearances on the angiogram. The pathology of the pulmonary vasculature reveals hypertrophy of the pulmonary arterial walls and a decrease in the number of branches [163].

### Functional abnormalities

There is usually some evidence of airways obstruction and an increase in RV. Bronchspirometry shows diminished oxygen uptake in the affected lung, which may be only

5 or 10% of the total for both lungs. Radioisotope ventilation–perfusion scanning shows very little ventilation or blood flow to the affected lung [860]. In some of these patients, the main bronchus may be seen bronchoscopically to collapse on expiration, but at least in one case repair of the bronchus did not improve the condition, indicating that there was also distal damage to the bronchi [163].

### Clinical features

Most patients are diagnosed on a routine chest radiograph and are often asymptomatic. In older patients, there may be coincidental chronic bronchitis. When larger bronchi are affected, secondary infection may occur that results in bronchiectasis and chronic infection.

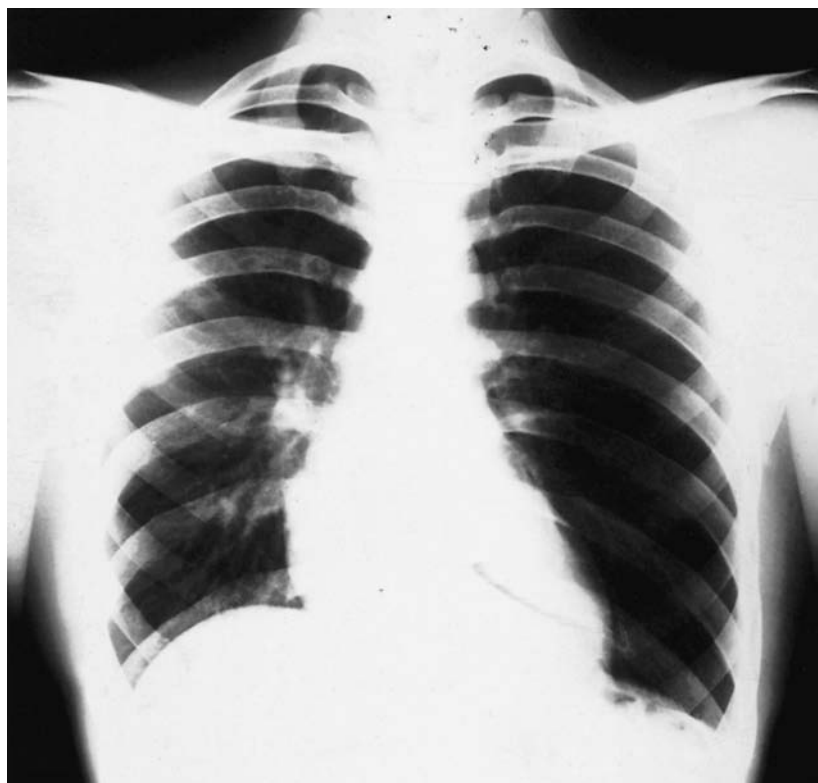
### Radiology

Chest radiography shows unilateral hypertransradiancy with decreased vascular markings both at the hilum and in the lung (Fig. 23.20). The mediastinum may be deviated to the affected side. The diaphragm may be normal in position or low in the chest. An expiration film may show air trapping, with deviation of the mediastinum to the contralateral side. On angiography, the pulmonary artery is small and there is poor peripheral filling. Bronchograms show poor peripheral filling and dilatation of the bronchi,

with absence of the normal narrowing peripherally or with frank bronchiectasis. Most of the bronchi are irregular, terminating either in an irregular tapering shadow or in a bulbar shadow [163].

### Differential diagnosis

Unilateral changes in chest wall soft tissues, such as paralysed muscles, congenital absence of the pectoral muscles or mastectomy, may give similar appearances that are resolved by examining the patient. In compensatory emphysema, the collapsed lobe can usually be seen and the vessels in the emphysematous lobe are fanned out. It may be more difficult to differentiate this condition from the local attenuation of generalized emphysema, although in the latter the heart is often long and narrow and the hilar vessels on both sides tend to be prominent rather than diminished. Diaphragms are likely to be low and a lateral film shows the enlarged retrosternal airspace in generalized emphysema, whereas in unilateral transradiancy due to bronchiolitis the lung is usually normal or decreased in size. Occasionally, one pulmonary artery is congenitally absent, and in congenital heart disease the blood supply is sometimes very much decreased to one lung. In both of these conditions, there is no evidence of air trapping. Occasionally, hypoplasia of one lung may occur without hypertransradiancy but with a small and shrunken lung [163].



**Fig. 23.20** Chest film of an asymptomatic patient with McLeod's syndrome showing overinflated and avascular left lung.



### Prognosis and treatment

The prognosis is good since there is usually adequate reserve in the unaffected lung. Occasionally, bronchiectasis may be severe enough to warrant resection.

### Lung volume reduction surgery

The growing number of patients with emphysema on waiting lists for lung transplantation has led recently to a re-examination of surgical techniques that might give symptomatic relief, particularly the work of Brantigan in the 1950s [863]. Cooper and colleagues [864] have pioneered the technique of lung volume reduction surgery (LVRS, pneumectomy or pneumoplasty). The rationale for this technique is to reduce the volume of overinflated emphysematous lung by 20–30%, with the aim of improving the elastic recoil of the lungs, diaphragm configuration, chest wall mechanics and gas exchange. The problem of persistent air leaks after this operation was overcome by the use of strips of bovine pericardium to buttress the stapling line. The technique is usually performed via a median sternotomy, without the need for cardiopulmonary bypass. There have been no controlled trials of this technique, although Cooper argues that the results of his published series, where the patient acts as his/her own control, are sufficiently striking to obviate the need for such a trial. The initial report on 20 patients with severe COPD suggests that careful selection is necessary, on the basis of a distended thorax, predominantly upper lobe disease (demonstrated by CT) and severe functional disability despite a programme of pulmonary rehabilitation

[864]. The early results are encouraging, with no early or late deaths. The improvements that have occurred up to 6 months after surgery are impressive and are better than can be produced by conventional medical treatment with bronchodilators or corticosteroids.

Thoracoscopic laser pneumoplasty has been developed as an alternative technique to the more conventional excisional surgery. The Nd:YAG laser [865] appears to be a safer technique than the carbon dioxide laser [624] and relies on the fact that at operation the lung that remains represents the most affected areas and would absorb most energy; thus the scarring and contraction would be concentrated in these sites. Wakabayashi and colleagues [866] used a modified technique and have reported the largest series of LVRS, although follow-up data are incomplete [867] and both unilateral and bilateral procedures are reported. None the less, impressive improvements in lung function have been demonstrated. Recent case reports also suggest that LVRS may act as a bridge to lung transplantation [868].

Studies investigating the mechanism for the benefit derived from LVRS are clearly required. A recent study compared LVRS with single lung transplantation for emphysema [869]. The disease severity was greater in the lung transplantation group, and although the increase in FEV<sub>1</sub> and FVC was greater in this group, the increase in 6-min walking distance was similar in both groups.

A number of questions concerning this technique require answers from future studies, particularly knowledge of the duration of benefit, the best selection criteria for patients and the mechanism of the improvement [870].

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# RESPIRATORY FAILURE

WILLIAM MACNEE

When the lungs cannot fulfil their primary function of maintaining adequate gas exchange at rest or during exercise, respiratory insufficiency or respiratory failure is said to exist. This results in an inability to maintain normal blood gases, so that the  $P_{aO_2}$  is low, with or without a rise in  $P_{aCO_2}$ , usually but not always because of lung disease. Abnormal blood gases may occur in conditions not associated with respiratory insufficiency, such as the hypoxaemia associated with anatomical right-to-left intracardiac shunts or metabolic alkalosis. Respiratory failure has been rather arbitrarily defined by Campbell as a  $P_{aO_2}$ , measured at rest at sea level, of less than 8 kPa (60 mmHg) or a  $P_{aCO_2}$  above 6.5 kPa (49 mmHg) [1,2]. This defining level of  $P_{aO_2}$  was chosen since it is close to the critical point on the oxyhaemoglobin dissociation curve below which the curve becomes much steeper, so that relatively small falls in  $P_{aO_2}$  are associated with increasingly large decreases in oxygen saturation and blood oxygen content and hence in oxygen supply to the tissues. The position of the oxyhaemoglobin dissociation curve is often characterized in terms of the  $P_{50}$ , the partial pressure of oxygen at 50% saturation.

In chronic respiratory failure, abnormal gas exchange may first occur during exercise and later at rest. During exercise in normal subjects the distribution of ventilation-perfusion ( $\dot{V}_A/\dot{Q}$ ) ratios becomes more even than at rest [3]. The alveolar-arterial  $PO_2$  difference ( $P_{AO_2} - P_{aO_2}$ ) does not widen until the oxygen uptake is very high, when the central venous oxygen content has fallen to very low levels. In patients with respiratory disorders, impairment in gas exchange characteristically leads to widening of the alveolar-arterial  $PO_2$  difference and arterial oxygen desaturation.

Although dyspnoea is a common feature of the conditions causing respiratory failure, it is not an invariable accompaniment. For example, patients with primary alveolar hypoventilation and respiratory failure may not complain of dyspnoea. Conversely, many patients can achieve adequate alveolar ventilation by virtue of increased work of breathing and thus maintain virtually normal blood

gases. Thus although they do not by definition have respiratory failure, yet they can be very dyspnoeic. This classically occurs in patients with severe emphysema and in early restrictive lung disease.

Respiratory failure may be *acute*, for example in opiate overdose, or *chronic*, with permanent blood gas disturbances as in severe chronic obstructive pulmonary disease (COPD). The major mechanisms of blood gas disturbances involve ventilation-perfusion inequality, inadequate alveolar ventilation or a combination of both. Hypoxaemia without  $CO_2$  retention is sometimes called 'type I' respiratory failure and hypoxaemia with hypercapnia 'type II' respiratory failure or ventilatory failure [4,5].

## Type I respiratory failure

In general most pulmonary and cardiac causes of respiratory failure lead to hypoxaemia without hypercapnia. This type of respiratory insufficiency is most often associated with those conditions that affect the interstitium and alveolar walls of the lungs and result in lowered values for carbon monoxide diffusing capacity and a restrictive pattern of ventilatory abnormality, e.g. fibrosing alveolitis and pulmonary oedema, but is also seen in other conditions such as pulmonary embolism and pneumonia. It may also be seen in obstructive lung diseases, such as COPD and asthma. A list of the common causes is given in Table 24.1.

In all these conditions  $\dot{V}_A/\dot{Q}$  mismatching is marked, resulting in either increased dead space and wasted ventilation (increased lung units with high  $\dot{V}_A/\dot{Q}$  ratios) or venous admixture (increased lung units with low  $\dot{V}_A/\dot{Q}$  ratios).  $\dot{V}_A/\dot{Q}$  mismatching accounts for the hypoxaemia in the great majority of cases. A similar effect on tissue oxygenation also occurs when the  $P_{aO_2}$  is normal but blood oxygen content is low, for example in anaemia, carbon monoxide poisoning and methaemoglobinemia. Hypoventilation also results in hypoxaemia. In this case total ventilation is not matched to oxygen uptake and  $CO_2$  production and in order to maintain the respiratory quo-

**Table 24.1** Some common causes of type I (hypoxaemic) respiratory failure. The chapters relevant to these conditions are indicated in parentheses.

Chronic bronchitis and emphysema (23)
Pneumonia (13)
Pulmonary oedema (27)
Pulmonary fibrosis (31)
Asthma (34)
Pneumothorax (44)
Pulmonary embolism (25)
Thromboembolic pulmonary hypertension (26)
Lymphatic carcinomatosis (41)
Pneumoconiosis (54)
Granulomatous lung disease (40)
Cyanotic congenital heart disease (26)
Bronchiectasis (28)
Adult respiratory distress syndrome (27)
Fat embolism (25)
Crushed chest injury
Kyphoscoliosis (45)
Obesity (47)
Pulmonary arteriovenous fistulae (50)

tient,  $P_{aO_2}$  and  $P_{aCO_2}$  fall in a ratio of 0.8. A diffusion defect causing hypoxaemia is relatively rare and occurs in normal subjects exercising at high altitude, in interstitial lung disease such as fibrosing alveolitis, particularly during exercise, and in rare cases of capillary shunting associated with liver fibrosis.

If control of ventilation is intact, as it usually is in these patients, ventilation increases in response to a raised  $P_{aCO_2}$ , so that the excess  $CO_2$  is excreted by the normal areas of the lungs facilitated by the shape of the  $CO_2$  dissociation curve. This requires that the lungs are mechanically able to respond to the increased drive. Hyperventilation cannot result in much more oxygen being taken up in the normal areas of the lungs, since the blood there is already fully oxygenated. In lobar pneumonia, for instance, where ventilation-perfusion imbalance occurs but the respiratory system can respond to an increase in  $P_{aCO_2}$  by alveolar hyperventilation, there is hypoxia but a normal  $P_{aCO_2}$ . Generally, in the restrictive disorders and asthma the ability to ventilate and maintain a normal or low  $P_{aCO_2}$  is preserved until late in the course of the disease.

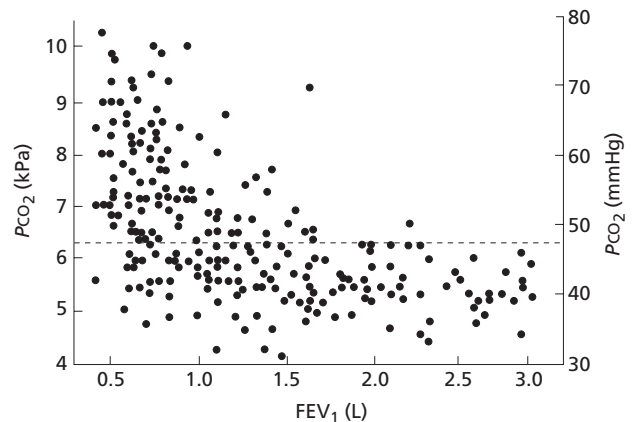
Oxygen is the critical therapy in the management of type I respiratory failure and can be given with impunity in this condition since there is no hypercapnia. In severe disease, such as intractable pulmonary oedema or the adult respiratory distress syndrome (ARDS) when there is failure to maintain an adequate  $P_{aO_2}$  on high-flow oxygen ( $P_{aO_2} < 8 \text{ kPa}$ , 60 mmHg) or when hypercapnia ensues, ventilatory support is required.

## Type II (hypercapnic) respiratory failure

When the  $P_{aCO_2}$  rises due to alveolar hypoventilation, the

**Table 24.2** Some causes of type II (hypercapnic) respiratory failure. The chapters relevant to these conditions are indicated in parentheses.

Chronic bronchitis and emphysema (23)
Asthma (34)
Drug overdose
Poisoning
Myasthenia gravis (45)
Polyneuropathy (45)
Poliomyelitis (45)
Primary muscle disorders (45)
Porphyria
Cervical cordotomy
Head and cervical cord injury
Primary alveolar hypoventilation (47)
Sleep apnoea syndrome (47)
Pulmonary oedema (27)
Adult respiratory distress syndrome (27)
Suxamethonium apnoea
Myxoedema
Tetanus
Laryngeal oedema
Foreign body



**Fig. 24.1** Relation of  $P_{aCO_2}$  to forced expiratory volume in 1 s ( $FEV_1$ ) in 13 patients with chronic airways obstruction. (After Lane *et al.* [6].)

$P_{aO_2}$  must fall; knowing one of these values, the other may be predicted using the alveolar air equation. Some causes of alveolar hypoventilation are listed in Table 24.2. The most common cause is COPD, which may result in acute to chronic hypercapnic (type II) respiratory failure that usually occurs during an acute exacerbations of this condition.  $CO_2$  retention in COPD is unusual when the forced expiratory volume in 1 s ( $FEV_1$ ) is greater than 1.2 L [6] (Fig. 24.1). Type II respiratory failure due to alveolar hypoventilation alone can occur in such conditions as poliomyelitis, polyneuritis, myasthenia gravis, sedative drug overdose, cerebrovascular accidents, chest injury and acute oedema of the larynx. If respiratory failure is of sudden onset, the acute rise in  $P_{aCO_2}$  results in a rise in hydrogen ion concen-

tration (a fall in pH). Respiratory failure that develops slowly allows renal compensation with retention of bicarbonate, often resulting in a near-normal pH. The presence of a raised bicarbonate therefore suggests acute-on-chronic respiratory failure, most commonly caused by an exacerbation of COPD. Suspicion of respiratory failure should immediately lead to blood gas determination since the clinical findings are often unreliable.

## Clinical features

### Clinical evidence of hypoxaemia

Hypoxaemia results in central cyanosis that is best assessed by examining the oral mucous membranes, since blood flow at this site is well maintained when the periphery may be vasoconstricted. The relationship between cyanosis and hypoxaemia is notoriously variable and there is wide interobserver variation [7,8]. Cyanosis is more easily observed in polycythaemic patients, whereas in anaemic patients there may be insufficient reduced haemoglobin to produce a blue colour to the mucous membranes.

Hypoxaemia affects the central nervous system (CNS) at an early stage, with the development of irritability, impaired intellectual function and clouding of consciousness. This may progress to convulsions, coma and death. A level of acute hypoxaemia that would kill a previously healthy individual may be surprisingly well tolerated by patients with chronic hypoxia. Hypoxaemia stimulates ventilation via the carotid chemoreceptors, increases the heart rate and cardiac output and dilates peripheral vessels. Cardiac dysrhythmias may occur, which may be exaggerated by concomitant digitalis or hypokalaemia due to diuretic therapy [9]. The pulmonary arteries respond to hypoxia by vasoconstricting, producing increased vascular resistance and pulmonary hypertension, with the later development of right ventricular enlargement or cor pulmonale.

Persistent hypoxia results in secondary polycythaemia due to increased production of erythropoietin. There is some evidence that cigarette smoking, with a resultant elevation of carboxyhaemoglobin levels, also contributes to the development of polycythaemia in hypoxaemic patients [10].

### Clinical evidence of hypercapnia

The lowest level of  $P_{aO_2}$  compatible with life is approximately 2.7 kPa (20 mmHg) [11,12]. Since there is a relationship between the fall in  $P_{aO_2}$  and the rise in  $P_{aCO_2}$ , and because patients with COPD have an increased alveolar-arterial oxygen gradient,  $P_{aCO_2}$  rarely exceeds 10.6 kPa (80 mmHg) in these patients when breathing room air [12]. The CNS effects of hypercapnia are variable

from patient to patient. There is a poor correlation between  $P_{aCO_2}$  and the development of these effects, as changes in  $P_{aCO_2}$  may be more important than the actual level. The CNS signs of hypercapnia are irritability, confusion, somnolence and coma [13,14]. Coma is uncommon in patients with COPD and respiratory failure when breathing room air because the level of  $P_{aCO_2}$  necessary to cause coma is usually associated with a  $P_{aO_2}$  incompatible with life [15]. The level of consciousness correlates with the cerebrospinal fluid pH, which itself is decreased in proportion to the blood pH level [16]. The rapidity of the increase in  $P_{aCO_2}$  and the severity of the associated hypoxaemia also contribute to the level of consciousness [17]. Acidemia itself can clearly contribute to the degree of impairment of consciousness, since levels of  $P_{aCO_2}$  up to 14.6 kPa (110 mmHg) have been noted in the absence of acidemia without producing obvious CNS signs [18]. Hypercapnia also produces tremor, myoclonic jerks, asterixis and even seizures [13]. The vasodilator properties of  $CO_2$  may result in increased cerebral blood flow and an increase in intracranial pressure, producing headache and papilloedema [14,18–21]. Hypercapnia tends to dilate the vessels of the peripheral circulation by a direct effect on vascular smooth muscle, but also produces vasoconstriction by sympathetic stimulation. Both the vasodilator properties and sympathetic stimulation produced by  $CO_2$  result in a warm flushed skin with a bounding pulse [17,22]. However, the resultant effect in an individual depends on the balance between the two and is variable. Sympathetic stimulation is also responsible for tachycardia and sweating. Marked hypercapnia, producing generalized vasodilatation, may be associated with hypotension. Other features occasionally encountered in severe and well-established respiratory failure are gastric dilatation and paralytic ileus. Headache on waking is common in chronic hypercapnia, presumably due to a progressive increase in  $CO_2$  retention during sleep.

Three major mechanisms contribute to hypercapnic ventilatory failure: (i) insufficient respiratory drive; (ii) excessively high ventilatory workload; and (iii) defective ventilatory pump or 'bellows'. There are many potentially reversible factors that may affect ventilatory drive and these include the use of sedatives, chronic loading of ventilation as in a prolonged asthmatic attack, and metabolic alkalosis. The ventilatory workload is related to the level of  $CO_2$  production, the ventilatory dead space, the pulmonary resistance or compliance and the need to compensate for a metabolic acidosis. Increased  $CO_2$  production also occurs in conditions associated with increased metabolism, as in patients with burns, sepsis or fever and in hypercaloric carbohydrate parenteral feeding [21].

The dead space comprises the anatomical and alveolar (physiological) dead spaces. Increases in dead space result in 'wasted ventilation'. In patients with emphysema, an

increase in dead space primarily results from enlargement of the anatomical dead space as a result of enlargement of distal airspaces. Increased alveolar dead space ventilation also occurs with changes in the breathing pattern, such as an increasing respiratory rate. Increased wasted ventilation also occurs in patients with pulmonary emboli or other conditions that produce occlusion of the pulmonary arteries or capillaries.

Bellows or pump failure is a less common cause of ventilatory failure and may occur in patients with neuromuscular diseases and severe impairment of phrenic nerve function. Patients with neuromuscular diseases characteristically breathe with rapid shallow tidal volumes. Orthopnoea is a frequent symptom especially in the presence of diaphragmatic or bilateral phrenic nerve involvement. The development of tachypnoea often maintains normal blood gases until respiratory reserve is markedly diminished. Thus repeated evaluation of patients with neuromuscular diseases is necessary to anticipate the development of ventilatory failure. Bedside spirometry, the prevention of atelectasis and taking precautions against aspiration can be helpful. Ideally patients at high risk are identified before complications develop and are intubated electively.

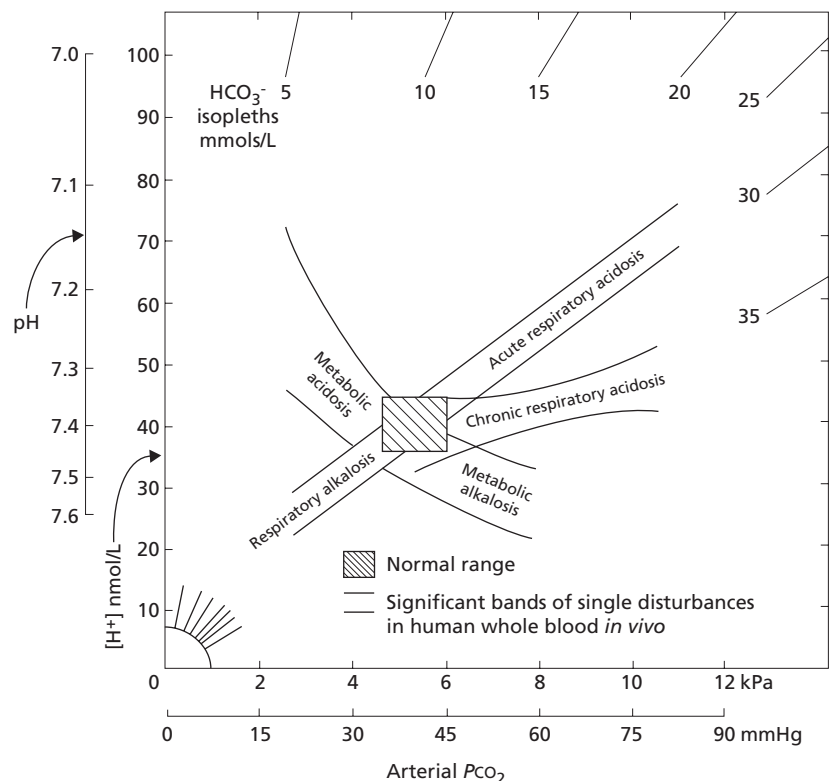
## Diagnosis

The diagnosis of respiratory failure rests on measurement of arterial blood gases. The conventional definition of res-

piratory failure is a  $P_{aO_2}$  when breathing air at sea level of less than 8 kPa (60 mmHg) [1,2], although in some studies a  $P_{aO_2}$  of less than 7.3 kPa (55 mmHg) is used [5]. Since mixed metabolic and respiratory acid-base disturbances can occur, and because a rise in  $P_{aCO_2}$  is a normal compensatory response to a metabolic alkalosis [23,24], it is important to measure the arterial pH or to determine the primary acid-base disturbance. In addition, the chronicity of the respiratory failure should be assessed by evaluating the pH and the degree to which this is compensated by an increase in the serum bicarbonate. An acute increase in  $P_{aCO_2}$  of 1.3 kPa (10 mmHg) is roughly associated with a decrease in pH of 0.08 units and an increase in serum bicarbonate of 1 mEq/L, whereas a chronic increase in  $P_{aCO_2}$  of 1.3 kPa (10 mmHg) is associated with a decrease in pH of 0.03 units and an increase in bicarbonate of 3.5 mg/L [25,26]. Plotting blood gas and acid-base parameters on an acid-base diagram is a useful way of determining the acid-base status and also following the response to treatment in patients with acute exacerbations of COPD and respiratory failure [4] (Fig. 24.2).

As indicated above, the  $P_{aO_2}$  has to be at a very low level to threaten life. Indeed, in a study of patients presenting with acute-on-chronic respiratory failure, the level of hypoxaemia when breathing air on admission did not relate to survival during the acute episode [27,28]. A relatively modest increase in  $P_{aO_2}$  is all that is required when treating such patients with oxygen. However, when supplemental oxygen is given to patients with COPD in acute

**Fig. 24.2** A non-logarithmic acid-base diagram derived from the measured acid-base status of patients within the five abnormal bands illustrated and of normal subjects (hatched box). This plot of  $P_{aCO_2}$  against hydrogen ion concentration (pH) allows the likely acid-base disturbance and calculated bicarbonate value (obtained from the relevant isopleth) to be rapidly determined, while changes during treatment can be plotted serially for each patient. (After Flenley [4] with permission.)





respiratory failure, a proportion of these patients show a rise in  $P_{aCO_2}$ . In one study, approximately one-third of patients showed a rise in  $P_{aCO_2}$  of greater than 0.5 kPa (3.75 mmHg) when given controlled (24–28%) oxygen therapy, one-third did not show this rise and one-third showed a fall in  $P_{aCO_2}$  [28]. Thus even controlled oxygen therapy can produce some  $CO_2$  retention [11]. Traditionally, this is thought to result from the dependence of COPD patients on their hypoxic drive to breathing and the fact that their ventilatory response to  $CO_2$  is also believed to be impaired [11]. Thus, removal of the hypoxic drive to breathing with supplemental oxygen is thought to result in a fall in minute ventilation and a rise in  $P_{aCO_2}$ . Furthermore the blunted  $CO_2$  responsiveness prevents a subsequent increase in minute ventilation. However, experimental studies do not support this hypothesis.

In patients with respiratory failure, Aubier and coworkers [29] found that the rise in  $P_{aCO_2}$  when breathing 100% oxygen could not be accounted for by the fall in minute ventilation. These authors attributed the increase in  $P_{aCO_2}$  primarily to an increase in the dead space to tidal volume ratio ( $V_D/V_T$ ), although this contention remains controversial [30]. Measurements of the mouth occlusion pressure ( $P_{0.1}$ ), an index of central respiratory drive, are increased in patients with acute respiratory failure [31]. Furthermore,  $P_{0.1}$  fell when supplemental oxygen was given but the values still remained higher than those obtained in patients in the chronic state. Recent studies in ventilator-dependent patients with COPD suggest that hyperoxia produces both a decrease in respiratory drive and an increase in  $V_D/V_T$ . In addition, correction of hypoxaemia shifts the  $CO_2$  binding curve (the Haldane effect), which increases  $P_{aCO_2}$  for a given  $CO_2$  content. Thus, it is likely that the mechanism by which oxygen supplementation worsens hypercapnia is multifactorial [32].

## Management

The priorities in the management of acute respiratory failure vary according to the aetiology. The primary aims of treatment are the same in all cases: (i) to maintain a patent airway and ensure adequate alveolar ventilation and oxygenation; and (ii) to treat, if possible, the primary condition.

Transplantation in the management of respiratory failure is dealt with in Chapter 59.

### Type I respiratory failure

This condition usually presents little difficulty and, apart from the use of oxygen, treatment of the primary cause, e.g. antibiotics for lobar pneumonia, may be all that is required.

Arterial hypoxaemia when extremely severe can be life-threatening and therefore should have the highest priority when managing acute respiratory failure. The goal should be to increase saturation of haemoglobin to at least 85–90% without risking significant oxygen toxicity. As a general rule, very high  $F_{IO_2}$  levels can be safely used for brief periods of time while efforts are being made to reverse the underlying process. The use of positive end-expiratory pressure (PEEP), changes in position, sedation and paralysis may be helpful in lowering  $F_{IO_2}$ . Fever, agitation, over-feeding, vigorous respiratory activity and sepsis can all markedly increase  $\dot{V}O_2$ . Measures should be taken to eliminate these stimuli.

It is important to remember that oxygen delivery is calculated as the product of oxygen content and cardiac output. It is therefore possible to treat hypoxaemia not only by raising the inspired oxygen concentration but also by increasing the cardiac output or increasing haemoglobin concentration with packed red blood cells.

Prolonged exposure to high concentrations of oxygen ( $F_{IO_2} > 50\%$ ) should be avoided because pulmonary toxicity depends on both the duration of treatment and the  $F_{IO_2}$  [33]. If an  $F_{IO_2}$  of 50% fails to produce a  $P_{aO_2}$  of 6.7 kPa (50 mmHg), this implies a significant interpulmonary shunt, as occurs in ARDS. The major question in patients with type I respiratory failure is when to begin assisted ventilation. This obviously depends on the clinical situation. However, the general indications for ventilation are as follows:

- 1 inadequate oxygenation despite an increasing  $F_{IO_2}$ ;
- 2 increased  $P_{aCO_2}$  associated with decreased mental status or increasing fatigue;
- 3 failure to control secretions.

### Type II (hypercapnic) respiratory failure

In the UK by far the commonest cause of type II or hypercapnic respiratory failure is an exacerbation of COPD. Indeed 'respiratory failure' is frequently regarded as synonymous with this condition.

#### Natural history of respiratory failure in patients with COPD

The development of arterial hypoxaemia occurs insidiously in most patients with COPD, although in some the fall in  $P_{aO_2}$  can be as rapid as 1 kPa (7.5 mmHg) per year. In the industrial city of Sheffield, where both occupational exposure and the prevalence of smoking are high, it has been estimated that 0.3% of the population over the age of 45 have arterial oxygen tensions of less than 7.3 kPa (55 mmHg) [34]. Hypoxaemia that develops slowly may produce little in the way of breathlessness and chronic hypercapnia can be tolerated for many years with few symptoms, although early morning headache is relatively

common. Many patients tolerate arterial hypoxaemia well for many years before decompensation occurs. There is no universally accepted definition of acute-on-chronic respiratory failure in a patient with a background of COPD, although acidemia in the presence of a raised  $P_{aCO_2}$  with a raised bicarbonate indicates acute decompensation with a chronic respiratory acidosis. One of the problems resulting from the lack of standardized blood gas criteria to define acute-on-chronic respiratory failure is that the reported survival, both during the acute event and over the longer term, in different series of patients with respiratory failure varies widely, largely due to variation in the criteria used for inclusion of patients into the studies [35] (Fig. 24.3).

The most common definition of acute respiratory failure in such patients is a  $P_{aO_2}$  of less than 6.7 kPa (50 mmHg) with a  $P_{aCO_2}$  of greater than 6.7 kPa (50 mmHg) when breathing air, often associated with respiratory acidosis, in a patient whose symptoms have worsened compared with the stable clinical state [27,28]. The association of acidosis with more or increasing symptoms differentiates acute from chronic respiratory failure. There is also a huge variation in the ventilation rates and criteria for ventilation in patients with acute-on-chronic respiratory failure as a result of COPD, which makes it difficult to make comparisons of survival rates between studies. Using these blood gas criteria, mortality in the acute event in the UK, where ventilation rates are as low as 3%, is around 12% [27,28], which is as good as most series from throughout the world.

Once acute respiratory failure is suspected the diagnosis must be confirmed by arterial blood gas analysis. As

described above, the pH (hydrogen ion concentration) is helpful in assessing the degree of acute vs. chronic respiratory failure. The pH is compensated for by renal retention of bicarbonate, which usually takes several days to have its maximal effect.

The general principles of management are: (i) to correct life-threatening hypoxaemia; (ii) to correct life-threatening acidosis; (iii) to treat the underlying cause; and (iv) to prevent complications.

### Relief of hypoxia

The first priority in treatment of acute-on-chronic respiratory failure that occurs during exacerbations of COPD is the relief of hypoxia by the cautious administration of oxygen. Barach and Woodwell in 1921 [36] were the first to describe the adverse effects of the administration of high inspired concentrations of oxygen in two patients with 'shallow breathing'. In 1949, Donald [37] described decreased conscious levels in patients with respiratory failure who were given high concentrations of oxygen. Thereafter the use of controlled oxygen therapy was introduced with the development of safe and reliable modes of oxygen delivery with an  $F_{iO_2}$  of 30% or less [38,39].

Supplemental oxygen should be administered by nasal prongs at flows of 1–3 L/min or by a Venturi mask with the flow set to deliver 24–28% oxygen [40]. The Venturi mask produces the most predictable inspired oxygen concentrations. Concentrations from nasal prongs are less predictable, but the device is better tolerated by patients [41]. However, if nasal prongs are used, blood gases should be rechecked after 30 min [42]. On average, the

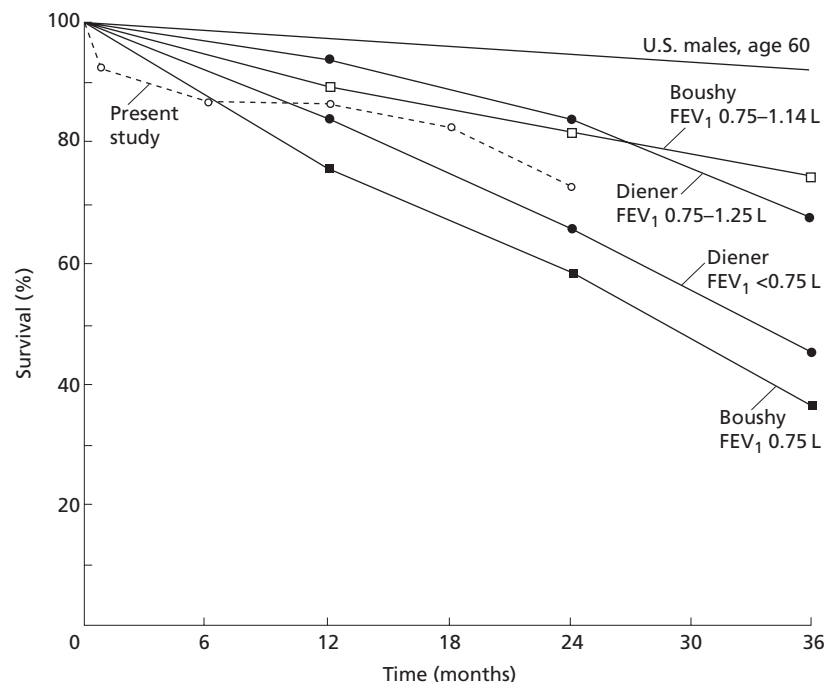


Fig. 24.3 Survival curves after an episode of acute-on-chronic respiratory failure in patients with chronic obstructive pulmonary disease. (After Martin *et al.* [132].)

$P_{aO_2}$  increases by 1.3 kPa (10 mmHg) as the  $F_{IO_2}$  is increased from 21 to 24% in patients with acute respiratory failure, and by 2.6 kPa (20 mmHg) when the  $F_{IO_2}$  is increased to 28% [40]. It is important to remember that an oxygen flow of 2 L/min by nasal prongs produces an  $F_{IO_2}$  of 25–35% [43]. Ideally, the goal of supplemental oxygen therapy should be to achieve a  $P_{aO_2}$  of greater than 8 kPa (60 mmHg). However, a  $P_{aO_2}$  of 6.6 kPa (50 mmHg) has been recommended as being adequate in acute-on-chronic respiratory failure [28]. Pulse oximeters have been used to measure the degree of oxygenation non-invasively, but provide no information on  $P_{aCO_2}$ . Moreover, the 95% confidence limits of pulse oximeters is 4% [44]. In most cases arterial blood gas measurements are required for accurate measurements of both  $P_{aO_2}$  and  $P_{aCO_2}$ .

Sedatives, especially opiates which further depress the ventilatory drive, should be avoided. In patients with a history of COPD aged greater than 50 years, oxygen at an  $F_{IO_2}$  of more than 28% via a Venturi mask or at 1–2 L/min via a nasal prongs should not be given until the arterial blood gases are known.

Respiratory stimulants such as doxapram (see Chapter 9) may be considered in patients with acidosis as a result of hypercapnia and hypoventilation in order to assist the patient for 24–36 h until the underlying factors precipitating the exacerbation improve, and so avoid the need for invasive mechanical ventilation [28,45]. The use of respiratory stimulants is somewhat controversial, particularly as studies have demonstrated that central respiratory drive is high in such patients [31,46,47]. An early study showed benefit, in terms of blood gases, from the use of doxapram compared with placebo [48]. Indeed, in this study, the number of patients requiring subsequent mechanical ventilation was similar in both the placebo and doxapram-treated groups. Jeffrey and colleagues [28] examined the effect of doxapram in a series of patients with COPD and hypercapnic respiratory failure. Again, there was a low incidence of mechanical ventilation and a mortality rate of only 12%, comparable with other studies in which mechanical ventilation was more frequently employed [35]. In this and an earlier study from the same group, the best predictor of death during an episode of acute respiratory failure was an arterial pH of less than 7.26 (hydrogen ion concentration  $>55$  nmol/L), which was associated with a higher mortality [27,28]. Based on these studies the authors suggested that oxygen should be administered to achieve a  $P_{aO_2}$  of more than 6.6 kPa (50 mmHg), while maintaining a hydrogen ion concentration of less than 55 nmol/L. If this could not be achieved the use of short-term doxapram was suggested [28]. Close monitoring of these patients is required to determine whether there is a response to such conservative treatment. If the patient's hydrogen ion concentration remains greater than 55 nmol/L, ventilatory support should be considered.

The decision to institute invasive ventilation should be made by a senior physician, who should consider the patient's premorbid state and any wishes of the patient and close relatives. The factors that encourage or discourage the use of invasive ventilation are discussed in Chapter 58 (see also Table 24.3).

### **Non-invasive ventilation in exacerbations of respiratory failure**

Recently, non-invasive positive pressure ventilation (NIPPV) via nasal masks has become available. Several early uncontrolled studies demonstrated the feasibility of NIPPV in patients with acute exacerbations of respiratory failure due to COPD [49–57]. These studies showed variable improvements in blood gas tensions. NIPPV has been shown in randomized controlled trials to be better than placebo [58,59]. The main advantage of NIPPV is the avoidance of tracheal intubation and hence the need for sedation. Furthermore, the technique can be applied in a high-dependency unit or a general ward, without the need for intensive care [60]. Thus this treatment can be applied to patients with severe COPD and respiratory failure who would be considered unsuitable for intubation.

The aims of NIPPV should be to improve gas exchange in order particularly to rectify acidosis, since pH or hydrogen ion concentration has been shown to be an important predictor of survival in patients with respiratory failure and COPD [28]. In addition the performance of the respiratory muscles is compromised in patients with severe COPD, since lung overinflation results in these muscles acting at a mechanical disadvantage [61]. In addition, the load on the muscles is increased as a result of increased airflow obstruction and the presence of intrinsic PEEP and because of the effects of hypercapnia and acidosis [62,63].

A number of studies have shown that NIPPV can improve hydrogen ion concentrations and reduce respiratory muscle work in respiratory failure [50,58,59,64]. However, there have been only three randomized controlled trials on the use of NIPPV in exacerbations of respiratory failure in patients with COPD [58,59,65]. In a study from the UK, Bott and colleagues [58] compared a control group of patients with an exacerbation of COPD and respiratory failure who received conventional treatment with a similar group who received NIPPV. Some patients in both treatment groups also received doxapram but in a non-standardized fashion. Small improvements in pH and breathlessness were demonstrated in the NIPPV group. Mortality was also less in the NIPPV group but only when patients who could not tolerate NIPPV were removed from the analysis. However, the pH in these patients when NIPPV was commenced was not at a level where many physicians would consider ventilation was indicated.

In another study of NIPPV, Kramer and colleagues [65] showed a significant fall in intubation rates for patients with respiratory failure, from 67% in those treated conventionally to 9% in those undergoing NIPPV. This study highlights the differences in the treatment of this condition in the USA, where all patients with respiratory failure who deteriorate on either conventional treatment or NIPPV are offered invasive ventilation, whereas in the UK relatively few patients who deteriorate despite treatment are offered intubation and ventilation [58]. However, the study from the USA showed that there was no difference in mortality between the NIPPV and the control group, although relatively few patients with COPD were included in this study [65].

A study by Brochard and coworkers [59] from several European centres again showed that the need for intubation could be reduced by the use of NIPPV. In this case, mortality was also significantly less in the NIPPV group (9%) compared with the conventionally treated group (29%). However, the differences in mortality disappeared after adjustments for intubation were made, suggesting that the benefit from NIPPV was due to a reduction in the need for intubation. In this study the mean pH was 7.28 and 7.27 in the standard treatment and NIPPV groups respectively, which is closer to the level where others have shown predicted survival [7,26–28].

These reports highlight two problems with all studies of patients with respiratory failure [35]: the first is the lack of standardization of the inclusion criteria, particularly the levels of blood gas abnormalities, and the inclusion of patients with respiratory failure due to different conditions; the second is the wide variation in intubation rates [66]. This makes comparisons between different studies difficult.

The selection criteria for treatment with NIPPV are therefore critical and more studies are required to determine at what stage in the exacerbation of respiratory failure NIPPV should be initiated. There is also a need to undertake a controlled trial of the respiratory stimulant doxapram as against NIPPV, particularly in the UK where this drug is still used, since in one study conventional treatment that included doxapram produced a mortality of only 12% in acute exacerbations of respiratory failure, which compares favourably with most other studies [35]. The selection criteria in most studies appears to be a pH of less than 7.35, a respiratory rate of greater than 30 breaths/min and a  $P_{aO_2}$  of less than 6 kPa (45 mmHg) [60]. Exclusion criteria are numerous, and include patients who require immediate intubation or who have had a recent cardiac arrest and those who have any specific cause of their decompensation, such as pulmonary embolism or septic shock. In a retrospective study, Ambrosino and colleagues [64] suggested a poor outcome from NIPPV was more likely in those patients who were underweight and had a reduced level of compliance with NIPPV, impaired

conscious levels and higher APACHE scores. In general these patients had a higher  $P_{aCO_2}$  and a lower pH, again suggesting the need to introduce NIPPV early to prevent deterioration.

Meacham Jones and colleagues [67] have compared the different modes of NIPPV in patients with exacerbations of COPD. They found that 1 h after the initiation of treatment the use of volume- or pressure-cycled ventilation and continuous positive airway pressure (CPAP) could all improve oxygenation, although CPAP had little effect on  $P_{aCO_2}$ . The addition of expiratory positive airway pressure was poorly tolerated and produced no additional benefit. It is useful therefore to have both volume- and pressure-cycled equipment available.

The use of NIPPV requires resources, both in terms of equipment and trained personnel. Further studies are required to determine the factors that predict the successful use of this treatment, and at least one recent study has cast some doubt on its previously uniformly successful outcome [68]. The controversy over the use of doxapram vs. NIPPV in patients with exacerbations of COPD and in respiratory failure remains. There has been no large controlled trial comparing these treatments. However, a recent report in a small group of patients, nine of whom received NIPPV and eight doxapram, with similar baseline  $P_{aO_2}$ , showed that both treatments improved  $P_{aO_2}$  although this improvement was not maintained with doxapram at 4 h [69]. NIPPV caused a fall in  $P_{aCO_2}$ , whereas those who received doxapram had no improvement in  $P_{aCO_2}$ . Interestingly, there was a significant improvement in pH with both treatments, although again the level of pH at the institution of treatment (7.3) was perhaps higher than in previous studies of doxapram.

### Mechanical ventilation

The priorities in the management of acute respiratory failure vary according to the aetiology. However, the primary aims of treatment are the same in all cases: to maintain patent airways, ensure adequate alveolar ventilation and oxygenation while treating, if possible, the primary condition.

### Indications

The most common indication for mechanical ventilation is during and following major surgery [70]. In most non-surgical patients being considered for mechanical ventilation the indications are clear-cut in that adequate respiratory effort cannot be maintained using other supportive means and alveolar hypoventilation occurs, as shown by a high or rising  $P_{aCO_2}$  and a falling pH. Thus without such ventilatory support the patient may die. Patients with non-hypercapnic respiratory failure can be

maintained initially by increasing the concentration of inspired oxygen via a conventional or full-face mask with CPAP. Modest gains in oxygenation must be balanced against the risks of intubation and positive pressure ventilation [71].

The assessment is clearer in patients with hypercapnic respiratory failure, since if conventional treatment and non-invasive ventilation have failed then without mechanical ventilation the patient will die. In conventional clinical practice, a  $P_{aO_2}$  of less than 8 kPa (60 mmHg), despite an  $F_{IO_2}$  of greater than 0.6, and hypercapnia are the common indications for ventilation. Patients with COPD can obviously have high stable levels of  $P_{aCO_2}$  without evidence of respiratory distress. Other factors that favour the institution of mechanical ventilation are a rapid increase in hypercapnia, producing uncompensated respiratory acidosis, mental confusion due to either severe hypercapnia or hypoxaemia, tachypnoea (>35 breaths/min) and a clinical judgement of impending exhaustion in the patient.

It is critical when considering mechanical ventilation to assess the patient's condition prior to the onset of respiratory failure and ensure that mechanical ventilation is justifiable. It may be inappropriate, even over the short term, to ventilate patients who have advanced malignant disease, progressive neurological disorders or chronic respiratory diseases with poor quality of life. The British Thoracic Society guidelines for the management of COPD list the factors that influence the institution of mechanical ventilation in these patients [72] (Table 24.3).

### *Airway access*

Mechanical ventilation initially requires access to the airway, usually obtained by an endotracheal or nasotracheal tube. The latter has the advantage that it is easier to secure once *in situ* and tends to be more comfortable for the patient and hence less sedation is often required. However, nasal tubes are narrower and longer and therefore have a greater resistance and are more likely to

become obstructed by secretions. Laryngeal and tracheal trauma can occur from endotracheal tubes, although this is less of a problem than previously thought [73]. Improvements in endotracheal tube design, together with advances in airway management, have reduced the number of patients requiring tracheostomy. However, this is necessary in patients who require long periods of ventilation, or for the relief of upper airway obstruction or the management of copious secretions in patients who have an inadequate cough. Endotracheal tubes can be tolerated for at least 3 days in most patients and often somewhat longer [74]. In addition, tracheostomy is sometimes required in patients who are difficult to wean from ventilators. However, tracheostomy is associated with several complications, for example haemorrhage, infection, erosion of the tube into the oesophagus, tracheal stenosis, tube blockage and respiratory infection.

### *Modes of ventilation*

#### *Intermittent positive pressure ventilation (IPPV)*

This is the usual form of ventilation in the operating room. The patient is anaesthetized and paralysed and therefore makes no spontaneous respiratory effort; a simple ventilator intermittently inflates the lung at a tidal volume and respiratory rate sufficient to maintain appropriate gas exchange. A similar form of ventilation is used in patients in the intensive therapy unit (ITU) who are paralysed with muscle relaxants or who are unable to make any inspiratory efforts.

#### *Intermittent mandatory ventilation*

In this form, the patient receives ventilation at a predetermined rate and volume from the ventilator but can also breathe spontaneously through the ventilator circuit [71]. Interactive ventilators have been developed that can sense the patient's breathing and avoid coincidental, spontaneous and ventilator-assisted breathing, which can result

**Table 24.3** Factors that influence the institution of mechanical ventilation in patients with COPD.

#### *Factors to encourage use of IPPV*

A demonstrable remedial reason for current decline, e.g. radiographic evidence of pneumonia or drug overdosage  
The first episode of respiratory failure  
An acceptable quality of life or habitual level of activity

#### *Factors likely to discourage use of IPPV*

Previously documented severe COPD that has been fully assessed and found to be unresponsive to relevant therapy  
A poor quality of life, e.g. being housebound, in spite of maximal appropriate therapy  
Severe comorbidities, e.g. pulmonary oedema or neoplasia

NB: Neither age alone nor the  $P_{aCO_2}$  are a good guide to the outcome of assisted ventilation in hypercapnic respiratory failure due to COPD. A pH of >7.26 is a better predictor of survival during the acute episode.

IPPV, intermittent positive pressure ventilation.

in high airway pressures and is uncomfortable for the patient.

#### *Synchronized intermittent mandatory ventilation (SIMV)*

In this form of ventilation, the ventilator senses the ventilatory pressure generated by the patient and does not always deliver a mechanical breath, although the patient breathes through the ventilatory circuit. However, sufficient mandatory breaths synchronized to the patient's inspiratory efforts are delivered to the patient and it is therefore critical that the ventilator has a sensitive trigger mechanism. Thus SIMV allows adequate ventilation while enabling patients to take spontaneous breaths.

#### *Mandatory minute ventilation*

This technique enables a preset minute volume to be achieved which, if exceeded by the patient, results in no additional ventilation being provided. Thus the ventilator provides the shortfall in minute ventilation either by inspiratory pressure support or SIMV.

#### *Inspiratory pressure support (IPS)*

This form of ventilation is useful in patients who are spontaneously breathing but whose efforts are insufficient to achieve an adequate tidal volume [75]. Thus each inspiration is assisted by raising the airway pressure to a preset value. The respiratory rate is determined by the patient.

#### *Proportional assisted ventilation*

In this form of ventilation, the ventilator senses the inspiratory flow achieved by the patient and delivers pressure support proportional to the ventilatory effort made by the patient [76,77]. Thus if the patient increases the inspiratory 'effort' so does the ventilator. Although this form of ventilation is highly interactive and often very comfortable for the patient, it does require an alert patient who can initiate appropriate respiratory efforts.

#### *High-frequency ventilation*

This is achieved by injecting volumes of gas at high frequencies, up to 300/min [78]. Thus tidal volume is small, and indeed is less than the dead space and thus does not improve gas exchange by conventional means. The advantage of this form of ventilation, which can be used in spontaneously breathing patients, is to reduce peak airway pressures. It is most commonly used in ARDS when pulmonary compliance is low. It has also been used in patients with cardiac failure or bronchopleural fistula.

#### *Positive end-expiratory pressure*

This technique applies positive pressure at the end of expiration and thus lung volumes, particularly functional residual capacity (FRC), are increased [78]. The aim of this treatment is to prevent small airway closure and thus improve ventilation, reducing intrapulmonary hypoxaemia and hence pulmonary shunt. The disadvantage is a reduction in venous return and cardiac output, which can counteract the improvement in arterial oxygen tensions by an overall reduction in tissue oxygen delivery [79].

#### *Ventilator management*

In the case of routine surgical patients requiring mechanical ventilation on the ITU, analgesia and sedation is usually given with opiates and/or benzodiazepines and muscular paralysis is not usually necessary. It is important that all the staff in the ITU are completely familiar with the ventilator being used; this is more important than the particular type used. Patients can be ventilated by volume- or pressure-cycled machines. Volume-cycled machines deliver a fixed predetermined tidal volume and generate whatever pressure is required, breath by breath, to achieve that volume. In contrast, pressure-cycled machines deliver a predetermined pressure, and tidal volume therefore depends on the overall impedance to inflation and varies over time. Volume-cycled machines are often preferred since they continue to deliver a preset tidal volume irrespective of changes in the patient's airway resistance. However, when using nasal ventilation, large tidal volumes are required for adequate ventilation (approximately twice those of intubated patients) in order to compensate for upper airway dead space and the inevitable leaks around the mask, and volume-cycled machines may therefore be less suitable for this type of ventilation. Nomograms exist for the calculation of expected volumes, although it is always advisable to check the arterial blood gas tensions after instituting IPPV.

The tidal volume is usually set at approximately 10 mL/kg body weight and respiratory rate at 10–20 breaths/min and therefore minute ventilation is 100–150 mL/kg. In patients with COPD the tidal volume is often set at a lower level (7–9 mL/kg) in order to avoid the development of auto-PEEP (see p. 706).

#### *Ventilating patients with airway diseases*

There are many problems with ventilating patients who have severe airways obstruction [80,81]. Patients with severe asthma and COPD are hyperinflated and require high peak pressures during mechanical ventilation and hence the risk of pneumothorax and pneumomediastinum is increased [82]. It should be remembered that it is not necessary to correct the  $Paco_2$  rapidly in patients

with severe hypercapnia due to COPD. To keep inflation pressures down, a small tidal volume is used. To minimize gas trapping, a prolonged expiratory time is required with an inspiratory–expiratory ratio of 1:4 or 1:5. Peak inflation pressures are usually best kept below 30–35 cmH<sub>2</sub>O (2.94–3.43 kPa). Thus to avoid overinflation and high airway pressures and thus prevent barotrauma it may be necessary to accept a degree of hypercapnia [83].

Most patients require 35% inspired oxygen. Regular blood gas analysis allows the inspired oxygen concentration and the level of PEEP to be adjusted against the  $P_{aO_2}$  and the minute ventilation against the  $P_{aCO_2}$ .

#### *Auto-PEEP (intrinsic PEEP)*

Auto-PEEP, or intrinsic PEEP, occurs because patients with COPD and acute respiratory failure have severe airways obstruction and decreased pulmonary elastic recoil. Maximum expiratory flow is markedly reduced and there is a prolonged expiratory time, greater than required to permit a complete exhalation of inspired gas. In addition, the patients are commonly tachypnoeic and these factors produce a shortened expiratory time, so that inspiration starts before expiration has been completed, resulting in dynamic air trapping and an alveolar pressure that remains positive at the end of expiration. The resulting increase in lung volume forces the patient to breathe at the upper, less compliant portion of the pressure–volume curve, which increases the elastic load to breathing. This overinflation results in the respiratory muscles operating in an unfavourable position on their length–tension curve. Such auto-PEEP can have significant circulatory effects [84], since positive alveolar pressure can impede venous return and hence impair circulatory function. Dynamic overinflation and auto-PEEP may also increase the development of barotrauma during mechanical ventilation. Auto-PEEP can be measured during mechanical ventilation by the end-expiratory port occlusion method, where the expiratory port is occluded near the time when the next inspiration is anticipated. Because the expiratory flow is blocked, pressure in the ventilatory tube equilibrates with alveolar pressure, allowing the level of PEEP to be measured on the ventilator manometer [85]. The occlusion method is difficult to apply in patients who are making spontaneous inspiratory efforts, and under these circumstances auto-PEEP can be measured by inserting an oesophageal balloon and recording oesophageal pressure and inspiratory flow [86]. The majority of patients with an exacerbation of COPD severe enough to cause respiratory failure develop auto-PEEP, and the levels may be high (>10 cmH<sub>2</sub>O [>1 kPa]) [80,87].

#### *Inspiratory muscle fatigue*

In exacerbations of COPD the increased work of breathing

is borne largely by the inspiratory muscles [88]. The additional problem of dynamic overinflation, which puts the inspiratory muscles at a considerable disadvantage, and metabolic factors such as hypocalcaemia, hypophosphataemia, hypomagnesaemia, malnutrition and respiratory acidosis all decrease respiratory muscle strength and may lead to inspiratory muscle fatigue [63,89–92]. There is debate over the optimal mode of ventilation in patients with COPD and respiratory failure, largely resulting from controversy about the importance of inspiratory muscle fatigue in these patients.

#### *Ventilating patients with alveolar diseases*

Patients with reduced pulmonary compliance also have specific problems related to mechanical ventilation [83,93–95]. These patients are commonly those with ARDS, and in this case adequate mechanical ventilation necessitates high inflation pressures, a high  $F_{IO_2}$  and PEEP. This therefore increases the risk of barotrauma and pneumothorax. These side-effects can only be limited if airway pressures are kept as low as possible, necessitating small tidal volumes and the acceptance of a degree of hypercapnia [83]. Certain patients may benefit from use of high-frequency ventilation, thus allowing adequate gas exchange at lower peak airway pressures. PEEP is extremely useful in these patients, both by opening closed small airways, thereby improving oxygenation, and by lifting the lung on to a more compliant part of the pressure–volume curve.

#### *General management of ventilated patients*

Managing patients undergoing IPPV requires continuous skilled nursing support and immediate access to staff competent to deal with ventilator and intubation problems. Frequent or continuous monitoring of the ECG, heart rate, oxygenation, arterial blood gases and arterial blood pressure, urine output and ventilator parameters is required on a standard chart. The  $P_{aCO_2}$  should not be lowered precipitously, particularly in patients where the resting level is known to be high. It is better to aim for a normalization of pH rather than for a specific  $P_{aCO_2}$ .

Sedatives and analgesics are commonly administered by constant infusion in the form of opiates [96]. This may result in problems associated with respiratory distress, depression, vasodilatation, reduced gastric motility and tolerance. The duration of action of benzodiazepines can be a problem. Midazolam can be useful in this regard, since it has a relatively short half-life of several hours and can be given by continuous infusion [97]. Regular clearance of airway secretions by suction is often necessary. Continuous monitoring of oxygenation by oximetry and regular blood gas measurements are essential, particularly in the early stages of treatment.



Since many factors influence oxygen delivery to, and uptake by, the tissues, monitoring of cardiac function is often crucial. Depending on the circumstances, systemic arterial, pulmonary arterial and pulmonary wedge pressures, cardiac output, pulmonary and systemic vascular resistance, and mixed venous oxygen tensions and saturations may be required. Venous oxygen tension is a particularly useful index of the balance between oxygen supply to, and extraction by, the tissues [98]. Oxygenation should also be judged in the light of the patient's usual  $P_{aO_2}$  rather than by normal values. The  $F_{iO_2}$  can be increased, although high concentrations of oxygen, particularly for a long periods, can lead to oxygen toxicity. Clearly it would be unwise to run the risk of the patient dying of hypoxia for fear of pulmonary oxygen toxicity if a higher  $F_{iO_2}$  is needed, and some compromise has to be found in each case. As a rough guide, if an  $F_{iO_2}$  of 0.7 does not produce acceptable values for  $P_{aO_2}$ , then it may be better to apply PEEP rather than increase the  $F_{iO_2}$ . PEEP will result in a further increase in mean thoracic pressure and hence a greater decrease in venous return. Clearly this disadvantage has to be set against the benefit of improved oxygenation. In practice it may be necessary to measure mixed venous  $P_{O_2}$  and cardiac output in order to compute the best level of PEEP in an individual patient given these conflicting effects. If PEEP is ineffective or inadequate, then of course the  $F_{iO_2}$  has to be increased. In clinical practice it is not uncommon to have to use a high  $F_{iO_2}$  and then apply PEEP in the hope of being able to reduce the  $F_{iO_2}$ .

#### Nutrition

Adequate nutrition is crucial in ventilated patients [99]. This is particularly true in those with sepsis, who have a very high oxygen consumption, or in those who require prolonged ventilation. Muscle wasting affects all muscles including those of respiration and leads to difficulties in weaning [100]. Electrolyte and calcium disturbances, hypophosphataemia and hypomagnesaemia can also cause muscle weakness [101]. The  $CO_2$  load can be reduced in patients with hypercapnia by providing less of the calorie requirements as carbohydrate and more as fat. However, there have been no randomized controlled studies examining the role of nutrition in patients with COPD [102]. In addition complications as a result of either enteral nutrition or total parenteral nutrition are frequent. In addition, malnutrition, which may coexist in patients with COPD [103], may be exacerbated by mechanical ventilation [104]. There is some evidence from retrospective uncontrolled studies of patients requiring long-term (>3 days) mechanical ventilation that nutritional supplementation improved the weaning rate in these patients [105]. It would therefore seem reasonable to provide nutritional support for patients who are malnourished at presenta-

tion or who require prolonged ventilation. The enteral route is the preferred mode of administration.

#### Physiotherapy

Most patients, particularly those with airway diseases, have an increase in airway secretions during mechanical ventilation and have impaired cough effectiveness. Thus it would seem reasonable to employ chest physical therapy to assist removal of secretions. However, several studies have been unable to show any improvement in pulmonary function or objective evidence of improved removal of secretions when physiotherapy is employed in patients with exacerbations of COPD [106,107]; there is certainly no benefit in patients with scant sputum production [108,109]. Physical therapy can also worsen  $P_{aO_2}$  and should only be considered in patients with large amounts of sputum production [108]. It is therefore a relative contraindication in most patients with COPD and respiratory failure.

#### Weaning from mechanical ventilation

In most patients with respiratory failure, weaning can be achieved without much problem by the withdrawal of sedation and muscle relaxants, allowing the patient to breathe spontaneously prior to extubation. In a minority of patients weaning is difficult and this is particularly true of those with COPD. Successful weaning relates to several factors, including achievement of adequate oxygenation with an  $F_{iO_2}$  of less than 0.4, recovery of the underlying condition that precipitated mechanical ventilation, attainment of stable cardiovascular function and the resolution of infection [110] (Table 24.4). The most important factors determining the success or failure of weaning are the load imposed on the respiratory system, respiratory drive and the capacity of the muscle pump [110]. Every effort should be made to reduce the load imposed on the respiratory system before weaning is attempted, for example by treatment of bronchoconstriction and pulmonary oedema. CPAP is useful in patients in whom a reduction in FRC causes hypoxaemia and reduced pulmonary compliance. In addition, CPAP is useful in patients with airway obstruction who develop intrinsic PEEP. Thus in many

**Table 24.4** Measurements associated with failure of weaning from mechanical ventilation.

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Tidal volume, breathing spontaneously, <5 mL/kg
Vital capacity, <10 mL/kg
Alveolar-arterial oxygen tension difference, >40 kPa (300 mmHg)
Dead space/tidal volume, >0.6
Minute ventilation (MV), >10 mL/kg
Maximum voluntary ventilation, <2×MV
Maximum inspiratory pressure, >-20 cmH <sub>2</sub> O

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patients CPAP reduces the ventilatory work during weaning [111]. The disadvantage of CPAP is that it may increase the load on the muscles of expiration and may aggravate overventilation and thus hypercapnia.

Patients require a high respiratory drive and need to be cooperative during weaning. Thus sedative drugs must be withdrawn before weaning, bearing in mind the long half-life of some of these agents such as benzodiazepines. In order to optimize the effectiveness of the respiratory muscle pump, adequate nutrition, control of sepsis and reversal of acidosis are particularly important. A good deal of support and encouragement is required from the ITU team during weaning. It is unlikely that a trial of weaning will be successful on the first attempt and it is important that patients are not deprived of sleep by repeated attempts. There is no definitive strategy for successful weaning. There have also been no controlled trials indicating that one technique is more successful than another. The usual technique is to gradually reduce the number of machine breaths with SIMV, allowing the patient to breathe spontaneously. Alternatively, the mechanical ventilation should be stopped and the patient allowed to breathe spontaneously with the withdrawal of ventilatory support for progressively longer periods of time.

IPS is increasingly used to aid weaning. This can be gradually reduced and the work progressively transferred from the ventilator to the patient. Proportional assist ventilation is a relatively recent technique that uses the mechanical ventilator to deliver pressure support in proportion to the patient's own inspiratory efforts, thus allowing patients to receive the correct degree of support which they perceive to be necessary on a breath-by-breath basis [74].

Non-invasive ventilation has also been used to facilitate weaning, although there are no controlled trials. However, uncontrolled studies suggest the benefit of NIPPV in chronically ventilator-dependent patients [112]. Before initiating NIPPV, patients should be capable of approximately 15 min of independent ventilation. Usually NIPPV is required for the first 48 h and thereafter for progressively shorter periods.

Weaning from mechanical ventilation is particularly difficult in patients with COPD [113]; again there are no published studies indicating the best technique to wean such patients. Traditionally the maximum inspiratory pressure ( $P_{I\max}$ ) has been used as a measure of respiratory muscle strength and as a reflection of the patient's ventilatory requirements. Previously it was thought that patients should be capable of generating a  $P_{I\max}$  more negative than  $-30\text{ cmH}_2\text{O}$  ( $2.94\text{ kPa}$ ) and have a minute ventilation of less than  $10\text{ L/min}$  to be successfully weaned [114], although this has subsequently been shown to have a high false-positive rate [115]. In a recent prospective study of weaning, the breathing frequency to tidal volume ratio, an

index of rapid shallow breathing, was found to be the most accurate predictor of weaning outcome [115]. A breathing frequency to tidal volume ratio of greater than  $100\text{ breaths/min/L}$  was associated with a 95% failure in a weaning trial. However, it should be emphasized that there is still much debate in this field [116].

## Complications

### Barotrauma

During mechanical ventilation in general ITU patients the incidence of pulmonary barotrauma is relatively low, occurring in 1–8% of patients [117,118]. The frequency increases significantly in patients with ARDS [117]. Factors associated with an increased incidence of barotrauma are high peak airway pressures, high levels of both external and intrinsic PEEP and high tidal volumes [117,119–122]. The ventilatory settings should be adjusted to try to maintain peak airway pressure below  $40\text{ cmH}_2\text{O}$  ( $3.92\text{ kPa}$ ).

### Gastrointestinal bleeding

Gastric erosions or ulceration producing gastrointestinal bleeding occur in patients with respiratory failure, with an incidence of around 20% in general ITU patients [123]. The incidence appears to be lower, around 9%, in patients with COPD. The risk of gastrointestinal bleeding is greatly reduced by continuous enteral feeding and maintenance of gastric pH above 4 may reduce the incidence [124]. However, the risk of raising intragastric pH is an increased growth of Gram-negative bacteria in the stomach and so an increased risk of nosocomial pneumonia [125,126]. However, it has been suggested that patients with COPD and acute respiratory failure may not benefit from ulcer prophylaxis, particularly if they are being fed enterally [127].

### Nosocomial pneumonia

Nosocomial pneumonia (see Chapter 13) in the ITU is usually caused by Gram-negative bacilli, which may be resistant to common antibiotics [128]. The most common source of organisms appears to be aspiration of microorganisms that colonize the pharynx [129], and this may occur within 72 h of admission to the ITU [130]. Other complications include cardiac dysrhythmias and pulmonary emboli. Psychological disturbances are also common among ITU patients.

## Prognosis

A detailed review of the prognosis in ventilated patients in ITU is beyond the scope of this chapter. Specifically in

patients with COPD, the short-term mortality in acute respiratory failure was established in a number of studies in the 1960s and 1970s and has been reviewed by Hudson [131]. In these early studies the mortality ranged between 22 and 34% during the acute episode. More recent studies have reported a mortality for an acute episode of respiratory failure of between 6 and 16% [27,28,44,45,132,133]. Differences in patient selection may well be the most important factor accounting for the variation in mortality between different studies. Indeed the study that showed the best prognosis included patients with the least severe disease [133].

Several studies have shown that the best predictor of mortality in patients with acute-on-chronic respiratory failure is the degree of acidaemia. Thus a pH of less than 7.26 (hydrogen ion concentration  $>55$  nmol/L) is associated with an increased mortality [27,28]. The  $Paco_2$  is much less predictive, because most of these patients have chronic hypercapnia and the severity of the acute phase is better reflected by the degree of acidosis rather than the absolute level of  $Paco_2$ . The initial level of  $Pao_2$  on admission was a determinant of mortality in some studies [40] but not in others [27,28]. It is interesting to note that mechanical ventilation during the acute episode is not itself associated with an increased mortality, although there are no studies that have specifically addressed this issue.

The long-term mortality of patients with COPD who survive an episode of acute respiratory failure is in general very poor; 50% of these patients are dead at 3 years [132–136].

## Specific types of respiratory failure

The causes of respiratory failure are identified in Tables 24.1 and 24.2 and are covered fully in the chapters indicated in these tables. Those that require further elaboration are considered here.

### Drugs

#### CNS depressants

Opiates, sedatives and tranquillizers may cause alveolar hypoventilation if taken as an overdose or if given in excessive therapeutic dosage. Intubation with mechanical ventilation may be required if respiratory depression is severe. All drugs that depress the nervous system should be used with caution in patients with pulmonary disease, particularly those with COPD who have chronic hypercapnic respiratory failure. Opiate antagonists, such as naloxone, are of value in opiate overdose and flumazenil is useful in benzodiazepine overdose. Rarely methadone or heroin overdosage can result in the complication of pulmonary oedema [137,138].

### Postoperative apnoea

Postoperative apnoea may be due to excessive premedication with opiates. It can also occur after the use of suxamethonium, particularly in patients with a hereditary deficiency of pseudocholinesterase. In these cases mechanical ventilation should be continued until the effects of the suxamethonium wears off.

### Poisoning

Organophosphorus compounds are used in insecticide sprays and may be absorbed through the skin (even through clothing) or mucous membranes. Poisoning results in tremors, twitching, convulsions, contracted pupils, salivation and bradycardia. Treatment is by repeated intravenous injection of atropine (2–3 mg immediately and 1–2 mg every hour). Sputum removal is accelerated by intravenous pralidoxime 1 g every hour. Nevertheless, mechanical ventilation may be required.

### Laryngeal oedema

Laryngeal oedema may result from inhalation of irritant vapours, clumsy attempts at intratracheal intubation or angioneurotic oedema. In the latter, other allergic manifestations such as wheeze, urticaria and sneezing may be present. Stridor is usual. Angioneurotic oedema should be treated immediately with 0.5 mL epinephrine (adrenaline) 1 in 1000 solution intramuscularly and intravenous injection of 200 mg hydrocortisone and 20 mg chlorpheniramine. Needle tracheotomy, using a large Medicut cannula inserted through the cricothyroid membrane, may be necessary as a stopgap measure if formal tracheotomy is required.

### Neurological disorders

Neurological disorders can result in respiratory morbidity and mortality due to depression of ventilation (whether caused centrally or via respiratory muscle weakness) or pulmonary oedema. This occurs in various acute cerebral insults and in recurrent aspiration from the upper airway as a result of a primary muscle disease or diseases affecting the brainstem. Abnormal breathing patterns can affect various levels of the CNS associated with the pathways of respiratory control. Respiratory depression can occur in various conditions associated with acute cerebral dysfunction, including encephalitis, stroke and tumours, which cause cerebral oedema and raised intracranial pressure.

### Pulmonary oedema

The so-called neurogenic pulmonary oedema syndrome is

associated with acute brain injury, especially following trauma, subarachnoid haemorrhage and severe convulsions. It is often associated with raised intracranial pressure and cerebral oedema. The mechanism is probably associated with a sudden rise in systemic and pulmonary vascular pressures as a result of a massive adrenergic discharge mediated by the hypothalamus [139,140]. An additional factor may be loss of integrity of the pulmonary capillaries, producing the high protein content in the oedema fluid. Oxygen is usually required, although if the  $P_{aCO_2}$  is raised positive pressure ventilation may be needed.

### Respiratory muscle dysfunction

The respiratory muscles include the diaphragm, intercostal muscles, scalene muscles and abdominal muscles. The pattern of dysfunction depends on which muscles are affected. In general there are three common patterns:

- 1 generalized weakness, as in the diffuse neuropathies and myopathies;
- 2 conditions where the diaphragm is spared but other respiratory muscles are involved, such as lower cervical quadriplegia;
- 3 unilateral and bilateral diaphragm weakness or paralysis resulting from disorders of the phrenic nerves, or muscle disorders that mainly affect the diaphragm. These are dealt with in greater detail in Chapter 45.

### Clinical assessment

A patient who presents with breathlessness, without pulmonary or cardiovascular disease, suggests the possibility of global muscle weakness. There may also be a history of ineffective cough or unexplained respiratory infections. A family history of diffuse neuropathy or myopathy is important. Clinical signs may not be obvious, although there may be generalized wasting of the peripheral muscles. Patients with severe diaphragmatic weakness show paradoxical inward abdominal motion during inspiration when breathing at rest, particularly in the supine position when the diaphragm is unable to counteract the weight of the abdominal contents.

### Investigations

Hemidiaphragm paralysis can usually be identified from a plain chest radiograph, although fluoroscopic screening during sniffing is sometimes required to produce the paradoxical upward movement of the paralysed diaphragm [141]. Bilateral diaphragm paralysis is difficult to assess on plain chest radiography or fluoroscopy.

A reduction in vital capacity (VC) is usual but is relatively non-specific. Therefore the combination of small VC and small clear lung fields on the chest radiograph is sug-

gestive of respiratory muscle weakness. Sequential measurements of VC may be a useful index of failing respiratory muscle function. Severe diaphragmatic weakness is associated with smaller VC when supine than when erect as a result of the abdominal contents affecting the diaphragm in the supine position. Normally VC falls by only 5–10% when moving from the erect to the supine position and even in patients with lung disease the fall is no more than 30% [142]. Patients with severe diaphragmatic weakness have a fall in VC of more than 30% [143].

In patients with respiratory muscle weakness, daytime hypercapnia does not occur until muscle strength is less than 30% of normal, unless there is coexisting pulmonary or airways disease or reduced respiratory drive [144]. Gradual development of global muscle weakness may result in hypoventilation, which occurs initially only at night during REM sleep [145]. This can be detected by continuous monitoring of oxygenation and  $CO_2$  tensions during sleep.

Respiratory muscle strength can be measured by assessing maximum static inspiratory ( $P_{I\max}$ ) and expiratory ( $P_{E\max}$ ) pressures at the mouth [146,147]. A  $P_{I\max}$  more negative than  $-80\text{ cmH}_2\text{O}$  (7.85 kPa) excludes clinically significant respiratory muscle weakness. Equivocal values can be difficult to interpret and may require further investigation.

### Myasthenia gravis

Myasthenia gravis is an uncommon autoimmune disease of neuromuscular junctions that leads to a reduction in the number and effectiveness of acetylcholine receptors and thus to impaired neuromuscular transmission, resulting in weakness and undue fatigue [148–152]. The characteristic fatigability occurs following repetitive action or prolonged contraction and recovers with rest. Extraocular, bulbar, neck, limb girdle, distal limb and trunk muscles are involved in that order. Patients with myasthenia gravis occasionally develop respiratory failure [153]. Anticholinesterase drugs (e.g. edrophonium), which increase the concentration of acetylcholine at the neuromuscular junction, are used in the initial diagnosis and treatment. The diagnosis may be confirmed by measurement of acetylcholine antibodies and electromyography. Intravenous edrophonium chloride is used in a diagnostic test and increases muscle strength within minutes in a patient with the disease. Longer-acting oral anticholinesterases, such as neostigmine or pyridostigmine, are used to maintain strength throughout the day. However, an overdose of anticholinesterase medication may result in a 'cholinergic crisis' with severe muscle weakness that may be difficult to differentiate from weakness due to worsening myasthenia, a 'myasthenic crisis'. Separation of the two types of crisis can be made by giving 10 mg edrophonium, which

increases strength in a myasthenic crisis but decreases it in a cholinergic crisis. It is wise to prepare for ventilatory support before administering edrophonium since hypoventilation, with a marked increase in retention of bronchial secretions, may occur in patients with a cholinergic crisis. Corticosteroids and immunosuppressive therapy are now becoming the initial treatment of choice for myasthenia, although a transient exacerbation may be seen in the early days of therapy. Ventilator support may be necessary until strength returns with appropriate readjustment of medication. Repeated measurements of inspiratory muscle pressure or VC are of value in monitoring the progress of the disease and in adjusting drug dosage. In many patients thymectomy produces a substantial improvement whether or not a thymoma is present.

### Polyneuropathy

Infective polyneuropathy (Guillain-Barré syndrome) is a progressive central demyelinating neuropathy of unknown aetiology. It is characterized by the fairly rapid development of flaccid paralysis of muscles following a viral infection. Progressive muscle weakness may occur over days or weeks. Weakness usually begins in the feet and ascends but may also begin cranially. The muscles of respiration may be affected leading to respiratory failure, which can develop fairly rapidly over 24–48 h. Monitoring of respiratory muscle function is vital. Twice-daily measurements of VC are usually recommended while the disease is progressing [154]. Monitoring of arterial blood gases is also recommended and artificial ventilation may be necessary in 20–50% of affected individuals [154,155]. Mechanical ventilation is necessary when the VC falls to between one-third and one-half of the predicted normal values. In practice the decision is more often made on clinical grounds because of a deteriorating respiratory effort, ineffective cough or inability to swallow [156]. Ventilatory support may be required for many weeks, necessitating tracheostomy, although most patients eventually make a good recovery. However, the potential for ventilator-associated complications including infections and pulmonary embolism is high. Suxamethonium should not be used since it may cause dangerous hyperkalaemia [157]. Autonomic dysfunction may complicate the management, with alternating bouts of tachycardia and bradycardia and fluctuations in blood pressure. Corticosteroid therapy is not now considered to be of value in the treatment of this condition, the management of which is largely supportive, although intravenous gammaglobulin or plasma pheresis may be helpful in some cases.

### Poliomyelitis

The high prevalence of poliomyelitis during the 1950s and

the requirement for ventilatory support with the iron lung has now receded in developed countries as a result of widespread immunization. Nevertheless, polio is still a common disease worldwide. Respiratory failure may be due to bulbar or spinal poliomyelitis or a combination of the two.

In spinal polio, the development of respiratory failure may be detected clinically as a feeble cough. However, serial measurements of VC and arterial blood gas tensions should complement clinical observations. Mechanical ventilation should be introduced when the VC falls to one-quarter of the patient's predicted value [158]. A mechanical ventilator can be used, thus avoiding tracheostomy. Should bulbar paralysis also develop, then tracheostomy is required with substitution of IPPV. In bulbar polio, laryngeal paralysis results in an ineffective cough and aspiration of secretions. Patients should be nursed in a 10° head-down position with regular aspiration of pharyngeal secretions. Feeding should be through a nasogastric tube. Tracheostomy may be required using a cuffed tube to prevent aspiration of secretions. It has been increasingly appreciated in recent years that late respiratory complications occur in poliomyelitis, up to 30 years after the original illness [159]. Muscles that were affected acutely are impaired as a result of late degeneration and the loss of motoneurons. The result is gradually increasing respiratory muscle weakness leading to respiratory failure. Ventilation in this case may be particularly troublesome at night, with resultant symptoms of daytime sleepiness and headache [160]. This so-called 'post-polio' syndrome tends to occur in those who developed respiratory muscle weakness during the original illness or in those who develop marked scoliosis [161]. Treatment with NIPPV may be necessary over the long term.

### Tetanus

Tetanus is a common cause of mortality in underdeveloped countries but in the developed world is now uncommon as a consequence of the widespread use of prophylaxis [162,163]. The condition results from infection of penetrating wounds with *Clostridium tetani*, which secretes an endotoxin taken up by nerve endings and transmitted to the CNS. The toxin interferes with the release of acetylcholine at the motor endplates and with the release of inhibitory neurotransmitters in the spinal cord. Muscle tone is markedly increased and the muscle is hyperexcitable, with resulting trismus and severe spasms in response to slight stimuli. Similar disinhibition of the autonomic nervous system may lead to labile hypertension, tachycardia, pyrexia and profuse sweating [164]. In the absence of intensive care facilities, death is usually due to asphyxia during respiratory muscle spasms. Control of the spasms with muscle paralysis using curare and IPPV reduces the respiratory death rate, although death may

still occur during autonomic storms due to myocarditis or brainstem lesions. Modern management in an ITU has reduced mortality to 11% [165].

Treatment consists of wound débridement, penicillin, passive immunization with immunoglobulin and active immunization. Spasms may be treated with high doses of diazepam or chlorpromazine [166]; if spasms are severe, curare and IPPV via a tracheostomy should be commenced. The autonomic cardiovascular changes can usually be controlled by intravenous beta-blockers or by morphine [167]. Enteral or parenteral nutrition is required.

### **Cervical cordotomy**

Bilateral high cervical cordotomy for intractable pain may result in alveolar hypoventilation, thought to be due to section of respiratory reticulospinal tracts. If the corticospinal pathways are left intact, the behavioural system may maintain ventilation when the patient is awake while hypoventilation and apnoea occur during sleep. Treatment is the same as for primary alveolar hypoventilation.

### **Myxoedema**

Occasional patients with myxoedema develop type II respiratory failure that responds to treatment with thyroxine. Ventilatory responses to hypercapnia and hypoxia are often reduced in these patients [168].

### **Inhaled foreign body**

An inhaled foreign body or food, most often a chunk of meat, can impact in the larynx and result in acute total airway obstruction, with choking, cyanosis and collapse. Prompt application of Heimlich's manoeuvre may be life-saving [169].

### **Respiratory failure in children: respiratory distress syndrome (hyaline membrane disease)**

Respiratory distress syndrome (RDS) in the newborn, or hyaline membrane disease, is a clinical syndrome that almost exclusively affects preterm babies. It is characterized pathologically by a hyaline membrane lining the alveoli and clinically by respiratory distress, which may be fatal. It results from maturational deficiency of lung surfactant. The clinical syndrome consists of tachypnoea, sternal recession and cyanosis, which are present from birth and worsen over the succeeding 24–48 h. The prevalence is inversely related to gestational age and has been estimated to be 15% in neonates born at less than 23 weeks of gestation [170]. Most deaths occur within the first 48–72 h. However, with the introduction of neonatal intensive

care, mortality is now rare in babies of more than 28 weeks' gestation. Full details should be sought in paediatric textbooks.

### **Aetiology**

In the newborn infant the alveoli are stabilized in order to allow gas exchange by the action of pulmonary surfactant, which is generated by type II pneumocytes. These cells synthesize and store surfactant from about 16–18 weeks of gestation [171]. By 24–26 weeks of gestation there is a 30-fold excess of stored surfactant compared with the lung surface area to be covered, and at this stage of gestation surfactant is released on to the alveolar surface. Fetal airways are fluid-filled and surfactant released into them is carried into the amniotic fluid, where levels can be measured to assess fetal lung maturity. In the absence of surfactant there is a tendency for the lung to collapse completely during expiration, which reduces the FRC and leads to a fall in dynamic compliance [172]. This is compounded by interstitial oedema that results from increased alveolar permeability [173]. Due to a reduction in lung compliance, the work of breathing is disproportionately increased, which eventually leads to diaphragmatic fatigue and respiratory failure [174]. Ventilation-perfusion mismatching occurs, partly as a result of airway closure, and dead space ventilation is increased and alveolar ventilation reduced. In addition there is an increase in right-to-left shunting through anatomical communications, which worsens hypoxaemia.

Gestational age is the single most important factor related to the development of RDS. However, one recent study has raised the possibility that there may be one or more human leucocyte antigen (HLA)-linked genes associated with an increased susceptibility, and may explain familial clustering [175]. Other factors associated with an increased risk of RDS are hypothermia, hypocalcaemia, hypoxia, hypovolaemia, asphyxia and shock.

### **Pathology**

The appearance of the lungs depends on the age of the infant [176]. Typically there is collapse of the alveoli, the lungs are completely airless and there is a prominent acidophilic membrane lining the respiratory bronchioles and alveoli, which are filled with proteinaceous exudate. There is interstitial and alveolar oedema and the pulmonary lymphatics are engorged. A hyaline membrane develops as a result of hypoxic injury to the type I and capillary endothelial cells, producing plasma leak into the interstitium and hence the alveoli, where a mixture of cells and protein forms a coagulum to produce the characteristic hyaline membranes in the alveolar spaces. Pulmonary vasoconstriction in areas of atelectasis also occurs.

### Functional abnormalities

As expected from the pathology, the lungs show low compliance. Minute ventilation may be increased but alveolar ventilation is decreased with increased  $V_D/V_T$  ratio and  $\dot{V}_A/\dot{Q}$  disturbance. In the early stages,  $P_{aO_2}$  and  $P_{aCO_2}$  may be only slightly lowered. Later there is gross hypoxaemia with acidosis and  $CO_2$  retention. Metabolic acidosis due to inadequate oxygenation of the muscles may occur. There may be systemic hypotension and a shunt through a patent ductus arteriosus potentiated by hypoxic arteriolar constriction. In addition, fetal haemoglobin, which binds more oxygen at a given  $P_{aO_2}$ , releases oxygen less readily to the tissues. Severe hyperkalaemia and hypercalcaemia may occur in infants who are hypothermic or who have occult cerebral haemorrhage. Hyponatraemia may be present in some infants, leading to complex effects on the immature kidneys. The excessive use of sodium bicarbonate to correct acidosis may also lead to hyponatraemia [177].

### Clinical characteristics and radiology

RDS begins from birth. The respiratory rate is raised, typically to around 100 breaths/min. Grunting and distressed respiration, flaring of the alae nasae, intercostal, supraclavicular and sternal respiratory retraction, tachycardia and cyanosis are manifestations of the fully developed condition. Auscultation reveals poor air entry but usually no crepitations. Oedema of the hands and feet is common. Respiratory distress increases for 24–48 h when a plateau is reached. Thereafter the signs and symptoms gradually improve, presumably because of surfactant production [178]. Survivors of uncomplicated RDS, usually in more mature babies, do not have an increased frequency of respiratory symptoms later in childhood and have been shown to have normal pulmonary function at school entry [179]. The chest radiograph shows diffuse fine granularity throughout the lungs. Later there is a more uniform opacification and the appearance of air bronchograms. More severely affected babies may continue to progress and to be dyspnoeic for many days or even weeks and may die.

### Diagnosis

The diagnosis can be presumed from the clinical features in a preterm baby with a characteristic chest radiograph. The diagnosis can be confirmed indirectly by measurement of surfactant activity in tracheal aspirates or amniotic fluid to assess fetal lung maturity. Two techniques are used, the lecithin–sphingomyelin ratio and the amniotic foam test, the latter helping to make the diagnosis more specific [180,181]. The differential diagnosis includes congenital pneumonia, typically caused by group B strepto-

cocci and which is radiographically indistinguishable from RDS [182], and transient hypoxaemia of the newborn, which closely mimics RDS clinically in the early stages but improves over the first 24–48 h [183]. In this condition the chest radiograph usually shows evidence of pulmonary oedema and may coexist with RDS.

### Prevention

Although a meta-analysis of prospective, randomized, controlled trials has demonstrated a reduction in RDS in babies whose mothers have been treated with corticosteroids, the use of these drugs is limited by the need for treatment for 36 h and this is not possible in over 50% of cases [184].

### Treatment

When a neonate at risk of RDS is born, prompt resuscitative measures should be initiated on the basis of the 1-min Apgar score [185]. Supportive treatment should be instituted, such as the maintenance of environmental warmth to prevent cold stress and the resultant increased oxygen consumption and aggravation of acidosis. Oxygen should be given sufficient to maintain a  $P_{aO_2}$  of 8–12 kPa (60–90 mmHg), since higher levels carry a risk of retrolental fibroplasia or pulmonary oxygen toxicity. When the blood pH is low this may be corrected, but not overcorrected, by intravenous bicarbonate. Close attention should be paid to fluid balance, serum calcium and glucose levels, and appropriate corrections made. Criteria for the ventilation of very ill babies have been developed, for example a  $P_{aO_2}$  of less than 5.3 kPa (40 mmHg),  $P_{aCO_2}$  greater than 11 kPa (82 mmHg) or pH less than 7.1 [186,187]. This strategy involves using a long inspiratory time to maximize mean airway pressure and thus improve oxygenation, while avoiding high peak pressures, which might contribute to barotrauma. Meta-analysis has shown the benefit of maintaining a short, as opposed to a long, inspiratory time [188]. CPAP has also revolutionized the management of these neonates, by improving oxygenation and preventing expiratory atelectasis [189]. High-frequency oscillatory ventilation and jet ventilation have also been shown to be both safe and effective in reducing lung injury [190]. Specific treatment is now available in the form of recombinant surfactant preparations, which can be instilled into the intratracheal tube. This treatment has been shown to improve prognosis in neonates with RDS [191,192]. Meta-analysis of 35 randomized controlled trials that used synthetic or natural surfactant have shown its benefit, although optimum dosage, timing and frequency of therapy have yet to be established definitively [193].



## Complications

Pneumothorax has been reported to occur in 15–35% of babies ventilated for RDS [194]. Pneumopericardium may also occur. Prompt intervention, with needle aspiration prior to insertion of a tube, may be life-saving.

Bronchopulmonary dysplasia, first described in 1967 and variously attributed to the severity of disease, oxygen toxicity and ventilatory assistance, is characterized by airways obstruction, poor clearance of secretions and chronic pulmonary oedema [195,196]. It is associated clinically with continuing retrosternal recession, tachypnoea and coarse crackles in the lung fields. Blood gases show CO<sub>2</sub> retention in addition to hypoxaemia. The chest radiograph shows patchy consolidation. Histologically the lung shows oedema, squamous metaplasia and fibroblastic proliferation. Despite these pathological findings, most affected infants survive, probably because the lung is still in a rapid phase of growth (see Chapter 56).

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# PULMONARY EMBOLISM

DOUGLAS SEATON AND ANTHONY SEATON

The term 'pulmonary embolism' implies clinically significant obstruction of a part or the whole of the pulmonary arterial tree, usually by thrombus that becomes detached from its site of formation outside the lung and is swept downstream until arrested at points of intrapulmonary vascular narrowing. This concept of pulmonary embolism, which was attributed to Virchow 150 years ago [1], excites considerable clinical interest because despite improved understanding of its pathogenesis that has led to the widespread use of preventive measures, it is still a major cause of morbidity and mortality and its accurate diagnosis and effective treatment remain problematical. From the point of view of diagnosis and management, modern usage regards the pulmonary embolus and its formation in the venous system as one condition, venous thromboembolic disease.

## Prevalence

The reported frequency of pulmonary embolism in hospital patients coming to postmortem examination varies between series. Coon [2] reported pulmonary embolism as the cause of, or a major contributory factor to, death in 7–9% of necropsy cases. Another study using a postmortem pulmonary angiographic technique reported double this rate [3]. The true reported prevalence may be much higher when smaller antemortem thrombi are recorded at necropsy, others having found evidence of embolism in 60% of subjects [4]. Considering living patients, a recent report from a large general hospital indicated a prevalence of acute embolism of about 1% of all patients and as contributing to a fatal outcome in 0.2%. It also confirmed that the prevalence of undiagnosed pulmonary emboli in necropsies had not altered over several decades [5].

There is disagreement about whether or not the frequency of pulmonary embolism is increasing. There is little doubt that the condition is reported more frequently [6,7], but this may reflect increased awareness on the part of clinicians and improved diagnostic techniques. A study

that made a comparison between two series completed by the same pathologist showed no significant difference in the incidence over two periods covering the years 1945–55 and 1967–74 [8]. Extrapolations from such data have led to the belief that pulmonary embolism is a major contributory factor to death in 50 000–200 000 patients per year in the USA, with a considerably greater numbers suffering non-fatal events [9,10]. Care should be taken before applying data obtained after death to the living, for although pulmonary embolism is commonly found after death, this population is highly selected and the true incidence of pulmonary embolism in previously healthy people remains unknown.

## Mechanisms of thrombosis

Virchow in 1857 listed a triad of factors that he considered to predispose to the formation of thrombus in the venous system: (i) relative venous stasis, (ii) injury to the wall of a vein, and (iii) increased coagulability of the blood itself. The passage of over 130 years has proved these early general postulates to be remarkably durable and has allowed a more detailed examination of risk factors, with particular emphasis on the prevention of venous thrombosis.

Venous stasis allows local accumulation of platelets and clotting factors, especially thrombin, in the vein. Stasis may be promoted by increased viscosity, as occurs in polycythaemia and dehydration. It also commonly occurs as a consequence of immobility (because of lack of muscle pump activity in forcing blood up the leg veins), raised venous pressure in patients with cardiac failure and, less commonly, compression of vein by tumour or atheromatous arteries.

The normal venous endothelium possesses natural antithrombotic molecules, including heparan sulphate (which neutralizes thrombin), thrombomodulin (which inhibits thrombin) and plasminogen activator (which promotes local fibrinolysis). These, and the vasodilatory factors prostacyclin and nitric oxide, act to keep the

venous lumen patent, but may all be impeded when endothelial damage occurs.

The complex and delicate balance between blood coagulation and anticoagulation, modulated by thrombin, platelets and plasmin, may be altered in disease, obesity, after surgery and in trauma. It has been a matter of common observation that some people appear particularly prone to the development of venous thromboses, and it was shown in the 1970s that possession of blood group A appeared to be a risk factor [11]. It is now apparent that, at least in some cases, it is possible to detect individuals with increased susceptibility to thrombus formation on account of hereditary thrombophilia. This was originally noted in patients with autosomal dominant familial deficiency of antithrombin III which, although rare, carries a well-documented risk of recurrent deep venous thrombosis and pulmonary embolism and may be fatal. Antithrombin III is a protease inhibitor, with a very similar structure to  $\alpha_1$ -antitrypsin [12], and deficiency leads to defective inactivation of thrombin. The diagnosis may be established by immunological assay of plasma antithrombin III levels [13].

More recently, genetic deficiencies of the natural anticoagulants protein C and protein S have been described and these, together with antithrombin deficiency, are responsible for some 10% of venous thromboses occurring in younger people [14–18]. Even more common is an inherited resistance to activated protein C due to a mutation in the gene encoding factor V (so-called factor V Leiden mutation), which occurs in up to 5% of the normal population and which is now recognized as the most frequent explanation of familial thromboembolism [19]. In view of the complexity of the thrombin–plasmin systems, it would not be surprising if many more such genetic abnormalities promoting venous thrombosis were found in the future.

Coagulation factors are also altered in a wide range of disease states, for example as an acute-phase response and in malignant disease. In disseminated lupus erythematosus, chronic thrombocytopenic purpura and a number of other autoimmune diseases, an antiphospholipid antibody or 'lupus anticoagulant' may be found that paradoxically promotes clotting and is associated clinically with both venous and arterial thromboses [20].

Although venous thromboembolic disease may occur *de novo* as an apparently isolated phenomenon (and in these circumstances a primary or secondary thrombophilia should be suspected), the problem is usually multifactorial, particularly in hospital populations where it may be difficult to determine which of several contributory factors is predominant.

## Factors predisposing to thrombosis

### Immobilization

The formation of thrombus requires the local presence of activated clotting factors. With normal venous blood circulation these are not able to accumulate in sufficient quantities to initiate clot formation and are dispersed and cleared by the liver, their activity also being balanced by that of the fibrinolytic system. However, local venous stasis in the presence of activated clotting factors has been shown experimentally to result in the production of fibrin with thrombus formation.

Immobilization results in diminished muscle activity in the legs, which in turn reduces the rate of venous return [21] and increases the chance of deep venous thrombosis in both healthy individuals [22] and patients [23], the risk increasing in proportion to the duration of immobility [24]. Any local factors that immobilize leg muscles, such as the wearing of a plaster splint or muscular paralysis, increase the likelihood of thrombosis [25].

### Trauma

Both surgical and accidental trauma predispose strongly towards venous thromboembolism by the liberation of activated clotting factors and by the immobility that may result from the injury. An early analysis of thromboembolic deaths in accidental trauma cases found that femoral and tibial fractures were associated with the highest post-mortem incidence of pulmonary embolism, followed by pelvic, spinal and other fractures in diminishing order of frequency [26]. Severe burns also carry an increased risk of pulmonary embolism [2,26]. A more recent study of victims of major trauma has shown that venographic evidence of deep vein thrombosis occurred in 58% of patients; in 18% these thromboses were in the potentially dangerous proximal veins. The risk was greatest in injuries of leg and spine, and was increased by old age, need for blood transfusion and surgery [27].

Pulmonary embolism may account for about 15% of all postoperative deaths [28], leg amputations and hip, pelvic and spinal surgery having a relatively high incidence of venous thromboembolism [29,30]. Postoperative death after routine elective surgery, such as herniorrhaphy, cholecystectomy and hysterectomy, is most commonly caused by pulmonary embolism [31]. The type of operation used to achieve the same objective may also have an important influence on the likelihood of thromboembolic complications. Thus transurethral resection of the prostate and vaginal hysterectomy are both associated with a much lower risk of leg vein thrombosis than the same procedures carried out retropubically and abdominally [32].

The association of trauma with thrombosis is related

only in part to immobilization, since changes in coagulability also occur, with rises in factor VIII and fibrinogen, thrombocytosis and a reduction in fibrinolysis.

### Heart disease

Heart disease is a major risk factor in the genesis of venous thromboembolic disease in hospital, pulmonary embolism being over three times more common in patients aged 30 years and over dying of heart disease than an age-matched control group without heart disease or cancer [33]. This trend occurs irrespective of the aetiology of the heart disease, congestive failure and dysrhythmias being important contributory factors [34]. The majority of emboli arise in the veins of the legs rather than in the heart itself, probably as a consequence of reduced peripheral venous flow [2,35], although acute-phase increases in factor VIII, fibrinogen and antifibrinolysis occur after myocardial infarction.

### Malignant disease

Thrombophlebitis migrans was associated with gastrointestinal tract carcinoma over 125 years ago by Trousseau [36,37]. Since then many abnormalities of haemostasis have been demonstrated in patients with a wide range of cancers and different mechanisms appear to operate in different patients, including reactive increases in fibrinogen and expression by tumour cells of tissue factor and factor X. Not all neoplasms are associated with venous thrombosis; of those that are, pancreatic carcinoma is the most notable, followed in descending order of frequency by carcinomas of the bronchus, genitourinary tract, colon, stomach and breast [2]. The occurrence of venous thrombosis without obvious cause, especially if recurrent, should raise the possibility of a latent tumour.

### Pregnancy and the puerperium

Venous thromboembolic disease occurs more frequently in pregnancy and the puerperium than in age-matched non-pregnant controls and is the leading cause of maternal mortality in the UK. The reported incidence varies widely, from 1 in 200 [38,39] to 1 in 1400 deliveries, the latter figure being taken from a review of over 72 000 deliveries [40]. Thromboembolic events are more frequent in older multiparous women in the last trimester and puerperium (>35 yrs), and the incidence is further increased by Caesarian section [41]. Although fatal events are rare, occurring at a rate of 1–2 per 100 000 pregnancies [42], they have nevertheless been considered a major cause of maternal death [43,44]. The mechanisms for these observations include reduced venous return from the legs, which may result from direct pressure of the gravid uterus on pelvic veins, decrease in fibrinolytic activity and

increase in the levels of certain clotting factors [41,45,46], the act of parturition itself serving to trigger thrombus formation. However, it is now clear that hereditary thrombophilias are important in determining which women develop thrombotic disease during pregnancy and while on oral contraception [41,47,48].

### Oestrogen therapy

It is something of a paradox that oestrogen seems to be responsible for protecting women from thrombotic episodes as a result of increased fibrinolysis [49] yet oestrogen-containing oral contraceptives have been shown to increase the chance of venous thromboembolic disease significantly in otherwise healthy women. The increase in risk is proportional to the oestrogen content of the preparation and has been much reduced by the introduction of modern low-oestrogen pills, to the point that it is now generally accepted that the health benefits of oral contraceptive use outweigh the risks [50,51]. There is also evidence that risks are increased among women taking postmenopausal hormone replacement therapy. The relative risks appear to be increased about threefold, although the absolute risks are small, about 20–30/100 000 per annum [52–54], and in most cases are outweighed by the advantages of the therapy. Increased risks of thromboembolism are attached to the use of high-dose oestrogens, such as used in the treatment of carcinoma of the prostate [55]. The mechanism of thrombogenesis is unclear but depression of antithrombin III levels has been reported [56]. It is likely also that hereditary or acquired thrombophilic states, particularly the common factor V Leiden mutation, are important determinants of development of disease when taking oestrogen preparations [57,58].

### Other factors

Numerous other disorders have been claimed to carry an increased risk of thromboembolism. These include obesity [9], chronic bronchitis and emphysema [59], ulcerative colitis [33], diabetes mellitus [2], Cushing's syndrome [60], Behçet's syndrome [61], homocystinuria [62], polycythaemia rubra vera [63], essential and postsplenectomy thrombocythaemia [64,65], paroxysmal nocturnal haemoglobinuria [66] and Gram-negative sepsis [60]. Sickle cell disease also predisposes to pulmonary infarction and is discussed further in Chapter 53.

### Thrombogenesis and pulmonary embolism

Over 75% of pulmonary emboli originate from the veins of the lower extremities [67], probably arising as a result of the aggregation of small numbers of platelets usually in the vicinity of the venous valve sinuses. The release of



activated clotting factors may then result in a 'coagulation cascade', with the formation of red thrombus. This is normally removed by fibrinolysis or fixed by a combination of fibrinolysis and organization, the former process diminishing the bulk of the thrombus and permitting residual clot to be incorporated into the wall of the vein by an overgrowth of endothelium, which restores intimal continuity at the expense of producing incompetence of any venous valves that might be involved. The organization of established thrombus is thought to occur quickly, the process being completed within 7–10 days in a dog model [68]. In contrast to their arterial counterparts, venous thrombi occur more usually in the absence of any damage to the vessel wall, stasis being the most important initiating factor; however, there are exceptions to this rule, such as the trauma to the femoral vein that may occur during hip surgery.

Evidence exists to suggest that 60% of deep venous thromboses found at postmortem examination are associated with pulmonary emboli [24]. It would also appear that whereas thrombus may originate around a venous valve, propagation of clot occurs both proximally and to a lesser extent distally. The most common vessels of origin appear to be the plantar, common femoral and superficial femoral veins. Deep venous thrombi that propagate proximally tend to remain attached at their point of origin within the valve sinus but may contain a friable floating segment, consisting of red cells and platelets enmeshed in fibrin, that is liable to form an embolus by separating from its parent thrombus [69]. The length of such an embolus may vary greatly, from only a few millimetres to a coil of several centimetres that may be retrieved from the pulmonary artery in the necropsy room. When deep venous thrombosis is extensive, it is found to be bilateral in 80% of cases [24]. The majority of thromboses that present a serious threat to life detach themselves from the larger veins between the knee and the inguinal ligament [70]. Patients with thrombosis affecting the superficial veins of the leg (superficial thrombophlebitis) are not ordinarily considered to be at risk of pulmonary embolism from these veins [71] nor, curiously, are patients with axillary or subclavian vein thrombosis [70].

A small proportion of pulmonary emboli may arise in the pelvic veins, including the prostatic venous plexus in men, and also from the right side of the heart, both following myocardial infarction and in right ventricular failure due to a variety of causes [72]. Septic pulmonary emboli may arise from bacterial endocarditis in patients with septal defects, from the tricuspid valve in drug abusers, and from foreign material such as central venous lines, ventriculoatrial and arteriovenous shunts and pacemaker wires [73]. Such emboli present as recurrent febrile illness associated with patchy pneumonic shadows on chest radiography (Fig. 15.1), and are often misdiagnosed as pneumonia if the significance of the cardiac lesion is missed.

## Non-thrombotic pulmonary emboli

Material of extravascular origin may occasionally cause pulmonary emboli, although this is a relatively uncommon occurrence except in certain well-recognized situations [74].

*Fat embolism* is probably a common subclinical event following bony trauma [75,76]. Evidence of fat embolism was found in 39% of a group of 79 patients who died during the Korean War as a result of wounds and was considered to be a major cause of death in 10. Similarly, orthopaedic procedures involving the long bones risk displacing marrow fat into the circulation, and study of such patients by transoesophageal echocardiography has shown emboli passing through the heart in a high proportion [77]. In such circumstances complex pathological consequences may occur, including systemic embolization through a patent foramen ovale and activation of the clotting cascade with disseminated intravascular coagulation. Operations involving reaming of pathological lesions and cementing of hip arthroplasties seem to be those most likely to cause problems. Some series report clinically significant fat embolism in as few as 1–2% of long bone fractures, and in rather less than 1% of intramedullary operations [78], while others record up to 20% in cases of tibial and femoral fractures [79]. It seems likely that the syndrome may be detected very commonly in a mild form by those who look for it after appropriate trauma. Fat embolism is also a recognized complication of sickle cell disease and occurs as a consequence of bone infarctions [80].

Following such trauma, neutral fat may pass into the circulation from injured long bones, be carried to the lungs and become lodged in the pulmonary vasculature. Such neutral fat may be relatively innocuous [81], but hydrolysis to fatty acids is thought to result in local haemorrhagic tissue damage and pulmonary oedema. There may be a latent period of between a few hours and several days from the time of bony trauma to the onset of symptoms, and this may represent the time taken for the pulmonary injury to develop. In severe cases the patient presents with dyspnoea, hypoxaemia and hypotension; petechial haemorrhages, characteristically around the upper trunk and in the axillae, are a frequent accompaniment. The radiograph is often normal in spite of the dyspnoea, although evidence of adult respiratory distress syndrome may develop. Hypocalcaemia and anaemia may also occur. More rapid hypotension and death due to right ventricular failure have been described, possibly as a result of the mechanical obstruction of the pulmonary vasculature by a large volume of fat. The diagnosis is made on clinical grounds, and demonstration of fat in macrophages derived from bronchoalveolar lavage is no longer thought to be sufficiently specific to be worth doing [82]. There is no specific treatment and management is supportive.

Mechanical ventilation may be required. The subject of fat embolism has been reviewed in the orthopaedic literature [83].

*Tumour emboli*, which are usually microscopic, have been found in 2.4% of over 1000 necropsies carried out in patients dying as the result of solid malignant tumours [84]. A few of these subjects had been breathless in the absence of obvious lung parenchymal metastases. The condition may simulate thrombotic pulmonary embolism, particularly when larger pulmonary vessels are occluded by macroscopic emboli, but it differs in its lack of responsiveness to anticoagulation [85]. Tumours that have been implicated most frequently include carcinoma of the breast, stomach, colon and cervix, hepatomas, choriocarcinomas and hypernephromas.

*Air embolism* may be the result of faulty cannulation of the neck veins, therapeutic insufflation of air into a fallopian tube or intrauterine manipulations, including criminal abortion, in which a frothy solution may be introduced into the uterus under pressure. Small amounts of air are reabsorbed without harm but large amounts can cause mechanical obstruction of the pulmonary circulation and death. The subject of air embolism in diving is discussed in Chapter 57.

*Amniotic fluid embolism* is a rare but very serious complication of pregnancy [86,87]. It usually arises during labour or Caesarian section, but is not predictable or recognized as occurring because of any particular mishap. It causes respiratory distress with pulmonary oedema and shock. Maternal and fetal mortality have both been reported at 60%. It has been suggested that plasma zinc coproporphyrin concentrations in maternal plasma greater than 35 nmol/L indicate amniotic fluid in the blood [88]. Treatment is supportive, with ventilation if necessary to maintain  $P_{aO_2}$ .

## Pathophysiological response to pulmonary embolism

Pulmonary embolism results in the sudden obstruction of part of the pulmonary circulation and the pathophysiological response to this depends upon (i) the degree of reduction in the cross-sectional area of the pulmonary arterial tree, determined by the size and number of emboli, and (ii) the state of health of the myocardium and pulmonary parenchyma before the embolus [89].

### Cardiovascular effects

The mechanical obliteration of a part of the pulmonary arterial tree may be made worse by the release of vasoconstrictor substances such as serotonin from platelets contained within the embolus itself [90,91]. Although this loss of vasculature tends to increase pulmonary arterial resistance, the capacitance of the pulmonary circulation is such

that mean pulmonary pressure does not increase in the previously healthy lung until about 50% of the vascular bed is shut down [70]. Once this point is reached, the afterload on the right ventricle starts to increase and with it right ventricular end-diastolic pressure. If the mean pulmonary artery pressure exceeds 40 mmHg, which is the pressure required to maintain perfusion despite the loss of about three-quarters of the pulmonary vascular bed, then even a healthy right ventricle will fail. This produces a decline in pulmonary blood flow and in turn reduced filling of the left ventricle, which is no longer able to maintain a normal systolic blood pressure. This sequence of events occurs more readily in patients with pre-existing cardiopulmonary impairment [92] but otherwise only becomes evident if the pulmonary emboli are large or recurrent.

### Respiratory effects

Pulmonary embolism produces mismatching of ventilation and perfusion by preventing blood in the pulmonary artery from reaching the ventilated lung (increased alveolar dead space) and, paradoxically but perhaps more importantly, by interfering with the ventilation of lung that is still perfused (increased intrapulmonary shunting) [93]. This shunting results from (i) bronchoconstriction, (ii) alveolar collapse and (iii) pulmonary oedema. Various stimuli may produce bronchoconstriction following pulmonary embolism, the most important of which include alveolar hypocapnia arising in ventilated but unperfused lung [94] and the release of chemical mediators from platelets enmeshed in the embolus itself or from the surrounding lung. Alveolar collapse is due to loss of surfactant, which becomes deficient within a short time of embolism, causing alveolar instability. This in turn may result in those areas of atelectasis of sufficient size to be radiographically detectable (see below), and which may be haemorrhagic due to increased alveolocapillary permeability [95]. This increased membrane permeability may also result in a more widespread 'leaky lung', with consequent pulmonary oedema [70]. It is not surprising that the foregoing disturbances of cardiopulmonary physiology may combine to produce significant systemic arterial hypoxaemia in the presence of a large pulmonary embolus.

### Pulmonary infarction

Otherwise healthy lung tissue usually remains viable despite the interruption of the pulmonary arterial blood supply by embolism and pulmonary infarction is uncommon in such cases [96]. This is because the lung receives adequate oxygenation via the bronchial arteries and to a lesser extent the airways, and because an occluding embolus seldom completely obliterates the vessel

lumen [70]. When it does occur, infarction is more likely to be found with peripheral rather than central occlusions [96].

### Embolus resolution

It is common for large pulmonary emboli to fragment within a short time of impaction, and this may explain those cases in which profound hypotension and syncope occur but are of short duration [97]. As with venous thromboses, further dissolution of the embolus occurs within a short time as a result of fibrinolysis. There is evidence to suggest that when the embolus is composed of freshly formed thrombus dissolution may occur within a few days, whereas emboli formed from older thrombus may become organized into the pulmonary artery wall over a matter of weeks [70]. These mechanisms appear to be remarkably effective in restoring the patency of the pulmonary arterial tree to normal, provided that repeated emboli do not occur [98].

## Clinical features

### Deep venous thrombosis

A consideration of the clinical features and diagnosis of deep venous thrombosis in the legs is inseparably bound up with the subject of pulmonary embolism, as at least 75% of pulmonary emboli have their origin in the lower limb veins [67].

### Value of symptoms and signs

The symptoms and signs of deep venous thrombosis depend on inflammation of the vessel wall producing local pain, redness and heat (dolor, rubor and calor) and venous obstruction producing oedema. In fewer than 1% of cases of symptomatic deep venous thrombosis the leg suddenly becomes grossly swollen and tense both above and below the knee, and in this situation bedside diagnosis is likely to be accurate [99]. Unfortunately, however, in the large majority of cases the symptoms and signs are not so obvious and are non-specific to the point of being misleading. Diagnostic dilemmas arise because oedema and swelling may be associated with a paralysed limb or with heart failure, and pain (sometimes with swelling) may be produced by local trauma, muscular strain, calf haematoma, cellulitis, lymphangitis or a ruptured Baker's cyst, and may even occur after muscular cramps [100]. Despite the repeated observation, based on venography, that clinical judgement in the diagnosis of deep venous thrombosis is incorrect in about 50% of suspected cases [101], the results of a survey in 1982 showed that almost half of responding consultant physicians in Scotland relied only on physical signs in reaching the diagnosis

[102]. Furthermore, extensive involvement of the femoral vein by thrombosis may be present in the absence of any symptoms or signs since, provided that the superficial venous system and lymphatics are competent, oedema need not occur unless thrombus extends as far as the saphenofemoral venous junction. This accords with the frequent absence of bedside signs of venous thrombosis in patients with pulmonary embolism. In spite of this generally pessimistic view of the likelihood of making a clinical diagnosis, the odds of being right may be improved by considering a number of major and minor factors in order to arrive at a probability score [103]. On the aetiological side, major factors are active cancer, paralysis or immobilization of a leg, more than 3 days in bed or major surgery within 4 weeks, and a strong family history of venous thrombosis; major signs are tenderness over the leg veins and swelling of calf and thigh, or more than 3-cm swelling of calf. Minor evidence includes recent trauma, oedema, dilated veins and erythema of the symptomatic leg. The suggested method of clinical assessment is shown in Table 25.1, which is derived from Wells *et al.* [103].

Once made on clinical grounds, the diagnosis of deep venous thrombosis is rarely rejected in the absence of venography or other diagnostic tests. Because clinical diagnosis alone has a high false-positive rate, failure to

**Table 25.1** Clinical method for predicting probability of deep venous thrombosis.

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#### Checklist

##### Major points

- Active cancer
- Paralysis or plaster lower limb immobilization
- Recently in bed >3 days or major operation within 4 weeks
- Localized tenderness along distribution of deep leg veins
- Both thigh and calf swollen
- Calf swelling >3 cm asymptomatic side, 10 cm below tibial tuberosity
- Family history of deep venous thrombosis in two or more first-degree relatives

##### Minor points

- History of trauma to symptomatic leg within 60 days
- Pitting oedema in symptomatic leg
- Dilated superficial veins in symptomatic leg (not varicose)
- Hospitalization in last 6 months

#### Clinical probability

##### High

- Three or more major points and no alternative diagnosis
- Two or more major, two or more minor and no alternative diagnosis

##### Low

- One major, two or more minor plus alternative diagnosis
- One major, one or more minor plus no alternative diagnosis
- Three or more minor plus alternative diagnosis
- Two or more minor plus no alternative diagnosis

##### Moderate

- All other combinations
-

make proper use of ancillary diagnostic tests commits large numbers of patients to the potential hazards of prolonged anticoagulation and to the social and financial disruption of an unnecessarily prolonged treatment period [104]. It is therefore desirable to have a strategy for further investigation if the condition is suspected. The tests available are venography, impedance plethysmography and ultrasound.

Venography is generally taken as the gold standard but is less comfortable for the patient. When the injection is made in the foot veins, it can show the entire deep venous system of the leg. Demonstration of pelvic veins depends on the now rarely used bilateral femoral intratrochanteric injection method, which usually is done under anaesthetic. Impedance plethysmography and Doppler ultrasound methods, although based on different physical principles, both depend upon venous outflow from the leg being obstructed by extensive venous thrombosis. Both make use of an additional artificial obstruction to venous outflow by the application of either an inflatable cuff or manual compression. This produces pooling of blood in the leg veins, and when the obstruction is suddenly released the speed with which pooled blood leaves the leg is slowed by the presence of thrombus in veins in the thigh and above.

### Venography

Ascending venography as described by Rabinov and Paulin [105] is the accepted reference standard in the diagnosis of deep venous thrombosis [106] and its use has increased with the growing awareness of the unreliability of diagnosis based on history and physical examination alone. The technique requires the injection of a radio-opaque contrast medium into a vein, usually on the dorsum of the foot, under fluoroscopic vision (Fig. 25.1). It has the advantage of visually demonstrating thrombus in a vein. It has the disadvantage of being an invasive test that may be painful and in a small percentage of patients is associated with systemic reactions to the contrast medium [107]. Local reactions may occur as a result of extravasation of contrast into subcutaneous tissues and endothelial damage may lead to superficial thrombophlebitis and even deep venous thrombosis in a few patients in whom the venogram was previously normal [107]. This investigation requires a high degree of technical and interpretative skill is required in order to obtain an adequate result. In less experienced hands, artefacts produced by non-opacified blood flowing from a small vein into a larger opacified vessel may be misinterpreted as thrombus. An intraluminal filling defect that remains constant on different projections and during a Valsalva manoeuvre is regarded as positive proof of thrombus. The failure of a segment of the deep venous system to fill properly is suggestive of thrombosis but may be artefactual, in which

case a false-positive diagnosis of deep venous thrombosis may be made. The various disadvantages of this test have to be set against the risks of unnecessary anticoagulation in large numbers of patients [108].

### Impedance plethysmography

This test is based on the physical principle that changes in blood volume in the calf result in changes in electrical impedance (resistance) to the passage of a known current across the calf muscles. These changes in blood volume and therefore in impedance are reduced by the presence of thrombus in the popliteal vein and in veins proximal to it [109].

The patient lies supine with the leg elevated to about 25° and the knee slightly flexed. An occlusive pneumatic cuff 15 cm wide is applied to mid-thigh and inflated to a pressure of 45 mmHg for 2 min. The original method made use of a maximum respiratory effort to produce flow changes [110] but this technique is unreliable and has been superseded by the occlusive cuff method. Changes in electrical impedance are detected by circumferential calf electrodes and recorded electronically. Sequential readings are made in order to achieve maximal venous filling. The change in impedance during cuff inflation (reflecting venous capacitance) is plotted along the horizontal axis of a graph, and the change in impedance during the first 3 s after cuff deflation (indicating venous outflow) is plotted on the vertical axis. The intersection point of the two readings on the graph is read as normal or abnormal according to whether it falls above or below a straight line obtained from testing large numbers of patients with normal venograms [109,111].

This test is non-invasive and easy to apply being a safe alternative to venography [112]. It is sensitive to obstruction above the knee, which is the site from which most emboli break off, although less so than compression ultra-sound. It is insensitive to calf thrombi that produce relatively little venous obstruction, and this may produce false-negative results. False positives are uncommon but may be produced by incorrect positioning or by isometric muscle contraction, which can result in venous constriction in anxious patients but which may be detected by the incorporation of an electromyography electrode into the recording device. Further false-positive values may be produced as a result of venous compression by an extravascular mass, in congestive cardiac failure and in severe arteriosclerosis affecting the legs.

### Compression Doppler ultrasound

This test uses the physical principle of the apparent change in frequency (pitch) of a source of sound when it is moving relative to a stationary observer (Doppler effect).



**Fig. 25.1** Contrast venography showing finger of thrombus extending up femoral vein. (Courtesy of Dr Lesley Gomersal.)

In practice the 'source' of ultrasound is an electrical oscillator and a piezoelectric crystal contained in a hand-held probe. The 'moving object' is the column of blood cells contained in the vein over which the probe is held. The 'stationary observer' is a second piezoelectric crystal, also contained in the probe, that receives a reflected beam of ultrasound. If the column of blood is stationary, then the apparent frequency of the reflected beam equals that of the incident beam and no signal is recorded. However, movement of the column of blood results in the ultrasound beam being reflected at an apparently different frequency, the change of which is proportional to the rate of flow of the blood. This difference in frequency may be amplified to produce an audible signal [113].

The test is performed with the patient in a semi-recumbent position and free from the compressive effects

of corsetry. When the probe is placed over the femoral artery and moved medially, a typical low-pitched flow sound is produced by blood in the femoral vein. Normally the pitch of the sound varies cyclically with respiration but obstruction to venous flow above this level may abolish this cyclical variation. Manual compression of the vein proximal to the probe also reduces the signal, which in normal subjects is briefly augmented and then restored when the compression is suddenly released, whereas in proximal venous obstruction this augmentation may be reduced or abolished. Similarly, squeezing of the calf or thigh muscles may also produce augmentation of the flow signal in normal subjects, whereas this does not occur in those with venous thrombosis that significantly reduces flow rates. The patency of the superficial femoral vein may be examined by following its course with the probe, with

alternate use of proximal muscle compression with sudden release and distal muscle squeezing. The popliteal vein may be studied by compression and sudden release of the thigh muscles and by squeezing the calf, and the posterior tibial vein by compression and release of the calf and by squeezing the foot.

Although Doppler ultrasound depends heavily on the experience of the observer, technical advances and increased availability have made it the preferred non-invasive modality for symptomatic deep venous thrombosis, with greater overall sensitivity than impedance plethysmography. It is sensitive to proximal thrombosis in the popliteal veins and above, but suffers the same deficiencies with regard to the detection of calf vein thromboses [114], although these may be better displayed with the use of colour Doppler [115].

### Other tests

The radioactive fibrinogen test depends upon  $^{125}\text{I}$ -labelled fibrinogen being incorporated into actively forming thrombus so that it can be detected using a surface counter. It has been a useful research tool in objectively determining by serial measurements the frequency with which venous thrombosis occurs in high-risk groups such as surgical patients, and used in this way it may detect approximately 90% of acute calf vein thrombi.

The test is carried out by injecting 4 mBq of labelled fibrinogen into an arm vein; 100 mg of sodium iodide may be given intravenously 30 min beforehand to block the uptake of radioactivity by the thyroid. Recordings may be made at the bedside from 2 h to about 1 week after injection, the leg being elevated  $15^\circ$  above the horizontal to prevent calf vein pooling. The portable rate meter gain is adjusted to read 100% over the heart, and recordings are then made at 8-cm intervals down the course of the femoral vein in the thigh and from the popliteal fossa down the posterior aspect of the calf. The presence of uptake is indicated by a repeatable 20% or more difference in readings between adjacent points on the same leg or between corresponding points on the opposite leg. An experienced operator takes less than 15 min to carry out the examination.

The major disadvantage of this test is that patients in whom the diagnosis of deep venous thrombosis is suspected clinically may already have well-established thrombus, in which the radioactive fibrinogen becomes incorporated only very slowly so that positive readings may take 24–72 h to achieve or may not occur at all if anticoagulation has been started. A further problem is the unreliability of fibrinogen scanning over the upper thigh and pelvis due to high counts from pelvic vessels and the bladder, although this drawback is offset by the general belief that pelvic and upper thigh vein thrombosis is unusual in the absence of calf vein thrombosis [32]. The

radioactive fibrinogen uptake test is contraindicated in pregnancy and during lactation and it has to be remembered that its prior use invalidates a lung scan should this also be required. False-positive results may occur in the presence of local trauma, inflammation or haematoma formation.

Various blood tests have been used to detect recently formed thrombus and these include the detection and measurement of fibrinogen degradation products [116] and the measurement of D-dimer, the split product of fibrin [117]. The former test lacks sufficient sensitivity and specificity to be routinely applicable, but the latter has shown some promise as a quick test in order to screen out suspected venous thrombo-embolic disease (see p. 730) [118, 119].

### Diagnostic strategy

A patient with a leg that becomes suddenly and uniformly swollen and tense from top to bottom has a deep venous thrombosis and can be treated as such without more ado. Relatively few patients fall into this category and the diagnostic pathway followed depends to a large extent on the facilities and expertise available locally. Investigations should not be contemplated unless there are leg signs or unless pulmonary embolism is suspected. The clinical suspicion may be graded as high, medium or low based on the features mentioned above [103]. In any case a non-invasive test should be carried out, and increasing confidence can now be placed in the use of ultrasonography, which has been shown to be both more sensitive and more specific than impedance plethysmography in the detection of the dangerous proximal thromboses [120]. If this is positive in the presence of clinical evidence, treatment should proceed. If it is negative despite strong clinical suspicion, contrast venography should be carried out as this demonstrates the calf veins as well as those more proximal. In experienced hands venography is efficient in diagnosing or excluding deep venous thrombosis and can be used as a front-line test [121], if the extra inconvenience and slight risk of side-effects are acceptable. In cases where clinical suspicion is low, there is no evidence of pulmonary embolism and ultrasound is negative, it is reasonable to withhold or discontinue anticoagulation. Since the objective of seeking deep venous thromboses is to prevent pulmonary emboli, if suspicion remains after a negative ultrasound scan a reasonable strategy is to withhold anticoagulants but to repeat the scan after 1 week to ensure that any undetected calf vein thrombosis has not spread into the popliteal or femoral veins whence the risk of embolization is high. This strategy has been shown to be effective in preventing embolism and to be cost-effective [122, 123]. A suggested diagnostic pathway is illustrated in Fig. 25.2. It will be noted that this scheme recommends venography if the point score indicates 'low risk' but the

ultrasound is abnormal, as it was found that venography showed the ultrasound false-positive rate to be substantial (37%) in this group [123].

## Pulmonary embolism

### Clinical presentation

Pulmonary embolism may present in many guises, sometimes with catastrophic and fatal suddenness and sometimes with gradually worsening breathlessness, so that the precise timing of the onset of the illness cannot be recalled.

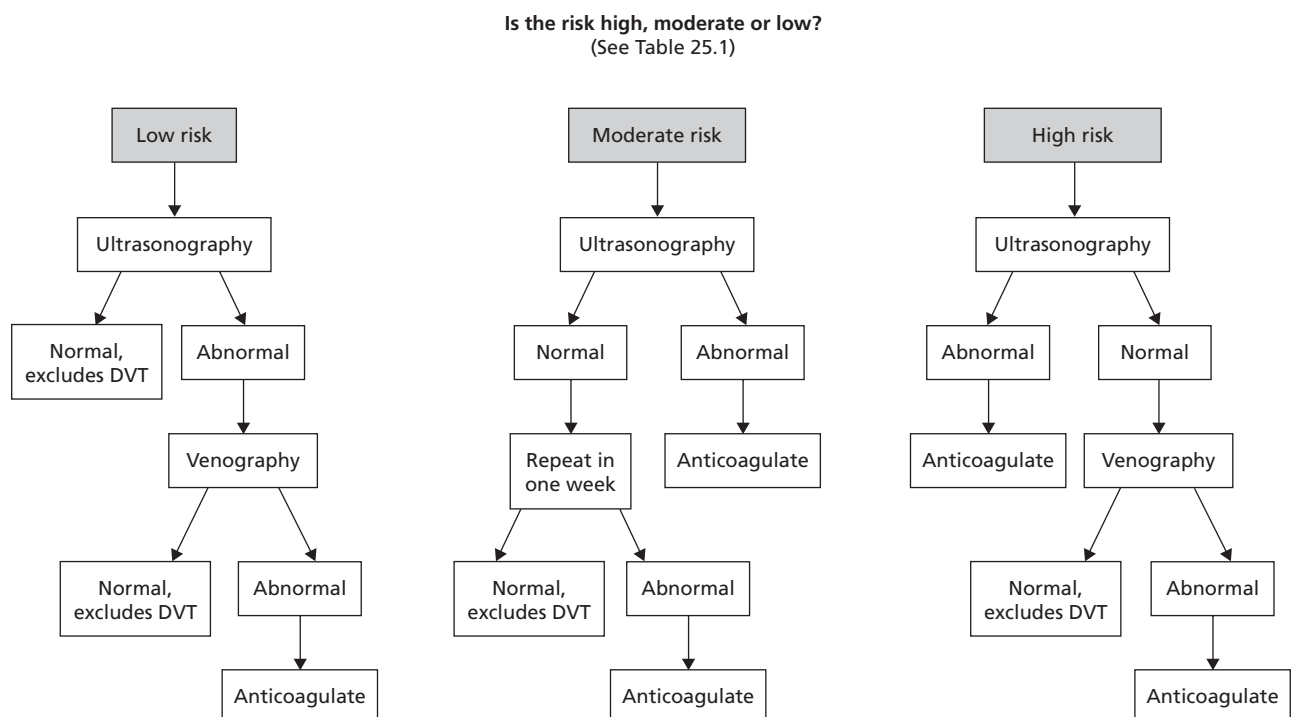
Massive pulmonary embolism occurs classically a week or more postoperatively or following some other period of immobilization. It may be immediately preceded by straining, such as during defecation, or by other minor physical exertion, such as that involved in getting out of bed or even laughing. When death occurs suddenly, it is likely to result from the profound hypotension associated with an abrupt cessation of pulmonary venous return to the left side of the heart. Those episodes in which syncope is followed by recovery of consciousness may be regarded as 'near misses', a major embolus fragmenting and passing away from the main pulmonary outflow tract

into more peripheral lung vasculature and allowing the re-establishment of sufficient left ventricular filling to prevent immediate death. These patients are dyspnoeic, restless, anxious, confused and cyanosed, with hypotension and tachycardia. Central chest pain as a result of reduced coronary artery perfusion may also occur.

Many patients with pulmonary emboli present in a more insidious manner, their symptoms resulting from smaller often recurrent emboli. Breathlessness is the most common symptom in this group and it may be incorrectly attributed to heart failure, emphysema or even to emotional instability. Supporting symptoms, such as cough, haemoptysis and pleuritic pain, may be absent, although when present may be wrongly ascribed to bacterial infection with pleurisy. Dyspnoea and pleuritic chest pain were the most common symptoms in an angiographically documented series of over 300 patients [34]. None of these symptoms are specific and the diagnosis should be considered in any patient in whom the level of breathlessness does not appear to be explained satisfactorily by coexisting disease. Suspicion should mount in the presence of supporting symptoms and when the patient is at increased risk, whether because of recent surgery, immobility or those other predisposing factors previously discussed.

Physical examination may reveal varying degrees of breathlessness with tachypnoea. Inspiration may be seen to produce pain due to pleuritic involvement and the patient is usually able to help the physician localize the site of this pain accurately. A pleural rub is often heard at

Fig. 25.2 Deep venous thrombosis: diagnostic pathway. (After Wells *et al.* [123].)





this point, if not during tidal breathing then on deeper inspiration, the effort of which may make the patient wince. With large emboli, tachycardia and a gallop rhythm are usual. Breathlessness is present both lying and sitting but is associated with no auscultatory signs in the lung, a most important negative feature. Jugular venous engorgement is usual but an accentuated pulmonary component of the second heart sound depends on the degree of pulmonary hypertension produced and whether the right ventricle can maintain its output against increased resistance. Occasionally wheeze may be heard as a result of secondary bronchoconstriction [124]. Pyrexia may be present and is very occasionally the dominant finding until anticoagulation is commenced. The syndrome of multiple pulmonary emboli leading to cor pulmonale is discussed in Chapter 26.

Although pulmonary emboli usually arise from the deep venous system in the legs, clinical signs of deep venous thrombosis are obvious in fewer than one-third of patients [124].

### Diagnostic confirmation

In most patients treated for pulmonary embolism it is evident that the diagnosis has been based on clinical suspicion in a patient sufficiently ill to merit anticoagulation while investigations are undertaken to substantiate the diagnosis. The order in which investigations are carried out is bound to depend upon their availability in the hospital but also on the circumstances of presentation and admission. It is usual for less definitive tests to be carried out first because they provide useful information, albeit of a negative nature, in excluding other possible diagnoses and in monitoring the patient's cardiopulmonary function. Furthermore, they are readily available to the admitting doctor and are relatively inexpensive.

### Electrocardiography and echocardiography

The ECG is usually abnormal in massive pulmonary embolism, but much less frequently in other circumstances [125]. There is often sinus tachycardia. Atrial fibrillation may occur, as may a bundle branch block, usually right. The limb leads occasionally show the much-quoted S1Q3T3 pattern and, most helpfully, T-wave inversion may be found in the anterior chest leads implying right ventricular strain. This change implies a large embolic event (Fig. 25.3). In severe cases, this pattern is associated with prolongation of the QRS complex, mimicking right bundle branch block. When the clinical features raise the suspicion of a pulmonary embolus but the ECG shows changes of a myocardial infarction, it should be remembered that it is not uncommon for the former condition to complicate the latter.

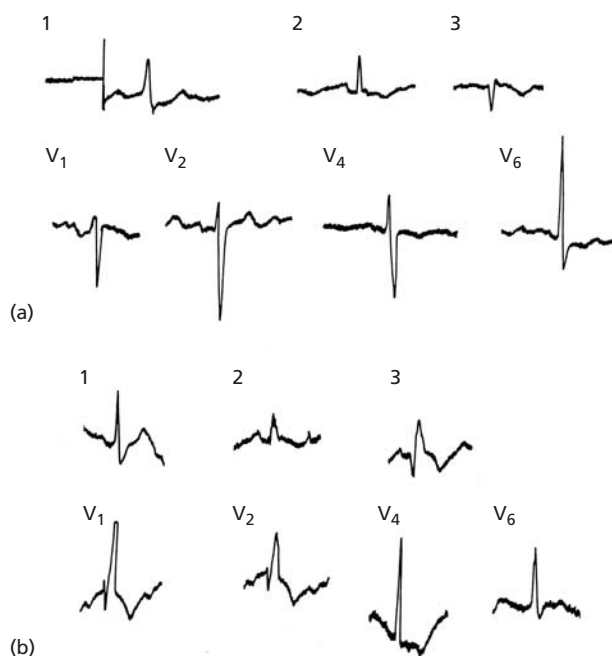
Echocardiographic findings may assist in the diagnosis

of major central pulmonary embolism, particularly when the cause of sudden hypotension and tachypnoea is unclear. In such cases it may show changes of acute right heart strain with ventricular hypokinesia and tricuspid regurgitation from which pulmonary artery pressure may be estimated [126].

### Chest radiography

It is often impossible to obtain good quality posteroanterior films in an ill patient, and the chest radiograph may simply serve to exclude other gross focal pulmonary pathology. When adequate technical results are achieved, the chest film in pulmonary embolism is frequently normal [127]. Paradoxically, this may be a most useful investigative finding in an acutely breathless patient in whom pulmonary embolism is suspected, since when coupled with consistent ventilation-perfusion lung scan findings and provided that there is no history of previous cardiopulmonary disease to account for them, the combination of a normal chest film and abnormal isotope scan is diagnostic of pulmonary embolism.

When the chest radiograph is abnormal, there are no findings that can be cited as pathognomonic of pulmonary embolism [128]. Non-specific infiltrates of virtually any configuration may occur and very few, if any, are wedge-shaped. These infiltrates, which need not be confined to the lower zone, usually abut a pleural surface and are dome-shaped (Fig. 25.4), although this need not be



**Fig. 25.3** ECG of patient with acute massive pulmonary embolus: (a) on admission, showing S1Q3T3; (b) following day, showing progression to right bundle branch block pattern with inverted T waves in anterior chest leads.

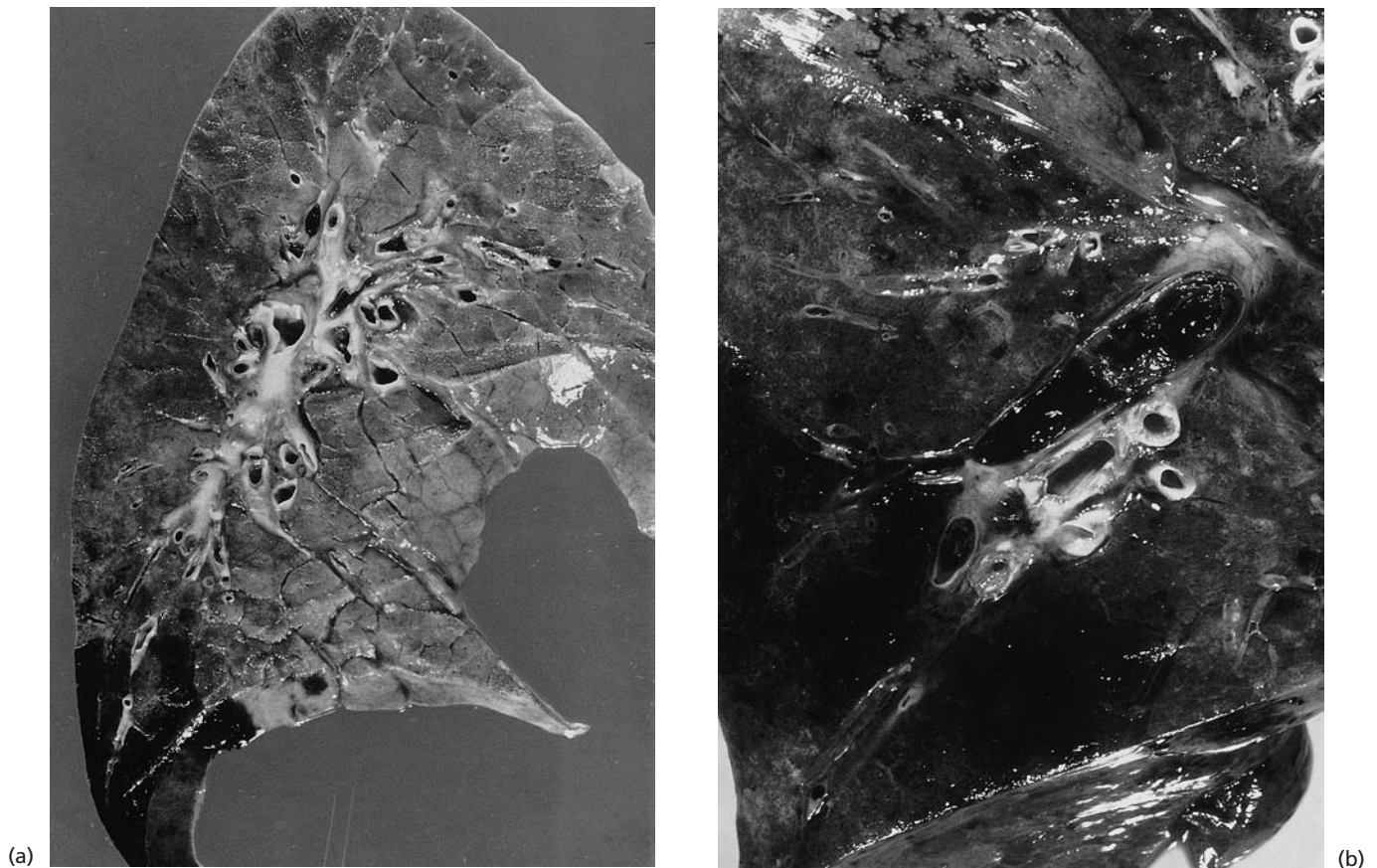
evident on a single projection. They probably represent areas of haemorrhagic atelectasis, hence their tendency to clear sometimes within a matter of a few hours. Those infiltrates in which true pulmonary infarction occurs are less likely to resolve radiographically and ultimately may be marked by a thin 'fibrotic' band shadow (Fig. 25.5). Elevation of a hemidiaphragm may occur with or without pulmonary infiltration and is indicative of ipsilateral volume loss. This is due to a combination of diminished pulmonary blood volume, localized bronchoconstriction and partial atelectasis. An avascular lung in association with consistent clinical features was described by Westermarck in Boston in the 1930s. It is an uncommon sign of massive embolism but is as close as the chest film gets to confirming the diagnosis when it occurs (Fig. 25.6). A pleural effusion, if present, is frequently haemorrhagic, although the cell and protein contents are too variable to be of any diagnostic assistance [129]. Other findings, such as an enlarged proximal pulmonary artery trunk or distal pulmonary oligoemia, are highly subjective and unreliable diagnostic signs.

### *Arterial blood gas analysis*

Arterial blood gases are of more therapeutic than diagnostic value in pulmonary embolism. While a reduced  $P_{aO_2}$  and  $P_{aCO_2}$  are characteristic, they are entirely non-specific findings. Furthermore, a normal  $P_{aO_2}$  does not exclude pulmonary embolism [124,130] and is not unusual in patients with no pre-existing cardiopulmonary disease. Pulmonary embolism cannot therefore be excluded on the basis of a normal arterial blood gas estimation, and earlier reports of the diagnostic usefulness of this test may mislead [131].

### *Plasma D-dimer and other blood tests*

Plasma D-dimer has been mentioned in relation to the diagnosis of venous thrombosis. Various ELISA assays are available as is a rapid bedside whole blood latex test which requires a visual reading with the potential for interobserver disagreement. The test has a low specificity with too many false positives to be diagnostically useful. False negative results are however unusual so the true high negative predictive value of the test may allow its



**Fig. 25.4** Postmortem lung of patient who had suffered major pulmonary embolism showing (a) infarcted lung inferiorly and (b) close-up of lower lobe artery occluded by thrombus, with infarcted lung below.



**Fig. 25.5** Chest film of patient with acute pulmonary embolism postoperatively showing bilateral band shadows.

incorporation into algorithms designed to exclude venous thromboembolism [118,119].

Other tests are mentioned largely to be dismissed, as individually they have no discriminatory value [34]. They include the presence of a leucocytosis and elevated erythrocyte sedimentation rate, plasma lactate dehydrogenase and bilirubin levels.

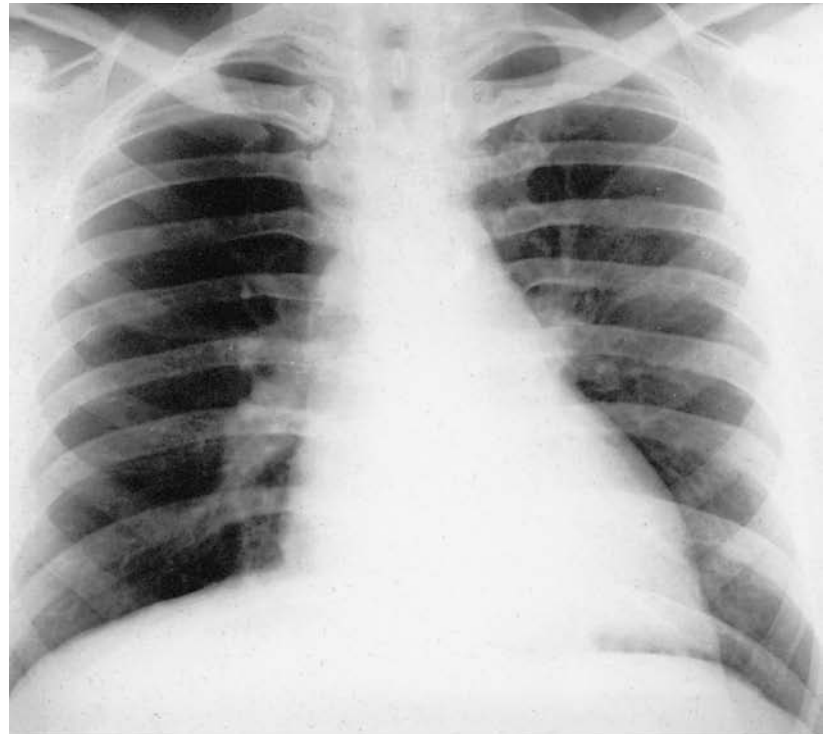
#### *Lung ventilation–perfusion ( $\dot{V}/\dot{Q}$ ) scans*

The  $\dot{V}/\dot{Q}$  lung scan remains the screening investigation of choice in most institutions for patients with suspected pulmonary embolism, although there is an increasing trend for the substitution of spiral CT. Lung perfusion scans are usually carried out using macroaggregates of human albumin that have been labelled with radioactive technetium-99m. A suspension of these particles (diameter 10–50  $\mu\text{m}$ ) is injected intravenously with the patient recumbent so that they behave as microemboli, becoming arrested in the pulmonary capillaries and precapillary arterioles. The ionizing radiation that they emit remains detectable for up to 2 h by means of a large-field gamma camera, from which scintigrams are produced that represent the distribution of pulmonary arterial perfusion. A normal scan shows a homogeneous distribution of activity throughout six views: anterior, posterior, left and right lateral and left and right posterior oblique (Fig. 25.7).

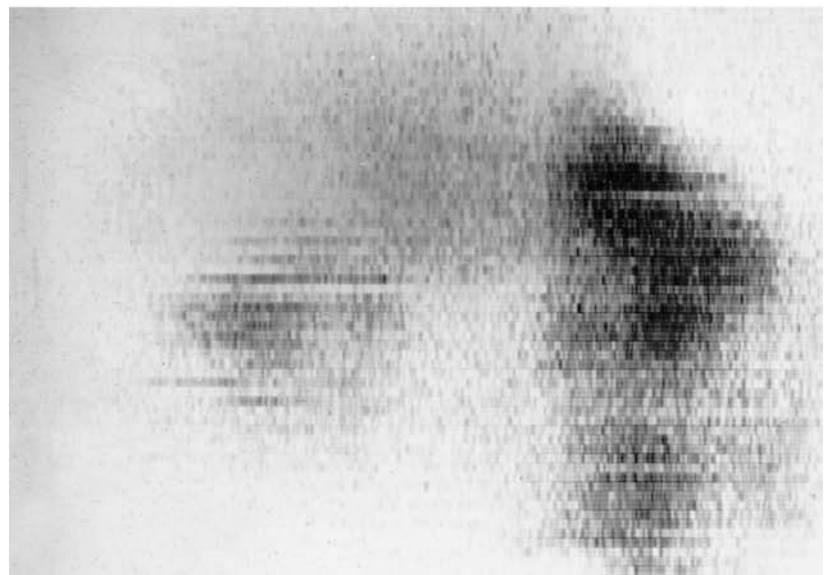
Lung perfusion scans are extremely sensitive in detecting blockage of vessels of diameter 3 mm and more, to such an extent that validated reports of angiographically detected pulmonary emboli in patients with normal per-

fusion scans are extremely rare [132,133]. A negative perfusion scan in a patient with suspected pulmonary embolism therefore virtually excludes this diagnosis. The most serious drawback of a positive perfusion scan is its lack of specificity [134], in that many common pulmonary disorders, such as pneumonia, asthma and emphysema, may produce perfusion defects that are indistinguishable from those seen in cases of pulmonary embolism. This is true to the extent that when a perfusion defect is seen that corresponds to a focal abnormality on the chest radiograph, then the result of the scan neither confirms nor excludes pulmonary embolism and must be regarded as indeterminate. For this reason it is common practice in most centres to also carry out a ventilation scan. Xenon-133 labelled air or technetium aerosols are often used for this although Krypton-81m is an alternative, this gas having a very short (13 s) half-life allowing multiple plane, higher resolution imaging.

$\dot{V}/\dot{Q}$  scans (Fig. 25.8) should be reported by experienced observers according to validated criteria, such as those adopted in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) project [135]. This, and other studies, using pulmonary angiography as the gold standard, found that a 'high probability'  $\dot{V}/\dot{Q}$  scan report correctly diagnosed pulmonary embolism in about 92% of cases, whereas the PIOPED frequency of pulmonary embolism in 'low probability' scans was 16%. Unfortunately, even with good technique, more patients fall into an 'indeterminate' or equivocal  $\dot{V}/\dot{Q}$  scan category than into the high or low probability categories. The results of  $\dot{V}/\dot{Q}$  scanning should therefore be interpreted in the light



(a)



(b)

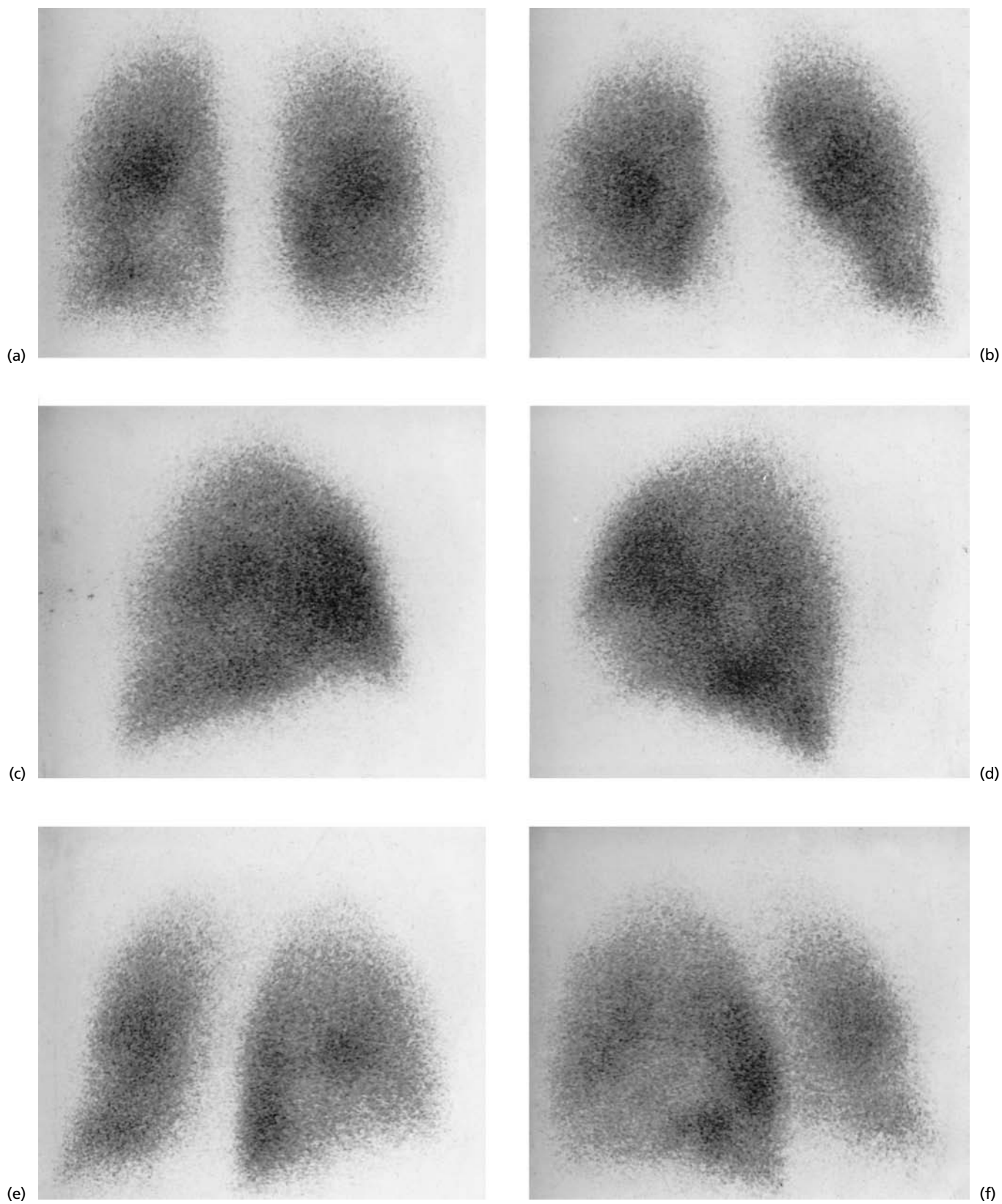
**Fig. 25.6** (a) Chest film of patient with acute cor pulmonale due to embolism showing unperfused right lung (Westermarck's sign). (b) Perfusion scan the same day confirming the lack of perfusion on the right, together with smaller left-sided defects.

of the clinical characteristics of the patients in order to make best use of the technique and an integrated diagnostic strategy (see p. 734), using as much relevant clinical information as is available should be followed [136,137].

Ventilation scans need not be carried out if the perfusion scan is normal or if it shows 'high probability' changes and the chest radiograph is normal in which case the diagnosis of pulmonary embolism is secure [138]. The 'low probability' interpretation on  $\dot{V}/\dot{Q}$  scans carried out in patients

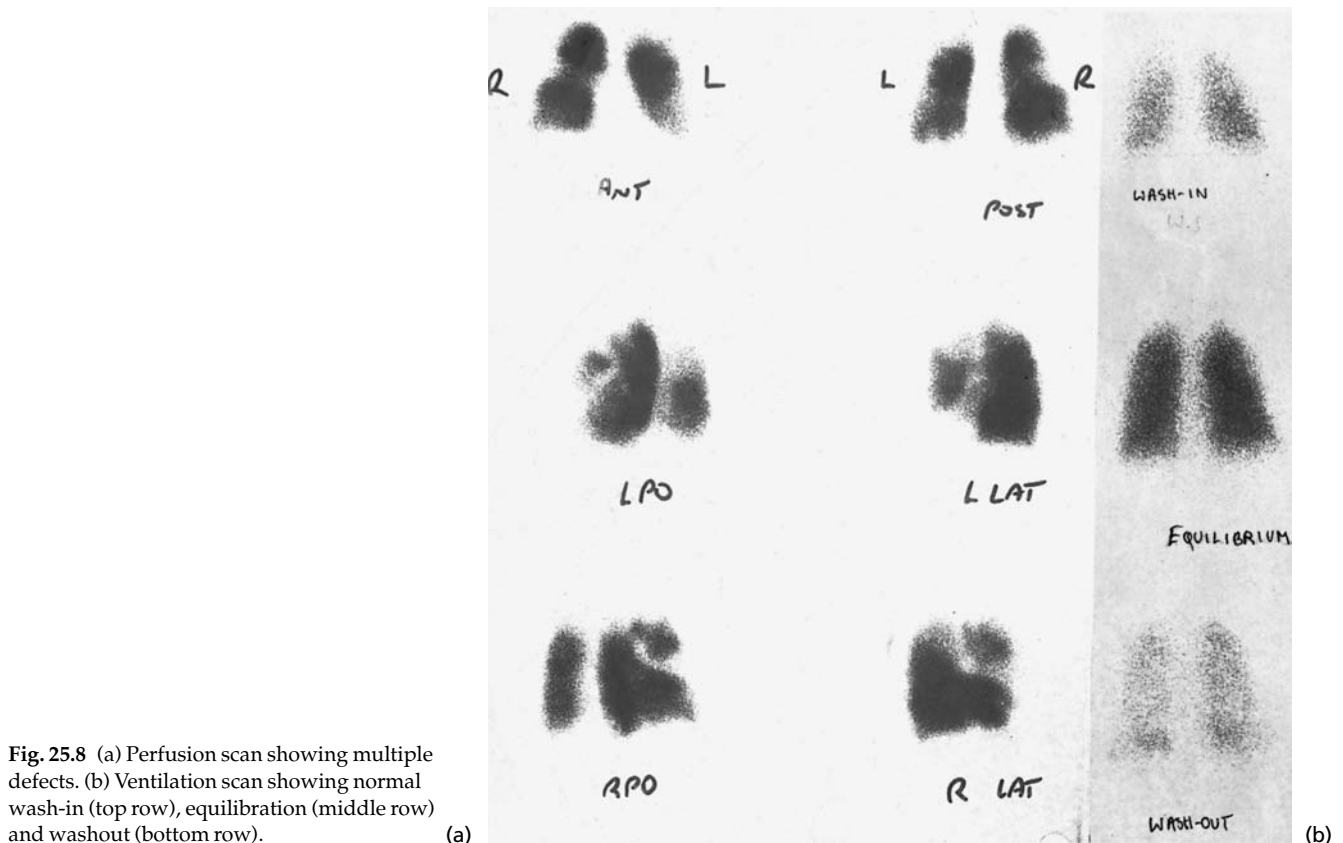
with 'poor cardiorespiratory reserve' has been shown to underestimate pulmonary embolism so that such reporting in this category of patient should be avoided or, if made, regarded as equivocal [139].

Provided that the limitations of  $\dot{V}/\dot{Q}$  scanning are understood, this method of investigation is still extremely useful in not only excluding but also diagnosing pulmonary embolism and will remain so until such time as newer investigations, such as spiral CT, have been more fully validated and become more widely available.



**Fig. 25.7** Normal conventional six-view perfusion scan: (a) posterior; (b) anterior; (c) right lateral; (d) left lateral; (e) right posterior oblique; (f) left posterior oblique.





**Fig. 25.8** (a) Perfusion scan showing multiple defects. (b) Ventilation scan showing normal wash-in (top row), equilibration (middle row) and washout (bottom row).

### *Pulmonary angiography*

Pulmonary angiography is the classic way to demonstrate pulmonary emboli radiographically. It is regarded as the 'gold standard' in the diagnosis of pulmonary embolism and is the method by which other investigative procedures are assessed [134]. The most satisfactory technical results require the placement of a cardiac catheter in the pulmonary artery trunk or in one of its branches in order to allow the selective injection of contrast material [140]. The catheter may be inserted through an antecubital fossa cut-down or percutaneously via the internal jugular or femoral vein, although the latter route carries the risk of dislodgement of venous thrombus. It is necessary for the radiologist to be prepared to take oblique as well as supine views in order not to miss an embolus [141], and the patient has to be sufficiently cooperative to remain immobile during the procedure. Pulmonary artery pressure may be measured using a simple manometric or other system. Positive evidence of pulmonary embolism is provided by the finding of abrupt termination of pulmonary vessels and by the presence of intraluminal filling defects (Fig. 25.9). The latter finding is the most common and reliable diagnostic criterion [34,70] and false-positive results should be rare. False-negative results are also rare. A study of 180 patients in whom a diagnosis of pulmonary embolism had been made clinically but in whom angiography was normal showed that during a 6-month period

of follow-up without anticoagulation no patient had a further clinical event suggestive of embolism, and of those who died no evidence of embolism or infarction was found at autopsy [142]. Needless to say, the diagnostic accuracy of the procedure is a function of the skill and experience of the medical practitioner performing it and, even among experts, there are inevitable interpretational disagreements, although these are significantly fewer than is the case with isotope scanning [131]. The mortality of the investigation in experienced hands is about 0.2–0.5% [134,140,143,144]. These deaths tend to occur in patients with cor pulmonale, in whom special caution needs to be taken with regard to the volume of hypertonic contrast medium used and the rate of injection. The morbidity is 1–3% and includes such complications as cardiac perforation, serious ventricular dysrhythmias, renal failure and hypersensitivity to the contrast medium [143,144]. The investigation is contraindicated in patients with a history of either a recent myocardial infarction or a propensity to ventricular dysrhythmias. From this discussion it is clear that pulmonary angiography is unnecessary in patients who have had a normal six-view lung perfusion scan, which effectively excludes the diagnosis.

Pulmonary angiography is mandatory if pulmonary embolectomy is proposed and is strongly recommended if the patient is to be subjected to any form of vena caval interruption or to treatment that carries a greater than



**Fig. 25.9** Pulmonary arteriogram showing large emboli in left upper and lower lobe arteries and in right upper lobe artery.

usual risk of bleeding, such as fibrinolytic therapy or standard anticoagulation in the presence of peptic ulcer disease. It has also been previously recommended in patients where lung scan results are equivocal for embolism in order to reduce the chance of unnecessary anticoagulation, with its attendant morbidity and mortality [145]. More recent diagnostic strategies have been developed, however, using serial non-invasive leg investigations for deep venous thrombosis in order to reduce the need for pulmonary angiography in this group of patients (see below) [150].

The timing of pulmonary angiography in relation to an acute episode of embolism is not critical. Complete resolution of a large pulmonary embolus within 2 weeks has been reported but is probably unusual [146], there being little experimental evidence to support rapid dissolution, so that angiography within a week of the episode may still demonstrate thrombus [140].

#### *Other radiological techniques*

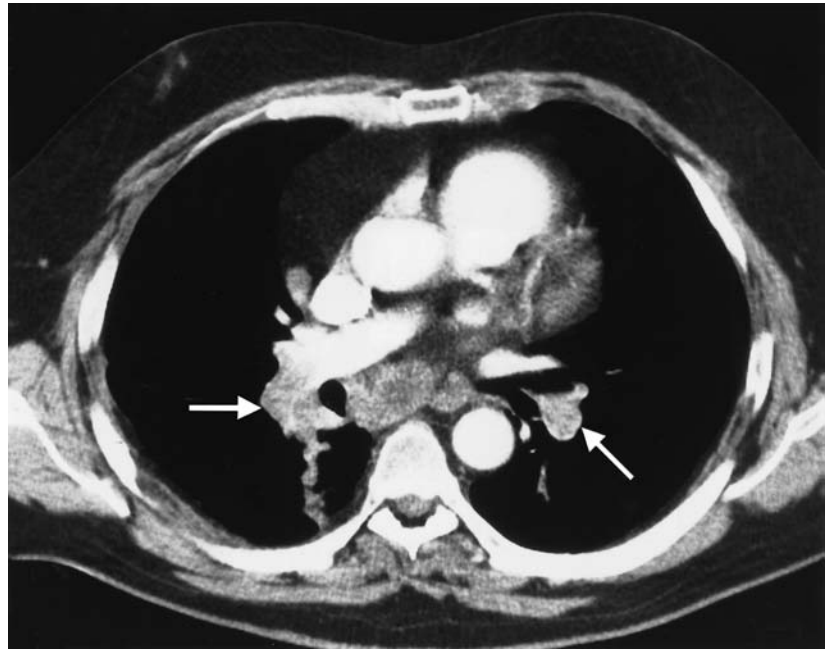
Digital subtraction angiography, using injection of relatively small amounts of contrast material either intravenously or through a flow-directed balloon catheter, is a procedure capable of producing good images in a relatively short time [147,148]. While it is associated with few complications and is used in some centres in place of angiography, it cannot yet replace it as the gold standard

for diagnosis. Contrast-enhanced spiral CT has also been used to demonstrate major vessel emboli [148]. While it has not yet been shown to have the sensitivity and specificity to replace angiography [138,149], as a safe and non-invasive procedure it is reasonable to suppose that it will soon become the investigation of choice, particularly once thinner section techniques have become increasingly available and more fully validated. It is capable of demonstrating embolus down to segmental pulmonary arteries (Fig. 25.10) but reservations have been expressed while data comparing spiral CT with pulmonary angiography are relatively sparse [149].

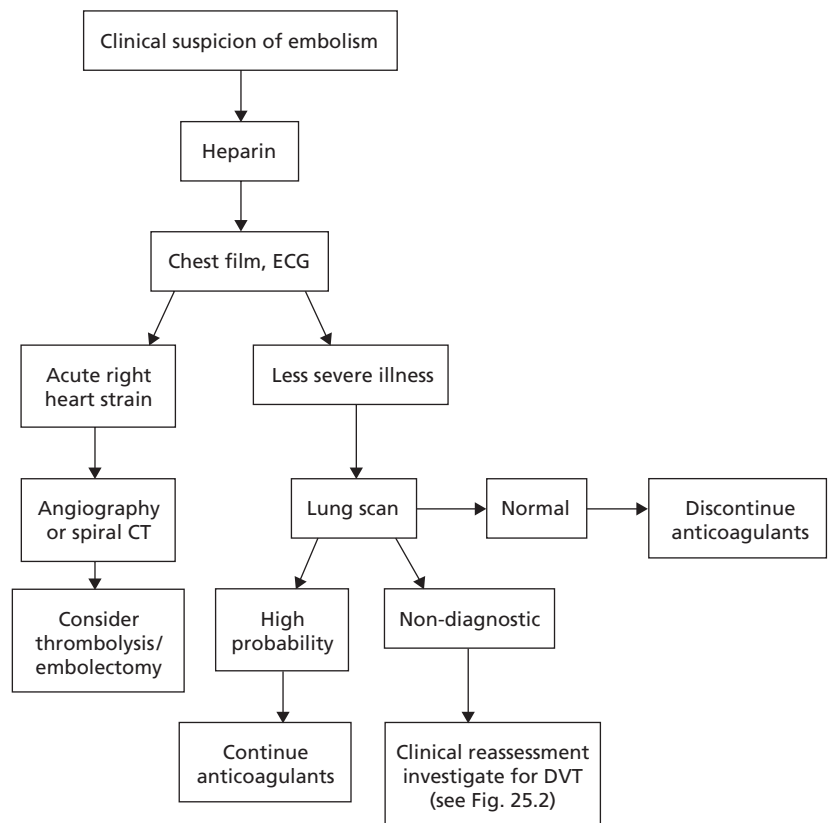
#### **Diagnostic strategy**

The strategy for diagnosis of pulmonary embolism should combine both clinical and investigative probabilities [150,151] (Fig. 25.11). On clinical suspicion of pulmonary embolism a chest radiograph and ECG are obtained. If the patient is severely ill and thrombolysis or embolectomy being considered, angiography (or, in centres with appropriate experience and equipment, contrast spiral CT) should be performed immediately. Echocardiography may provide 'stop-gap' surrogate evidence of the diagnosis. In other circumstances, provided that the chest film shows no obvious alternative pathology, anticoagulants are started while further investigation proceeds with a ventilation-perfusion isotope lung scan. If a six-view





**Fig. 25.10** Spiral contrast-enhanced CT image of emboli (arrowed) in right main and left lower lobe pulmonary arteries.



**Fig. 25.11** A diagnostic strategy for suspected pulmonary embolism (see text).

perfusion scan is normal, the diagnosis of pulmonary embolism has been excluded and anticoagulants should be stopped. When the isotope scan shows a high probability of pulmonary embolism (lobar perfusion defects or multiple segmental perfusion defects with normal ventila-

tion in corresponding areas), then the diagnosis is sufficiently firm for treatment to be continued without further invasive investigation. If the ventilation-perfusion scan is non-diagnostic, showing only small or matched defects (as is likely in the presence of an abnormal chest radi-

ograph due to coexisting disease), then after clinical reassessment compression ultrasonography or venography may be carried out while treatment is continued. If either of these two approaches gives a positive result for venous thrombosis, then this alone provides significant grounds for continuance of treatment with anticoagulants. However, if the result is negative then the argument for discontinuing anticoagulation and setting an alternative diagnosis is strong.

## Management

The spectrum of thromboembolic disease ranges from a patient with a sore calf or unexplained episode of chest pain to acute severe dyspnoea and cardiorespiratory collapse. In all cases, once the diagnosis is suspected and its likelihood confirmed by the above tests, treatment is likely to be necessary. The drugs available are the anticoagulants heparin, including its low molecular weight forms, warfarin or other coumarin drugs, and fibrinolytics. In rare cases, surgery in the form of embolectomy or caval interruption or clot disruption by catheter may need to be considered.

### Acute pulmonary embolism

It is accepted that anticoagulants are effective in the treatment of acute pulmonary embolism. However, the only randomized trial to test this was small because it had to be abandoned on ethical grounds following the deaths, from necropsy-confirmed pulmonary embolism, of one-quarter of the patients in the placebo-treated group, a further 25% having clinical recurrence; there were no observed fatalities or recurrence in the heparinized group [151]. Additional evidence in support of the effectiveness of anticoagulants is provided by the observation that the frequency of recurrent thromboembolism is increased when the level of heparinization is subtherapeutic, according to clotting tests [152].

Acute massive pulmonary embolism is a familiar emergency to most doctors. The clinical diagnosis is usually supported by a normal chest film and an abnormal ECG, and leads to angiography. This procedure may sensibly be combined with attempts to dislodge or disrupt the clot by the catheter or guide wire [153]. This technique has been reported to produce haemodynamic improvement when successful. There have also been reports of removal of clot from pulmonary arteries by catheter and of the use of stents introduced by catheter to bypass the clot [154–156]. Supportive measures include the administration of oxygen and the use of plasma volume expanders; vasodilators are of course contraindicated. Deterioration in spite of the above procedures should lead to attempted embolectomy. If cardiac arrest occurs, vigorous cardiac massage should be continued and if possible the patient

put on cardiopulmonary bypass prior to embolectomy or catheter disruption.

In less urgent cases it is nevertheless important to act speedily as soon as the diagnosis is suspected. Anticoagulation with heparin, unless contraindicated, should be started immediately and the diagnostic strategy outlined above adopted. The various treatment options are discussed below.

### Heparinization

Initial anticoagulation with intravenous infractionated heparin has been the mainstay of treatment in pulmonary embolism. Heparin is a sulphated mucopolysaccharide obtained from animal lung and gut mucosa. It is available as a sodium or calcium salt and combines with the naturally occurring clotting factor activator antithrombin III, improving the inhibitory effect of this substance on factors IIa (thrombin) and Xa [157]. The efficacy of heparin is severely impaired if the level of circulating antithrombin III falls below 60% of the normal value [158], a point clearly relevant to subjects with thromboembolism resulting from a congenital deficiency of this thrombin inhibitor.

Heparin, in common with other anticoagulants, does not lyse clot and the object of therapy is to prevent extension or recurrence of thrombus while avoiding haemorrhagic complications, the principal determinant of which is the dose of heparin used [99,158]. The dosage of heparin is measured in international units according to a biological animal assay rather than by weight, and its clearance is unaffected by renal or liver disease.

A dose of 500–600 units/kg daily is recommended, the aim being to produce a plasma level of 0.3–0.4 units/mL, the concentration that has been shown experimentally to prevent thrombus formation [160]. For a 60-kg subject this would amount to 5000–6000 units every 4 h, giving a total daily dose of 30 000–36 000 units. With the availability of reliable intravenous pumps, it became standard practice to infuse heparin continuously once an initial bolus dose of 5000 units (10 000 units in severe cases) had been given. The infusion can be commenced at a rate of 1400 units/h but as the pharmacokinetics of heparin are very variable, so that it is exhausted more rapidly in the presence of extensive thrombus [161], it is advisable to use the higher end of the dosage range (1500 units/h) for patients in whom embolism is judged to be extensive. In cases of massive embolism or in the presence of a pre-existing thrombophilia the dosage may need to be increased to 60 000 units or more daily according to careful laboratory monitoring [162,163].

The activated partial thromboplastin time (APTT) is the most commonly used test for controlling anticoagulation with heparin and, in common with the thrombin time, requires a value 1.5–2.5 times the control figure [164,165]. It is usual practice to check the APTT 4–6 h after com-

mencement of treatment. If the APTT ratio is within the target range of 1.5–2.5 times the control, no change is made and the measurement is rechecked daily. Should the APTT rise above or fall below the desired range, the infusion rate is decreased or increased as the case may be, according to a validated nomogram; the use of which is more effective in achieving adequate heparinization quickly than intuitive prescribing by individual clinicians, resulting in inadequate anticoagulation [165–167]. An additional APTT estimation should be made 6–10h after any dose change. There is a circadian variation in heparin activity, which is at its peak during the night [168], so that blood should ideally be taken for routine APTT estimation at about the same time each day. A pre-existing thrombophilia should be suspected when the APTT response to heparin is poor.

Animal experiments purport to show that thrombus takes 7–10 days to become firmly adherent to a vessel wall [169], and it became routine practice to continue heparin for this length of time in humans [167]. It is now more usual to discontinue heparin after 5 days, provided that concurrent oral anticoagulation has become effective (see below).

Low molecular weight heparin is establishing a place in the management of thromboembolic disease [170–172]. Several different products are available, produced by enzymatic or chemical depolymerization of heparin to produce compounds of 4–6.5kDa. This chemical change makes for greater bioavailability, a longer half-life and greater reliability in terms of dose–response and reduction in bleeding complications. In particular, they do not bind in a non-specific way to plasma proteins, a fact that may explain some cases of apparent resistance to unfractionated heparin [173]. The drugs can be given subcutaneously once or twice daily without the need for monitoring of clotting times, and this makes them ideal for prophylaxis of venous thrombosis in high-risk patients and for outpatient treatment of deep venous thrombosis. Although not fully established as treatment for acute pulmonary embolism, studies of ‘submassive’ embolism, such as those requiring thrombolytic therapy, have suggested that in appropriate dosage they may be of similar efficacy to unfractionated heparin, so that their use is becoming accepted in uncomplicated cases [172,174]. The different low molecular weight preparations have different activities and dose regimens and cannot therefore be used interchangeably. In patients at greater risk of bleeding, unfractionated heparin infusion with laboratory control may be safer.

### Oral anticoagulation

By virtue of its long half-life (approximately 2 days), warfarin sodium was once thought to be better suited to poisoning rats than to treating patients but is now the most

commonly prescribed oral anticoagulant. It belongs to a group of coumarin derivatives whose anticoagulant properties were found to be the cause of bleeding in cattle fed on fermented sweet clover hay in the 1920s. It has a similar structure to fat-soluble vitamin K<sub>1</sub>, which it competitively inhibits, thereby blocking the production and activation of clotting factors II (prothrombin), VII, IX, X and other proteins involved in the coagulation process [175].

Warfarin does not act immediately, since the circulating clotting factors whose production it inhibits are not usually sufficiently cleared for 48h [176]. The usual practice is to start warfarin as soon as the diagnosis of venous thrombo-embolism is reasonably secure (often day 1) and to spread the loading doses over 3 days during which time heparin is continued until adequate oral anticoagulation can be shown to have been achieved by laboratory testing, a procedure made necessary as individual patients’ sensitivities to warfarin vary considerably [177,178]. Stability is commonly achieved by the third day of warfarinization at which point heparin may often be discontinued, the maintenance dose of warfarin being predicted by laboratory control on the fourth day (see below).

The most common coagulation test used in monitoring oral anticoagulant therapy is the one-stage Quick test [179] or a commercially available alternative. Blood is taken into a citrated tube (to remove calcium ions) and the laboratory adds a standard thromboplastin and an excess of calcium ions (as calcium chloride solution), measuring the time thrombus takes to form. As Quick thought that this test was a measure of prothrombin (factor II) activity only, the term ‘prothrombin time’ was introduced and remains acceptable by virtue of its widespread use, although the activity of factors VII and X are also measured. The prothrombin time is valueless unless related to a control time for the particular batch of reagent in use, the result being expressed as a ratio, i.e. patient’s prothrombin time/control’s prothrombin time. Attention has been paid to the characteristics of available thromboplastins, as there were fears that some commercially produced preparations might underestimate coumarin effect and lead to bleeding in the early stages of treatment, even though the prothrombin ratio was within the therapeutic range. In order to achieve reliable standardization in the UK, a batch of thromboplastin known as Manchester comparative reagent (MCR) was independently checked by the British Anticoagulation Panel and designated British comparative thromboplastin (BCT). This BCT was used to calibrate other thromboplastins, and prothrombin ratios so obtained were called the British corrected ratios (BCR). International standardization under the auspices of the World Health Organization has used a batch of BCT to establish an international normalized ratio (INR), and this system of reporting has been adopted in the UK and elsewhere.

INR control of warfarin induction has been shown to be

essential, as blind adherence to a regimen of 10 mg daily for 3 days may cause up to 30% of patients to be over-anticoagulated by the fourth day [177]. Adherence to the following steps should result in satisfactory induction of oral anticoagulation in a patient who is adequately heparinized:

- 1 check prothrombin time (INR) before first dose of warfarin;
- 2 if  $\text{INR} < 1.4$  give 10 mg warfarin as an evening dose;
- 3 repeat INR the following morning;
- 4 if  $\text{INR} < 1.8$  repeat 10 mg warfarin as an evening dose;
- 5 repeat INR the following morning;
- 6 if  $\text{INR} < 2.0$  repeat 10 mg warfarin as an evening dose.

The time of blood sampling (with the exception of step 1) and the time of dosing should be the same each day. When the INR is found to be higher at steps 2, 4 or 6, the next dose of warfarin should be reduced according to a predetermined schedule in order to avoid under-treatment or bleeding [181,182]. Prothrombin time (INR) is reliable even though heparin is being used, provided that the APTT or equivalent test is not above the therapeutic range of 1.5–2.5 times the control value. If the APTT is too high, the effect of heparin on the INR can be neutralized by adding protamine *in vitro* [183]. After the fourth dose of warfarin, the prothrombin time is rechecked at least weekly until a stable dose is achieved. Once heparin has been discontinued, follow-up control is achieved by the outpatient anticoagulant clinic, at first with weekly checks and then according to the stability of the measurement, with at least once-monthly checks for the duration of a limited course of treatment, or up to 3-monthly in the case of long-term therapy [180]. Caution should be exercised in the induction of oral anticoagulation as some patients are particularly sensitive to warfarin. These include the elderly and those with high risk factors such as congestive cardiac failure, liver disease and those on drug therapy known to potentiate warfarin. A loading dose of less than 10 mg daily is recommended under these circumstances [182].

The British Society for Haematology has recommended a target INR of 2.5 for treating deep venous thrombosis, pulmonary embolism and symptomatic inherited thrombophilia, and 3.5 in the management of a recurrence of either condition whilst on warfarin [182].

The duration of a course of oral anticoagulants is somewhat empirical. It is accepted that recurrence is likely if treatment is not continued on an outpatient basis after episodes of venous thromboembolism in hospital [39]. It has also been shown that continuation therapy with subcutaneous heparin in patients who have had proximal venous thromboses is ineffective when compared with oral anticoagulants over a similar 3-month period [184]. The British Thoracic Society has reported a controlled trial in which 4 weeks of anticoagulation was as effective as 3 months' treatment for postsurgical venous thromboembolism, but was less effective in medical patients [185].

Thus 4 weeks of warfarin can be recommended for the uncomplicated postoperative patient, while a 3-month course of anticoagulation has been generally acceptable for both deep venous thrombosis and pulmonary embolism arising *de novo* or in a medical patient. This remains an area of controversy and ongoing study, a recent placebo-controlled trial that extended oral anticoagulation with warfarin beyond 3 months for the first episode of idiopathic venous thrombo-embolism was discontinued after a mean period of 10 months with the conclusion that 3 months of treatment in these circumstances was inadequate [186]. The British Society of Haematology currently recommends 6 months of anticoagulation for pulmonary embolism and proximal deep venous thrombosis, 3 months for non-surgical calf vein thrombosis and 6 weeks for post-operative calf vein thrombosis, provided that there are no persistent risk factors [182]. When episodes have been life-threatening or when there has been recurrence, treatment may be for longer periods or even indefinitely in those with persistent risk factors or if no remediable cause has been identified. Particular care has to be taken with regard to drug interactions when warfarin is used [180].

### Thrombolytic therapy

Conventional therapy with heparin followed by oral anticoagulation is adequate treatment in the vast majority of patients with pulmonary embolism, historical evidence for this satisfactory response having been provided by follow-up with repeat lung scanning. This approach prevents the formation of new clot or the extension of existing thrombus and depends upon natural fibrinolysis to remove emboli from the lungs. Thrombolytic drugs stimulate the natural process by activating the plasminogen–plasmin system, which acts on preformed thrombus but may also induce a plasma proteolytic state that impairs blood coagulability and can cause serious haemorrhage. The original agents were streptokinase, derived from group C  $\beta$ -haemolytic streptococci [187], and urokinase, obtained from urine or from tissue culture of renal parenchymal cells [188]. Recently, more fibrin-specific drugs, such as alteplase (recombinant tissue plasminogen activator or rt-PA), anistreplase (acylated plasminogen–streptokinase activator complex) and single-chain urokinase, have been introduced.

Despite the theoretical attractions of thrombolytic drugs, they are used infrequently as a first line of treatment, in part because compared with heparin they have not been demonstrated to reduce early mortality [189,190] or improve long-term clinical results [191], and in part because of concern about the possibility of haemorrhagic side-effects. In spite of this, the original agents have been shown to accelerate improvement in pulmonary angiography and isotope lung scan, to reduce pulmonary artery pressure and to improve parameters of left and right ven-

tricular function in randomized controlled clinical trials that have compared up to 24 h of thrombolytic therapy with heparinization. Indeed the degree of lysis seen in patients treated with thrombolytics after 12–24 h was similar to that seen in the anticoagulated group at 1 week [190,192,193]. Similar results have been obtained with recombinant plasminogen activator, suggesting a potentially important role for these drugs in acute severe pulmonary embolism where there are signs of right ventricular strain and no likely bleeding points [194–196]. If they are used, peripheral intravenous infusion is adequate and there are no advantages to be gained from catheter infusion into the pulmonary artery direct.

There is no unanimity about patient selection for thrombolytic therapy, but it is reasonable to use these drugs in two categories of patient:

**1** those who are critically ill due to pulmonary artery obstruction and in whom further cardiopulmonary deterioration is judged to be lethal unless an invasive surgical procedure such as pulmonary embolectomy is carried out;

**2** patients judged to have had a large pulmonary embolus who are deteriorating clinically or failing to improve despite 24–48 h of treatment with heparin.

In support of this method of selection, trials have shown that patients with shock show a more impressive clinical response to thrombolytic drugs and that clinical deterioration is more likely in such patients when treated with heparin [190,192,193,197].

In order to avoid unnecessary risk, the diagnosis of pulmonary embolism should be established as firmly as possible before starting thrombolytic treatment. Ideally, this should include either an isotope lung scan that lends significant support or a positive pulmonary angiogram or spiral CT. Thrombolytic therapy is usually only used if the embolus is thought to have occurred within a week of the onset of treatment, as the drugs are relatively ineffective against old thrombus, possibly because the plasminogen content of the clot falls with time [189], although there is some evidence that activity may extend to 2 weeks [198]. The same contraindications apply to thrombolytic as to anticoagulants but absolute contraindications include active or recent haemorrhage and any known potential intracranial source of haemorrhage. There are clearly also increased risks of bleeding in peptic ulcer or other potentially haemorrhagic gastrointestinal tract disease and following surgery or parturition within the preceding 7 days. There are risks of haemorrhage to the fetus in pregnancy and also to patients with severe hypertension.

Both streptokinase and urokinase should be given by continuous infusion. For streptokinase, a loading dose of 250 000 units is given over 30 min followed by 100 000 units/h for up to 24 h [199]. Urokinase has been given at a dose of 4400 units/kg initially over 10 mins followed by the same dose hourly for 12–24 h. Increasingly, those with

experience of thrombolysis are using recombinant plasminogen activator (rt-PA) in a single intravenous dose of 100 mg over 2 h, and this appears as effective and no more dangerous in terms of haemorrhage than the older drug regimens [196]. The simplicity of this regimen suggests that it may become a standard treatment for severe embolic episodes. At the completion of the course heparin should be introduced, but not until the thrombin time has fallen to less than twice the baseline value. Heparin should be given at this stage by continuous infusion without an initial bolus, which could produce bleeding.

The risks of life-threatening bleeding during fibrinolytic therapy are not very different from those associated with heparin treatment, about 7% [34,200]. Persistent bleeding or oozing from venepuncture sites, cut-downs, arterial punctures, etc. may occur, and these procedures should be avoided wherever possible. Allergic reactions may occur to streptokinase and its acylated derivative in 15% of patients. Hydrocortisone may be given to diminish the chance of these. Fewer such reactions occur with urokinase and rt-PA.

### Supportive measures

Supportive measures consist of adequate analgesia, usually in the form of morphine or pethidine (which should of course not be given intramuscularly in anticoagulated patients). Oxygen therapy is provided according to arterial blood gas or  $\text{SaO}_2$  measurements and colloid infusion may be necessary to support left ventricular function in severe cases.

### Vena caval interruption

A number of procedures have been described by which the inferior vena cava is either totally or partially interrupted between the iliac and renal veins, in order to prevent emboli from the legs reaching the lungs. However, it has never been shown that any of these measures reduce mortality compared with standard heparinization followed by oral anticoagulation [200]. The need for vena caval interruption therefore requires critical examination before its clinical application. Fortunately death due to recurrent thromboembolism is extremely rare in patients who have completed an orthodox course of anticoagulant therapy [191] and this form of treatment is preferable to all others in the vast majority of patients.

Many different techniques are available, including complete ligation of the vena cava, suture plication, partial obstruction with metal clips and the positioning of various filters or umbrella devices designed to prevent large emboli passing across them [201]. The operative mortality of ligation, plication or clipping is in the region of 5–15% [202,203] compared with 1–3% for those filtering devices inserted under local anaesthesia and under radiographic control using a guide wire with a femoral or jugular vein

approach [203,204]. These procedures interfere with venous return and, unsurprisingly, one-third or more of patients with ligation experience chronic dependent oedema. Ultimately, filter devices may also occlude, with a rate of over 70% for the Mobin-Uddin umbrella and at least 5% for the various Greenfield filters [200,205]. Even with these potential prices to pay, the patient is not guaranteed freedom from further pulmonary emboli, as in about 5% of patients these may still occur either by the development of large collaterals or via the formation of thrombus on the cardiac side of the interruption [162,205]. Occasionally filters may themselves embolize or may perforate the wall of the vena cava [200].

In view of these various constraints, vena caval interruption is rarely justified but may be indicated in those few patients who:

- 1 experience life-threatening pulmonary emboli despite 'adequate' anticoagulation;
- 2 have a firm diagnosis of pulmonary embolism or extensive deep venous thrombosis but who cannot be treated with anticoagulants owing to some absolute contraindication.

### **Pulmonary embolectomy**

This operation was first carried out by Trendelenberg in 1908, although it was not until 20 years later that the first patient survived surgery with removal of an embolus [206]. In the most experienced hands, and with or without bypass, mortality rates are now around 20% [207–209], although it is likely that the risks in less experienced centres reflect those obtained in the 1970s, about 50% [210,211]. Such figures need to be treated with caution, since the surgeon who only carries out an occasional embolectomy is not only likely to be less skilled but also takes more persuading and therefore tends to operate on more desperate cases, while the more experienced surgeon tends to include less severely ill patients. Because of the very high risks involved, surgeons do not usually attempt pulmonary embolectomy without angiographic confirmation of the diagnosis; however, since most patients who die of massive pulmonary embolism do so within 30 min of the onset of symptoms [212], this group is unlikely to be helped by surgery but may benefit from the catheter techniques mentioned above (p. 736). Of those patients who survive long enough for the diagnosis to be confirmed, the mortality with medical treatment is low, even if more than half of the pulmonary circulation is shown to be obliterated [213].

It follows that pulmonary embolectomy is rarely indicated and seldom performed, even in centres with both experienced personnel and availability of bypass. Pulmonary embolectomy can be considered in the unusual case with firmly diagnosed massive embolism associated with severe hypotension, hypoxia and a deteriorating

situation [214] despite 'adequate' treatment with heparin or thrombolytic drugs.

### **Deep venous thrombosis**

The standard management of deep venous thrombosis has been admission of the patient to hospital for heparin infusion and initiation of oral anticoagulation using the regimens described above. The introduction of low molecular weight heparins has already altered this in many cases by allowing outpatient management. Several of the new heparins have now been shown to be as effective as the standard regimen when given as a fixed subcutaneous daily or twice-daily dose [215–218]. At present it would be appropriate to treat a patient with uncomplicated venous thrombosis with a low molecular weight heparin for 5 days and to introduce an oral anticoagulant in the normal way as described above. In the future, it may prove possible to substitute longer-term low molecular weight heparin for warfarin for a more prolonged period. This has not yet been tested in a controlled trial and would carry the risk of thrombocytopenia.

### **Prophylaxis**

The consequences of venous thrombosis and embolism are so serious, both in individual morbidity and mortality and in costs to the health services, that routine prophylaxis has now become mandatory in the hospital setting [219–221]. The risks to the individual include the dramatic consequence of fatal pulmonary embolism and the less dramatic but very troublesome postphlebotic leg syndrome and venous ulceration. Prophylaxis involves making a risk assessment in individual patients and applying a locally agreed protocol of management depending on the results of the assessment.

### **Individual risk assessment**

Two factors contribute to risk of venous thromboembolism: personal predisposition and acute illness or injury (Table 25.2). Those at highest risk are people having major orthopaedic surgery, especially of the hip, pelvis or leg, or abdominal surgery for cancer and those with stroke involving a leg or paraplegia. Others with serious illness, major trauma or surgery who give a history of previous thromboembolic disease or of a thrombophilia should also be regarded as at highest risk. Such patients have been shown to have risks of venous thrombosis and fatal pulmonary embolism of around 50% and up to 10%, respectively. Major acute medical illness, such as myocardial infarct or heart failure, and major trauma constitute a moderate risk in the absence of predisposing factors, as does less severe trauma or surgery in the presence of predisposing factors. All other patients are regarded as at low risk.

**Table 25.2** Risk factors for venous thromboembolism.

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<i>Predisposing factors</i>
Increasing age
Obesity
Over 4 days in bed
Pregnancy and puerperium
Oestrogens (50 µg + daily)
Previous deep venous thrombosis or embolism
Thrombophilic disease
Homocystinaemia
 <i>Illness/injury</i>
Major trauma or surgery
Pelvic and abdominal cancer
Cardiac failure
Recent myocardial infarct
Leg paralysis
Severe infection
Polycythaemia
Paraproteinaemia
Nephrotic syndrome
Inflammatory bowel disease
Behçet's disease
Paroxysmal nocturnal haemoglobinaemia

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## Methods of prophylaxis

### Mechanical measures

Graduated elastic compression stockings have been shown to be effective in prevention of venous thrombosis postoperatively, and in one major meta-analysis appear to be as effective as low-dose heparin in reducing risks of pulmonary embolism after hip replacement [222,223]. Other mechanical devices that intermittently compress the legs are also widely used and probably equally effective. Leg compression has the advantages of not increasing risk of bleeding, except possibly after prostate surgery, and being suitable for all patients save those at risk of ischaemic leg complications. It is commonly combined with pharmacological measures.

### Low-dose heparin

Double-blind prospective randomized trials involving over 4000 patients have shown that low-dose unfractionated heparin is effective in reducing the incidence of deep venous thrombosis and fatal pulmonary embolism in patients over the age of 40 years undergoing abdominal, thoracic and pelvic surgery under general anaesthesia [224,225]. The recommended dose is 5000 units subcutaneously 2 h before the procedure, to be continued every 12 h until the patient is ambulant. Monitoring of clotting times is not necessary. An 8-hourly regimen may also be used but probably confers no additional benefit for a greater likelihood of bleeding [226]. An even smaller dose of heparin (1 unit/kg/h) has been used as a continuous

infusion, although this 'ultra-low dose regimen' never gained wide acceptance [227].

These small doses of heparin augment a naturally occurring factor X inhibitor [228] and, while they cannot be guaranteed to prevent thromboembolism, the reductions are highly significant, from approximately 25% to 7% for deep venous thrombosis and from 6% to less than 1% for pulmonary emboli [229]. These figures argue strongly for the widespread use of subcutaneous heparin, and it was estimated that 4000–8000 deaths per annum could be avoided in the USA by its routine prescription in these groups of patients [230,231]. Low-dose heparinization may be complicated by wound or intra-abdominal haematomas [224,232] but these are not usually of a serious nature [233] and there is a much lower risk of haemorrhage than with full anticoagulation. There is also a risk of thrombocytopenia, which occurs in 3–4% of patients on prophylactic heparin, sufficiently frequently for it to be necessary to monitor platelet counts in these patients. Low-dose heparinization is contraindicated in patients with a bleeding tendency or in those neurosurgical patients in whom postoperative bleeding could be disastrous.

Although the value of low-dose heparin at conventional doses in patients following abdominal, thoracic and pelvic surgery is undisputed, its efficacy in other at-risk groups is not established and remains a subject of controversy. One such high-risk group in which a convincing case cannot be made for low-dose heparin is that comprising patients who have had major orthopaedic surgery or suffered trauma associated with a high incidence of venous thrombus formation. Thus most series have shown that low-dose unfractionated, as opposed to low molecular weight heparin prophylaxis is ineffective in patients following total hip or knee replacements [67]. Because of the lack of clear benefit and because of conflicting data, this form of prophylactic therapy has not been widely used in these groups, particularly as it carries the risk of wound haematoma that might jeopardize the success of the surgical procedure [233].

Myocardial infarction is another risk group in which the beneficial effect of low-dose heparin is indeterminate, although the use of full, short-term anticoagulation appears to reduce the frequency of thromboembolic complications [234,235]; overall mortality has not been shown to be reduced unless the data from different trials are pooled [236]. Data regarding the efficacy of subcutaneous heparin in patients after myocardial infarction are conflicting [237].

Patients undergoing major urological surgery, including suprapubic prostatectomy and cystectomy, are inadequately protected by subcutaneous heparin [238], whereas this form of treatment is effective in transurethral prostatectomy [239]. The success of subcutaneous heparin in many groups of surgical patients has led to its more widespread



use in patients immobilized through medical illness, such as congestive cardiac failure and strokes [240].

### Low molecular weight heparins

These agents, and the heparinoid danaparoid, are also given by subcutaneous injection on a once- or twice-daily basis, without the need to monitor clotting times, although platelet counts do need to be measured as with standard heparin. They have been shown to be more effective in orthopaedic surgery and also to have some advantage in general surgical operations [241–243].

### Oral anticoagulants

The main use of oral anticoagulation has been in hip surgery, where these drugs have been shown to be effective. However, they have the disadvantage of the need for careful control of prothrombin time. It is usual to start therapy either with a low dose before surgery or with the full dose after surgery to reduce the risk of bleeding. A number of trials has shown low molecular weight heparin to be as effective as warfarin in hip surgery [243].

### Dextran 70

The plasma expander dextran has antithrombotic effects, both as a result of its haemodiluting effect and also because of a specific effect on platelet adhesiveness and fibrin formation [244]. It has been claimed that it has an equivalent prophylactic effect to warfarin if given before, during and in the early postoperative phase after elective hip surgery [245]. It is infused slowly over a period of about 24 h. Haemorrhagic complications are less common with this treatment but allergic reactions and volume overload are potential problems. Dextran may also interfere with blood cross-matching and biochemical estimations and can cause renal failure if given in the presence of dehydration. It is not normally used in those groups known to benefit from low-dose unfractionated heparin for, although it may be as effective [246], it is expensive and less safe to administer. Although it is effective following elective hip surgery, it is less than low molecular weight heparin [243].

### Aspirin

Aspirin inhibits thromboxane  $A_2$  and also reduces platelet adhesiveness, but unfortunately its efficacy as a venous thromboembolic prophylactic in the postoperative state was not demonstrated in a British Medical Research Council trial [247]. The reader should not be surprised to learn that some workers have found aspirin to be of limited effectiveness following total hip replacement [248], while others have not [249], and there is insufficient evidence to commend it for general use as a venous antithrombotic agent.

### Other agents

Conflicting claims have been made for many other drugs when used either alone or in combination. These include other prostaglandin inhibitors, such as sulfinpyrazone (sulphinpyrazone) and oxyphenbutazone, the antimalarial hydroxychloroquine, dipyridamole and drugs thought to enhance fibrinolysis, such as anabolic steroids and phenformin. The efficacy of all these agents is unproven.

### A preventive protocol

All patients at high or moderate risk should be given specific prophylaxis, while patients at low risk (Table 25.1) should only be subject to general measures to ensure early mobilization and leg muscle activity [219–221].

#### Patients at high risk

As with all hospital patients, those at high risk should be mobilized early and encouraged to do leg exercises. In addition they should receive specific prophylaxis. Patients having hip surgery should receive low molecular weight heparin (or heparinoid) or warfarin (adjusting the dose postoperatively to an INR of 2–3). Dextran 70 is a somewhat less secure option. In the case of patients at risk of bleeding, intermittent leg compression or graduated stockings are reasonably effective. Patients with hip or major leg fracture should be treated similarly, though here low molecular weight heparin appears to be the best option in terms of efficacy. In knee and major abdominal surgery, prophylactic heparin and leg compression should be combined, as they should in stroke and other conditions causing leg paralysis after intracranial haemorrhage has been excluded.

#### Patients at moderate risk

Patients over the age of 40 undergoing major surgery and with any of the risk factors in Table 25.2 should be given subcutaneous heparin, either low dose unfractionated or low molecular weight, or leg compression if they have a risk of bleeding. In medical patients immobile due to severe illness, low-dose heparin or adjusted-dose warfarin (INR 2–2.5) are recommended. Leg compression is suitable for those at risk of bleeding and who do not have ischaemic limbs, and may be combined with anticoagulation. In patients with myocardial infarction, aspirin and thrombolytic drugs are now used routinely, and full anticoagulation is sometimes indicated by complications such as mural thrombosis and atrial fibrillation. In other circumstances, if the patient remains immobile, prophylaxis with low-dose heparin or adjusted-dose warfarin should be considered. In neurosurgery and often in major trauma, anticoagulation is contraindicated and leg compression is essential.

### Management in pregnancy and the puerperium

The management of deep venous thrombosis or pulmonary embolism in pregnancy is constrained by considerations with regard to the developing fetus. First, in achieving a diagnosis it is desirable to expose the fetus to as little ionizing radiation as possible. Both compression ultrasound and impedance plethysmography are acceptable options for deep venous thrombosis and an isotope perfusion scan, followed if need be by a ventilation scan which is the investigation of choice for pulmonary embolism as the very low radiation dose poses a negligible risk to the fetus [250]. Conventional chest radiography and ascending venography are permissible with pelvic shielding although this may compromise visualization of the pelvic veins. Secondly, treatment requires a drug that is effective in preventing further thrombosis without harming the fetus or causing the mother to bleed excessively at parturition.

Coumarin compounds such as warfarin cross the placental barrier and are potentially teratogenic in the first trimester, being associated with multiple congenital abnormalities including chondrodysplasia punctata. Although there are those who believe that warfarin may be safely used with careful clotting control in the second and third trimesters, with discontinuance at 36 weeks, this policy is not recommended because of reports of neurological defects and because of the risk of fetal or maternal haemorrhage in the case of premature labour [43]. Warfarin may be taken by breast-feeding mothers without risk to the child [251].

Unfractionated heparin does not cross the placenta and is not teratogenic. It is the treatment of choice for both deep venous thrombosis and pulmonary embolism in pregnancy and should be given intravenously initially for 1–2 weeks at standard dosage with usual clotting control [251]. It is impracticable to continue it intravenously throughout pregnancy, and indeed this carries the risk of osteoporosis and thrombocytopenia. It can, however, be given subcutaneously at a dose of 5000 units either every 12h and can be self-administered satisfactorily in most cases [251] with laboratory APTT control, being replaced with intravenous heparin before elective induction, this being discontinued 6h before expected delivery with recommencement and conversion to warfarin on the first post-partum day [252]. This treatment can be continued after birth for up to 6 months. Low molecular weight

heparin is probably safe in pregnancy but there is currently insufficient data relating to efficacy in this condition so that its routine use cannot yet be endorsed [252].

In terms of prophylaxis, women who have had a previous episode, those with acquired thrombophilia (lupus or anticardiolipin antibodies) and those with other risk factors, such as pre-eclampsia, surgery or serious medical disease, should have subcutaneous heparin after delivery and standard warfarin therapy for 6–12 weeks. In the case of those with a previous history, antenatal prophylaxis with subcutaneous heparin or graduated stockings should be considered. If there is a known genetic thrombophilic disorder, antenatal and postnatal subcutaneous heparin are normally necessary and the advice of a specialized unit should be sought.

### Prognosis

The long-term prognosis of patients who survive episodes of acute pulmonary embolism is good, provided that there is no serious coexisting cardiopulmonary or malignant disease to influence the outcome. The overall mortality in subjects free of heart failure prior to the embolic episode is 8–9% [191,213], whereas in those with preceding heart failure it is five to eight times higher. In keeping with this, between two-thirds and three-quarters of lung perfusion scans show resolution within 1 year of diagnosis [192,252]. Sutton and colleagues [191,253] considered the prognosis of pulmonary embolism in four clinical categories:

- 1 acute massive, in which more than 50% of the pulmonary circulation is lost, with a very short history of less than 4h and with an acute episode of cardiovascular collapse;
- 2 subacute massive, in which also more than 50% of the pulmonary circulation is lost but with a longer history exceeding 2 weeks and with no episodes of acute collapse;
- 3 acute minor, in which less than 50% of the pulmonary circulation is lost but with a relatively short history of less than 2 weeks;
- 4 chronic, with a long history of months or years and with a pulmonary angiogram showing diminished pulmonary perfusion with irregular pulmonary vessels.

They found that the late prognosis for the first three groups was good, with no chronic pulmonary hypertension and cor pulmonale, but that 'chronic pulmonary embolism' (the smallest group) followed a progressively worsening course with right heart failure and eventual death.

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# PULMONARY HYPERTENSION

ANTHONY SEATON

## Physiological considerations

### Mechanics of the pulmonary circulation

The pressure in the pulmonary artery is determined primarily by left atrial pressure, the resistance to flow offered by the pulmonary vessels and the flow of blood through the pulmonary circulation. The proximal pulmonary arteries are of relatively high compliance and this is the main factor determining the low systolic pressure in the system. The diastolic pressure is determined by the resistance offered by the muscular precapillary vessels, and again in normal circumstances this is low. These relationships may be summarized by the simple formula:

$$P_{pa} = P_{la} + (\dot{Q}_p \times PVR) \quad [26.1]$$

where  $P_{pa}$  is the mean pulmonary arterial pressure,  $P_{la}$  the mean left atrial pressure,  $\dot{Q}_p$  the pulmonary blood flow and  $PVR$  the pulmonary vascular resistance. Of these, pulmonary arterial and left atrial pressures may be measured directly using cardiac catheterization. In many instances, a clinically acceptable estimate of left atrial pressure may be obtained by wedging a catheter in a small pulmonary artery rather than by the somewhat more complex method of atrial septal puncture. The blood flow through the pulmonary vessels may be calculated using the Fick principle as applied to the transport of oxygen by the blood [1]. If the uptake of oxygen ( $\dot{V}O_2$  in mL/min) can be measured, conventionally over 3 min with the use of an air-filled spirometer and carbon dioxide absorber, and the oxygen content (in mL/dL) of systemic arterial ( $CaO_2$ ) and mixed venous ( $C\bar{v}O_2$ ) blood determined, then blood flow is given by the equation:

$$\dot{Q}_p = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2} \times \frac{1}{10} \text{ (L/min)} \quad [26.2]$$

This simply states that during a period of 1 min a given volume of blood flowing through the pulmonary capillaries absorbs the amount of oxygen consumed and that this is the same amount as the difference between the con-

centration of oxygen in the main pulmonary artery and that in the left side of the heart. Clearly, an accurate measurement assumes steady flow conditions and no changes in oxygen consumption during the period of sampling. Nevertheless, it provides a figure that is of clinical value and which can be used with the pressure measurements to calculate PVR:

$$PVR = \frac{P_{pa} - P_{la}}{\dot{Q}_p} \quad [26.3]$$

The normal PVR is less than 2 mmHg/L/min, in contrast to the systemic resistance of 10–20 mmHg/L/min.

This traditional method of measuring cardiac output has now largely been supplanted by the somewhat less cumbersome method of thermodilution [2], a technique involving injection of 10 mL cooled dextrose solution into the right atrium via a cardiac catheter with a thermistor at its tip positioned in the pulmonary artery. The fall in temperature is sensed as a rise in resistance and a computer integrates the change against time to give a reading of output. Other methods of measuring cardiac output that have now fallen into disuse because of their complexity include dilution of injected dye or a relatively insoluble radioactive isotope such as krypton [3,4] and the rate of uptake of nitrous oxide while inside a plethysmograph [5].

The normal pulmonary artery pressure at rest is around 25/10 mmHg, with a mean of about 15 mmHg. During exercise, cardiac output increases and there is a roughly proportionate rise in pulmonary arterial pressure initially, followed by a plateau for about 7 min and then a fall to resting levels accompanied by a drop in vascular resistance [6,7]. The normal pulmonary blood flow at rest is about 4 L/min/m<sup>2</sup> and this can double during exercise [7]. Pregnancy increases cardiac output until the last trimester but is associated with a normal or low pulmonary artery pressure [8].

### Regulation of pulmonary vascular tone

The pulmonary vascular endothelial cell is central to the



control of tone in the pulmonary circulation, and recent advances in the understanding of this have important implications in the management of patients with pulmonary hypertension. The endothelium comprises active secretory cells that produce both vasodilator and vasoconstrictor substances [9,10]. Nitric oxide (previously known as endothelium-derived relaxing factor), prostacyclin and endothelium-derived hyperpolarizing factor are vasodilators, while endothelin 1 is the main vasoconstrictor. There is interaction between these two systems, with endothelin 1 promoting release of nitric oxide and conversely nitric oxide inhibiting production of endothelin 1, although the evidence suggests that PVR is normally kept low by active nitric oxide and prostacyclin secretion with smooth muscle relaxation and thus vasodilatation. Hypoxia appears to be a factor in both inhibiting release of nitric oxide and causing release of endothelin 1. In normal circumstances endothelin 1 seems to be removed by the pulmonary circulation, since arterial levels are lower than venous [11], but plasma concentrations rise in response to hypoxia [12]. In addition, hypoxia has been shown to close potassium channels in the membrane of pulmonary vascular smooth muscle cells, leading to depolarization, calcium influx and vasoconstriction [13,14].

Nitric oxide acts primarily by stimulating a rise in cyclic GMP in the smooth muscle cell via its action on guanylate cyclase. This results in the activation of potassium channels in the cell membrane, causing a rise in intracellular potassium, a corresponding fall in calcium, and muscular relaxation. Prostacyclin acts on adenylate cyclase to increase cyclic AMP, also decreasing calcium levels, while endothelium-derived hyperpolarizing factor acts directly on the potassium channels. Conversely, endothelin 1 acts on specific smooth muscle receptors, activating protein kinase C and leading to opening of calcium channels with a rise in intracellular calcium and muscle contraction.

This outline of the normal control of PVR provides a framework for understanding the mechanisms of pulmonary hypertension, especially if this syndrome starts with either extrinsic or intrinsic impairment of endothelial function and leads to muscular constriction and hypertrophy/hyperplasia with secondary changes in the media and development of abnormal vascular channels. While it therefore provides a possible unifying concept of the aetiology of several types of pulmonary hypertension, in many cases it does not explain the primary aetiological events that might lead to the activation or inhibition of the control mechanisms, and this remains an area of active research.

## Causes of pulmonary hypertension

From the foregoing, it can be seen that physiological rises in pulmonary arterial pressure accompany exercise.

However, a persistently raised pressure may result from a rise in pulmonary venous/left atrial pressure, an increase in PVR or an increase in the flow rate through the pulmonary vessels. As may be inferred from the changes that occur during exercise and in pregnancy, a high flow rate is not necessarily associated with pulmonary hypertension because the pulmonary vascular bed is able to increase its capacity, via recruitment of previously unperfused capillaries, and therefore lower its resistance to increased flow. The considerable spare capacity of the lung's vascular bed can be seen from the results of experiments on dogs, where removal of some 75% of the capillary bed is required to cause a doubling of pressure; this augmentation gradually reduces in the following years [15]. Nevertheless, this simple concept of the mechanisms of pulmonary hypertension allows a classification of its causes that is convenient for clinical differential diagnosis.

The important causes of pulmonary hypertension are shown in Table 26.1. It should be appreciated that pulmonary vascular obstruction is a common feature of prolonged pulmonary hypertension of all causes, although the pathological and clinical features of the diseases may differ considerably.

**Table 26.1** Causes of pulmonary hypertension.

---

### *Increased pulmonary vascular resistance*

#### *Hypoxic*

- Chronic airflow obstruction
- Restrictive lung diseases
- High altitude
- Hypoventilation syndromes

#### *Obstructive*

- Primary pulmonary hypertension
- Drug-induced and dietary causes
- Collagen diseases
- Hepatic cirrhosis
- Thromboembolism
- Tumour embolism
- Schistosomiasis, tropical eosinophilia
- Sickle cell and thalassaemia disease
- Veno-occlusive disease
- Myeloproliferative disorders
- Human immunodeficiency virus infection

### *Increased pulmonary venous pressure*

- Mitral valve disease
- Left ventricular failure
- Cor triatriatum
- Left atrial myxoma
- Dilated cardiomyopathy
- Hilar fibrosis

### *Increased pulmonary blood flow*

- Atrial septal defect
  - Ventricular septal defect
  - Patent ductus arteriosus
-

### Increased pulmonary vascular resistance

This group includes all the conditions of primary interest to the respiratory physician. Increased vascular resistance may occur initially as a response to chronic hypoxia, for example people who live at very high altitude or patients with chronic airflow obstruction, or as a result of blockage of pulmonary vessels due to either intramural changes or intraluminal disease. Examples of the latter are embolism by blood clot, tumour or *Schistosoma* ova, while the former is seen in drug-induced and idiopathic pulmonary hypertension and in veno-occlusive disease.

### Hypoxic pulmonary hypertension

#### *Cor pulmonale*

##### *Clinical features*

This condition is discussed in Chapter 24. It occurs characteristically in the patient with severe prolonged irreversible airflow obstruction who presents with breathlessness and episodes of congestive cardiac failure, but may also be seen in extensive bronchiectasis, cystic fibrosis and restrictive lung diseases. The clinical signs, apart from those of the lung disease, include an atrial gallop rhythm, best heard in the epigastrium, and elevation of the *a* wave of the jugular pulse. Atrial fibrillation is not uncommon and a third heart sound heralds the onset of right ventricular failure. Tricuspid regurgitation, with giant *v* waves in the jugular pulse and pulsatile liver, is a late manifestation. Signs of cardiac enlargement are often absent because of the overinflated lungs.

The arterial blood gases show hypoxaemia and a compensated respiratory acidosis; polycythaemia is frequently present. The ECG shows tall, vertically oriented P waves, a vertical or rightwards-pointing frontal QRS axis and persistence of an S wave round to  $V_5$  or  $V_6$  [16,17] (Fig. 26.1). It is unusual to see a dominant R wave in  $V_1$  in this condition. T waves are often inverted in the anterior chest leads. The important radiographic sign is widening of the pulmonary hilum and enlargement of the main pulmonary arteries [18,19]. Although measurement of the transverse diameter of the descending branch of the right pulmonary artery at its widest point is not a reliable guide to the absolute level of the pulmonary pressure, if it is greater than 20 mm pulmonary hypertension is likely to be present (Fig. 26.2). Transoesophageal echocardiography may demonstrate the relative thickness of right and left ventricular walls and the presence and amount of tricuspid regurgitation and, subject to a tendency to underestimation, may be used to calculate pulmonary arterial pressure [20–22].



**Fig. 26.1** ECG of patient with cor pulmonale showing tall peaked P waves in leads II and III, right axis deviation and S waves round to  $V_6$ .

##### *Pathology*

The right ventricular wall is hypertrophied and may even be as thick as that of the left ventricle [23]. Dissected free of the left ventricle and septum, the right ventricle is considered to exhibit hypertrophy if it weighs more than 80 g and if the ratio of the left to right ventricular weights is less than 2:1 [24]. The main pulmonary artery is dilated, often to an appreciably greater diameter than that of the aorta, and its wall may be thicker than that of the aorta [25]. Fatty streaking or atheroma may be seen in the intima. Microscopically, the main pulmonary artery shows much increased elastic tissue of the acquired type, i.e. the fibres are irregular in width and separated by wider spaces than those of the aorta [26]. The elastic pulmonary arteries (those vessels down to about 1 mm diameter) may show atheroma, medial thickening and dilatation, but the main changes occur in the pulmonary arterioles [27]. Slight medial muscular hypertrophy may occur in the smaller muscular pulmonary arteries, although they and the arterioles show the development of longitudinal muscle in the intima. Intimal fibrosis also occurs and the pulmonary arterioles develop a muscularized media between two elastic laminae. In any condition involving loss of alveolar surface area, be it emphysema or fibrosis, the capillary bed is reduced, and if this is extensive it may contribute towards the development of pulmonary hypertension [28,29].

In patients with extensive bronchiectasis or with cystic fibrosis, a prominent feature is a much increased bronchial circulation, reflected pathologically by dilated bronchial arteries and anastomoses between them and pulmonary arteries [30,31]. These vessels may make an important contribution to pulmonary hypertension, carrying blood at systemic pressures.

Pulmonary fibroses leading to honeycomb change are



**Fig. 26.2** Chest radiograph of patient with cor pulmonale showing marked enlargement of proximal pulmonary arteries.

associated with somewhat different alterations in the pulmonary arterial tree. Here there is marked intimal fibrosis and generalized medial hypertrophy of muscular pulmonary arteries, with ultimate fibrous obliteration [32,33]. In some cases, the development of thin-walled anastomatic vessels [34] may reduce the vascular resistance and thus prevent the development of pulmonary hypertension but, at the same time, increasing hypoxaemia by allowing shunting of blood across unventilated lung.

### *High-altitude disease*

#### *Clinical features*

As discussed in Chapter 2, residence at high altitude is associated with chronic hypoxaemia. Interesting differences have been described between the native people of the high Andes, whose ancestors have lived at 4000 m for tens of thousands of years, those residents of the Colorado Rockies whose ancestors have lived at over 3000 m for a century at most, and people who were born at sea level but have moved to high altitude [35]. The first group, the Quechua Indians of Peru, have relatively mild pulmonary hypertension, usually without adverse physiological effects [36], although a few develop Monge's disease [37,38]. The residents of Leadville, Colorado, tend to develop more severe pulmonary hypertension leading to

right-sided heart failure, often in childhood [39]. People moving to high altitude are at risk of acute pulmonary hypertension and pulmonary oedema (see Chapters 2 & 27).

Monge's disease occurs in the native people of the high Andes and is characterized by increasing cyanosis, hypoventilation, polycythaemia, finger clubbing, nail haemorrhages and severe pulmonary hypertension leading to cardiac failure. These changes are reversible and the disease remits if the patient is removed to lower altitudes, only to recur if he or she returns. It is not known why some individuals develop Monge's disease while most of those exposed to the same ambient oxygen tensions do not. The patient's age and altitude of residence may play a part, although the primary physiological abnormality appears to be loss of the adaptive altitude hyperventilation with insensitivity of the ventilatory response to carbon dioxide [40]. It may be that those who develop disease simply represent the extreme, least effective end of a spectrum of adaptation to hypoxia. In this respect, it is interesting to note that when chronic airflow obstruction occurs in people born and raised at high altitude the associated rise in pulmonary arterial pressure seems to be less than would occur at sea level for the level of hypoxaemia, indicating that the peripheral vascular bed itself becomes less sensitive to hypoxic stimuli in such people [41].

Studies of the comparative pathology of humans and animals living at high altitude and sea level have shed light on these adaptive changes [42]. Those animals, such as the llama, certain rodents and the yak, that have lived for millenia at high altitude in the Andes or Himalayas have a relatively low-resistance pulmonary circulation, with minimal muscularization of muscular pulmonary arteries; in contrast, native humans at these altitudes develop mild pulmonary hypertension and pronounced muscularization of these arteries. In the case of high-altitude animals, it appears that genetic *resistance* to pulmonary hypertension, expressed in morphological terms by absence of changes in pulmonary vessels, has developed, whereas in the indigenous humans a natural *acclimatization* has developed that is not always complete. Interesting cross-breeding experiments between high-altitude yaks and their low-altitude cousins (domestic cattle) have shown that resistance to hypoxic vascular change appears to be inherited as an autosomal dominant. Readers of this chapter who play Scrabble might like to know that the offspring of a yak and a cow is called a dzo, while that of a dzo and a bull is a stol!

### Pathology

The pulmonary vessels of dwellers at high altitude show the characteristic changes associated with prolonged hypoxia, namely muscularization of the pulmonary arterioles, with development of a distinct media, and the appearance of longitudinal intimal muscle. Proliferative changes are not a feature, in keeping with its potentially reversible nature.

### Alveolar hypoventilation

There are several clinical syndromes in which chronic alveolar hypoventilation occurs, leading to hypoxaemia, hypercapnia, polycythaemia and pulmonary hypertension (Table 26.2). Acute alveolar hypoventilation may occur after certain brain injuries and in intoxication with narcotic drugs. All the chronic forms may culminate in pulmonary hypertension, characterized pathologically by muscularization of the pulmonary arterioles, as in high-altitude disease.

### Mechanisms of hypoxic pulmonary hypertension

Teleologically, it is reasonable to postulate that constriction of small pulmonary vessels may occur as a response to alveolar hypoxia in order to preserve an appropriate balance between ventilation and perfusion in the lung. The presence of similar pathological changes involving the smallest precapillary vessels in a wide variety of conditions associated with alveolar hypoventilation, and their absence in patients with congenital cyanotic heart

**Table 26.2** Causes of chronic alveolar hypoventilation.

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Bronchopulmonary
Chronic airflow obstruction
Upper airway obstruction
Sleep apnoea syndromes
Adenoidal hypertrophy
Micrognathism
Laryngeal obstruction
Neuromuscular
Muscular dystrophies
Myasthenia gravis
Motoneurone disease
Bilateral diaphragmatic paralysis
Thoracic wall
Kyphoscoliosis
Ankylosing spondylitis
Poliomyelitis
Central
Post encephalitis
Parkinson's disease
Pickwickian syndrome
Ondine's curse
Idiopathic
Metabolic
Myxoedema
Chronic barbiturate intoxication

---

disease in whom the pulmonary circulation is protected from high flows by pulmonary stenosis, suggest that alveolar rather than mixed venous hypoxia is the initial stimulus. It is likely that hypoxia acts directly on pulmonary vessels, alveolar gas being able to diffuse to vessels of arteriolar size quite rapidly [43,44]. The evidence discussed above suggests that a fall in alveolar  $PO_2$  to below about 10 kPa (75 mmHg) is sensed by pulmonary smooth muscle both directly by its effect on potassium channels and indirectly by the influence of mediators released from endothelial cells, increase in endothelin 1 and decrease in nitric oxide both causing vascular constriction [45]. Such a mechanism acts by increasing calcium flux across the cell membrane, and it has been shown that inhibition of calcium influx reduces hypoxic vasoconstriction [46,47].

### Obstructive pulmonary hypertension

#### Primary pulmonary hypertension

##### Clinical features

Pulmonary hypertension of unknown cause may occur at any age, although there is an excess among female patients in the reproductive years so that the condition is seen more frequently in young women than young men. It is a rare condition, occurring in 1–2 per million per annum, reflected in the literature by the fact that specialized university hospitals have been able to report studies of only

three to five patients per year [48,49]. A familial type is recognized, being inherited as either an autosomal dominant or recessive, though this may be missed if careful investigations of the family history are not made [50,51]. In some studies an association with the major histocompatibility types HLA-DR3, DRw52 and DQw2 has been noted [52]. An association with autoimmune disease has also been suggested, since patients often seem to have Raynaud's syndrome and positive tests for autoantibodies [53]. There is also an association between systemic lupus erythematosus and pulmonary hypertension, although in this disease the pulmonary vascular involvement is usually mild [54,55]. In contrast, in hepatic cirrhosis a severe form of plexogenic pulmonary hypertension may occur, albeit rarely [56,57]; even more rarely the syndrome has been described in biliary cirrhosis, chronic active hepatitis and portal hypertension without cirrhosis [58,59]. There has been at least one report of regression after liver transplantation [60].

The patient usually presents at a stage when symptoms have occurred, and by this time the disease is well advanced in pathophysiological terms. The presenting symptoms are most commonly steadily increasing exertional dyspnoea, fatigue, chest pain of an anginal type, palpitations, dizziness on effort, and syncope [61]. Occasionally patients complain of ankle swelling. In a proportion of patients, in some series as many as 30%, there may be a history of Raynaud's syndrome [48,62]. As mentioned above, some others may have evidence of chronic liver disease, usually cirrhosis. The physical signs are characteristic: there is evidence of right ventricular enlargement with a left parasternal lift and tapping apex beat, together with a loud and often single second heart sound, a systolic ejection click, a fourth heart sound, a Graham Steell left parasternal diastolic murmur and elevated jugular *a* waves [63,64]. Recent studies suggest that the latter is in fact a summation of *a* and *v* waves [65]. In the absence of evidence of other primary heart or lung disease or of thromboembolic episodes, these signs allow the diagnosis to be made with confidence. It may be confirmed by ECG, which shows P pulmonale and signs of right ventricular hypertrophy (in this disease, a dominant R wave in  $V_1$  and  $V_2$  is characteristic; Fig. 26.3), and chest radiography, which shows large proximal pulmonary arteries and relatively avascular lungs (Fig. 26.4). A lung scan shows uniform distribution of perfusion even when the macroaggregates are injected with the patient in a sitting position (as opposed to the normal hypoperfusion of the upper zones in this circumstance). The characteristic moth-eaten appearance of the scan in multiple thromboembolic disease is absent.

Final confirmation of the diagnosis may require cardiac catheterization and sometimes lung biopsy. Both procedures are risky, deaths occurring during catheterization even in the absence of injection of hypertonic radiological

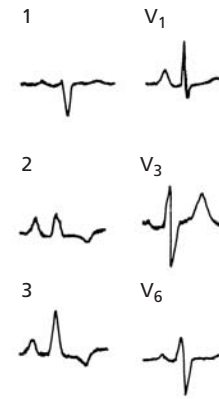


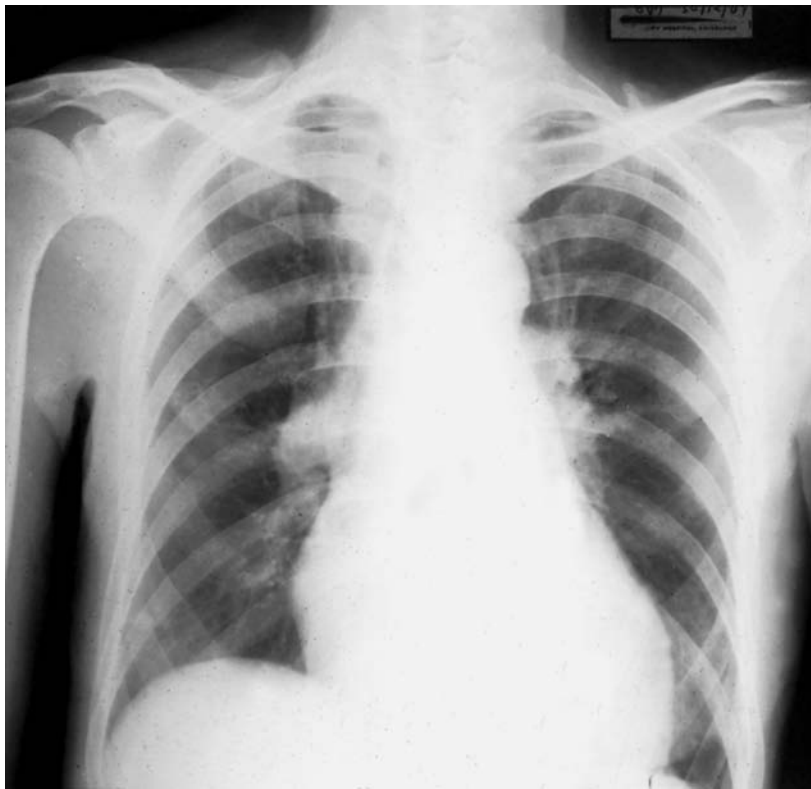
Fig. 26.3 ECG of patient with primary pulmonary hypertension showing P pulmonale, right axis deviation, dominant R wave in  $V_1$  and persistent S wave in  $V_6$ . Unusually, T waves remain positive in precordial leads in this patient.

contrast medium [48,66]. The potential benefits of these procedures should therefore be considered seriously before embarking on them, and in some cases it will be decided that they are not justified. The reason for performing them should be to exclude other, more readily treatable conditions or as a preliminary to a trial of treatment, in order to assess potential to respond.

The physiological abnormalities associated with primary pulmonary hypertension are non-specific [67,68]. Lung volumes and ventilatory capacity are usually close to normal, although a restrictive pattern may be seen. Diffusing capacity is characteristically reduced and does not rise on exercise. Arterial oxygen desaturation and hypocapnia are present and  $Pao_2$  falls further on exercise. This hypoxaemia is related to intrapulmonary shunting. The pulmonary arterial pressure and vascular resistance are of course much raised, but wedge pressure, if recordable, is normal.

While it is likely that primary pulmonary hypertension will be shown to include several distinct diseases, as with many clinical syndromes of unknown aetiology, until these have been separated it is useful to consider it a diagnosis of exclusion. This places two obligations on the clinician: first, to exclude other conditions that may mimic it and, secondly, to search for possible aetiological clues in individuals suffering from it. The differential diagnosis includes recurrent pulmonary thromboembolism, tumour embolism, pulmonary arteritis related to collagen diseases and, of course, pulmonary hypertension secondary to primary heart or lung disease. The characteristics of these conditions are discussed elsewhere in this chapter. Possible aetiological factors are discussed below.

While very rare spontaneous remissions have been reported [69], the untreated course of primary pulmonary hypertension is one of rapid deterioration to death, in part reflecting the fact that symptoms and signs are usually only detected at a late stage in its evolution [48,70]. The



**Fig. 26.4** Proximal pulmonary arterial dilatation, right ventricular enlargement and avascular lungs in patient with primary pulmonary hypertension.

median survival from diagnosis is about 2 years and only 10% survive as long as 10 years. Death results from progressive hypoxaemia and right-sided heart failure, often occurring in a sudden syncopal episode.

#### *Pathology*

The pathological changes consist of medial hypertrophy of the muscular pulmonary arteries, muscularization and reduplication of the elastic laminae of arterioles, and often extensive obliterative intimal proliferation [71–73] (Fig. 26.5). Characteristic of the condition, and distinguishing it from hypoxic pulmonary hypertension, is the presence of plexiform lesions, concentric laminar intimal fibrosis and non-inflammatory fibrinoid vasculosis (Fig. 26.6). The plexiform lesions appear to represent irregular recanalization of obliterated arterioles, and when this triad of pathological features is present the condition is characterized by pathologists as ‘plexogenic pulmonary hypertension’. It is also found in patients with pulmonary hypertension secondary to cardiac shunts and to hepatic cirrhosis. The changes in the heart and main and elastic pulmonary arteries do not differ from those in other forms of acquired pulmonary hypertension.

Having described the classical features of the disease, it is right to point out that about 50% of patients diagnosed in life as having primary disease are disclosed after death

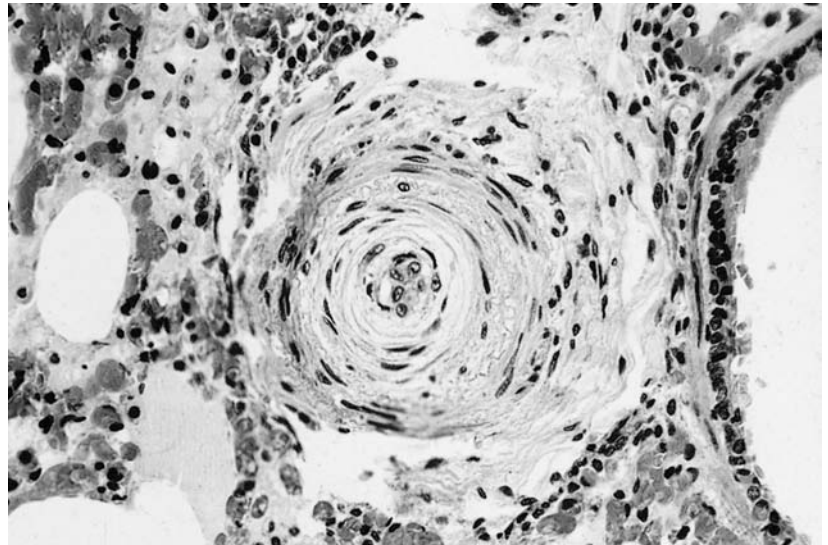
as having suffered from thrombotic disease, be it embolic or due to *in situ* clot formation [48]. This is the case even when careful clinical steps are taken to exclude venous thrombosis, and is a justification for carrying out open lung biopsy if the procedure is thought to be acceptably safe.

#### *Aetiology*

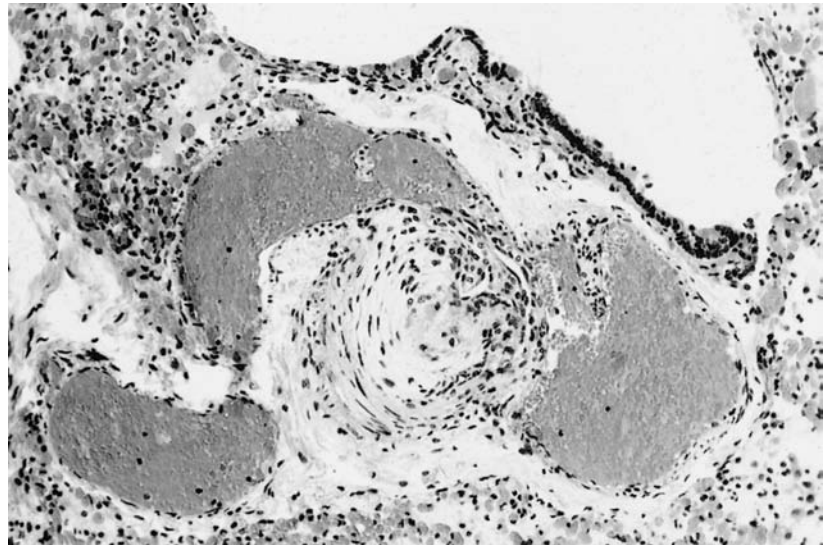
From the foregoing, it is important to remember that a proportion of patients with what appears clinically to be primary disease in fact have thromboembolic disease. This apart, the cause of the condition is not known. Its association with Raynaud’s disease suggests that in a proportion it may be a manifestation of generalized hyperreactivity of small vessels [62]. Similarly, the association with liver disease suggests that circulating vasoconstrictor substances, normally metabolized in that organ, may be responsible [56,74]. Perhaps in keeping with this, excess levels of endothelin 1, a pulmonary vasoconstrictor, have been found in the endothelium of patients with plexogenic pulmonary hypertension [75]. The predominance of the condition in females of reproductive years has given rise to the theory that female sex hormones may be responsible in some way [76], and this has been supported by the excess risk of pulmonary hypertension (and of thromboembolism) in earlier users of contraceptive



**Fig. 26.5** Necropsy specimen from patient with primary pulmonary hypertension showing arteriole with luminal obliteration by proliferated intima. Elastic laminae are just visible (haematoxylin & eosin  $\times 220$ ).



**Fig. 26.6** Another view of lung of patient in Fig. 26.5 showing obliterated small artery with some formation of new capillary channels within original lumen and dilated capillary spaces around it (haematoxylin & eosin  $\times 110$ ).



pills [77,78]. The fact that primary pulmonary hypertension may occur in families has pointed to a genetic predisposition; in familial cases it may be inherited as an autosomal dominant or recessive [50,79,80]. Finally, the occurrence of an epidemic in Europe in association with use of the appetite suppressant aminorex [81,82] has led to a search for other drug- and food-induced episodes. Fenfluramine, several other anorexigens and phenformin appear to have been associated with the disease [83–85]. In most cases the hypertension has been reversible on stopping treatment, although this is not always the case [86]. Seeds of the various species of *Crotalaria*, a plant that grows widely in tropical and subtropical regions, have

been shown to be a potent cause of pulmonary hypertension in rats and have thus provided a useful and much-exploited model of this rare disease [87]. Interestingly, aminorex itself has not produced pulmonary hypertension in rats or dogs [88].

It is perhaps reasonable to assume that reactivity of the pulmonary vasculature is distributed as a continuous variable in the population, and that some individuals are particularly susceptible to a number of potential causes of muscular contraction. Thus, in susceptible individuals, hypoxia, drugs or components of the diet may provoke sufficient muscular constriction to raise vascular resistance. Some support for this concept comes from the



description of plexogenic pulmonary hypertensive changes in the lungs of patients with familial high-altitude disease [39]. Another hypothesis is that some individuals develop disease as a result of a disturbance in the normal balance between vasodilator and vasoconstrictor influences in the pulmonary circulation, either circulating substances or endogenously produced mediators in vascular endothelium. While both these hypotheses are plausible and far from mutually exclusive, they raise the question as to what environmental factors are responsible for the disease developing in some and not in others. Nevertheless, the concept of increased active vasoconstriction has led to important advances in the management of the condition, as discussed below.

### Management

The first step in management is establishment of the diagnosis or, rather, exclusion of other conditions such as thromboembolism, sleep apnoea and primary heart and pulmonary diseases. This leaves the possibility of undiagnosed thrombosis and thus most authorities recommend treatment with long-term anticoagulants [48,89,90]. These should also prevent the occurrence of secondary *in situ* thrombosis. The second step is to establish whether a response occurs to pulmonary vasodilators. Inevitably, lack of controlled trials and no doubt selective reporting of small series of patients in the literature allow only general guidelines to be given. However, a response of a greater than 20% fall in vascular resistance may occur in up to one-third of patients, indicating possible longer-term responsiveness [91,92]. Therefore during catheterization the acute response to vasodilators should be assessed, as was done in the earliest studies of this condition [63,64]. Initially acetylcholine and tolazoline were used, but nowadays prostacyclin, adenosine or nitric oxide are the methods of choice [93–97]. All seem approximately equally effective. While nitric oxide may have fewer side-effects, it seems sensible to use the drug with which the physician has greatest experience; currently prostacyclin is the one favoured in most centres. Verapamil and hydralazine are no longer used for this purpose as they have been associated with a number of sudden deaths [98,99].

Long-term treatment with vasodilators has recently shown promise as effective management of this serious disease. Intravenous prostacyclin has been shown to increase survival and quality of life, although not without complications including sepsis derived from the intravenous delivery system [100–102]. However, this is very expensive treatment. High doses of calcium channel antagonists have now become the favoured treatment, and have been shown to produce falls in pulmonary resistance and substantial improvements in survival and quality of life in around one-quarter of patients [103,104].

This form of treatment requires careful adjustment of the dose, as fatal falls in systemic blood pressure can occur. Nifedipine and diltiazem seem to be the drugs of choice. Adenosine has also been used to supplement the effects of these drugs in patients who respond with a fall in vascular resistance [105]. Nitric oxide is a relatively safe vasodilator and can be used by inhalation, thus having no systemic effects [106,107]. As mentioned above, it has been used to assess reversibility of pulmonary vascular resistance [93]; in one case, it was administered by mask and then transtracheal catheter for 2 months while the patient was awaiting transplantation [108].

The greatest advances in management have resulted from the availability of transplantation for patients not responding, or responding inadequately, to vasodilator therapy. The first reports of successful surgery were published in the 1980s, involving transplantation of heart and lungs [109,110]. Since then it has become apparent that lung transplantation is to be preferred and that the right ventricle will recover if the graft is successful [111–114]. Recent studies have investigated the relative advantages of single and double lung transplantation, and it seems likely that in experienced hands good short-term and medium-term responses may be expected in both procedures [115], although there are haemodynamic advantages to the double lung operation [113,116,117]. This is discussed further in Chapter 59.

A scheme for the management of primary pulmonary hypertension is given in Fig. 26.7. It should be clear from this discussion that once the diagnosis of primary pulmonary hypertension is suspected, patients should be referred to a centre with special experience and with transplantation facilities, if such is available. The aim of management in the initial stages should be to establish whether clinical and haemodynamic benefits occur in response to treatment with vasodilators and anticoagulants [89]. Most authorities use a careful trial of prostacyclin and, if a response occurs, follow it with nifedipine or diltiazem, the dose being titrated to produce maximum haemodynamic benefit short of unacceptable side-effects. A proportion of responders improve significantly; those that do not, together with non-responders, should be assessed for lung transplantation.

### *Pulmonary hypertension associated with connective tissue disease*

Some 20–30% of patients presenting with apparent primary pulmonary hypertension show evidence of a more general vascular or connective tissue disease [62]. The associations with Raynaud's syndrome and cirrhosis have been mentioned [56,57,62]. It may also be a feature of the CREST (calcinosis, Raynaud's, (o)esophagitis, sclerodactyly, telangiectasia) syndrome and of full-blown systemic sclerosis [118,119]. Systemic lupus erythematosus

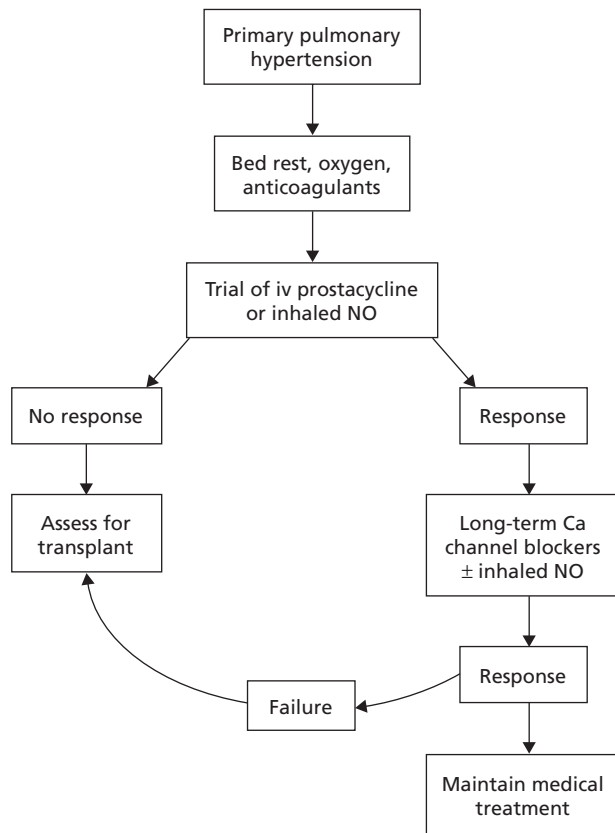


Fig. 26.7 Scheme for the management of primary pulmonary hypertension.

may occasionally be associated with pulmonary hypertension [120,121], especially when the syndrome includes the presence of the lupus anticoagulant, an immunoglobulin paradoxically associated with prolonged clotting time *in vitro* and a tendency to thrombosis *in vivo* [122]. It seems likely that the pulmonary hypertension in this syndrome is related to recurrent embolism or *in situ* thromboses [123–126]. An association of pulmonary hypertension with rheumatoid arthritis has also been described in one patient [127].

#### Embolic and other occlusive causes of pulmonary hypertension

Pulmonary embolism is discussed in Chapter 25. As noted above, a proportion of patients with apparently primary pulmonary hypertension are discovered at necropsy or on angiography to have had either multiple pulmonary emboli or possibly extensive *in situ* thromboses in small arteries [48,128]. Other patients may be detected clinically to have pulmonary hypertension as a result of repeated emboli from a recognizable venous thrombosis [129]. Embolic pulmonary hypertension may also occur in schistosomiasis and filariasis (see Chapter 22) and, rarely, as a result of disseminated tumour (see Chapter 42). Sick cell

disease and thalassaemia may also rarely cause *in situ* pulmonary arterial thromboses and lead to pulmonary hypertension [130,131]. The myeloproliferative disorders polycythaemia rubra vera and essential thrombocythaemia have also been shown to be associated with (probably thrombotic) pulmonary hypertension in a proportion of patients [132].

Acute massive pulmonary embolism is not associated with pulmonary hypertension, as the thin-walled right ventricle is incapable of generating sufficient pressure; right heart failure is the usual consequence. Moreover, since most such episodes are followed by either death or lysis of the emboli, very few appear to progress to chronic pulmonary vascular obstruction [129,133]. Somewhat more commonly, chronic venous thrombosis is associated with small, repeated and asymptomatic lung embolism. These patients usually only present at the stage when severe pulmonary hypertension has developed, the symptoms and signs being those of the primary condition [134–136]. Treatment is along the lines suggested for primary pulmonary hypertension, and the prognosis is apparently no better. Occasionally, when pulmonary angiography demonstrates widespread proximal arterial occlusion, removal of clot under cardiopulmonary bypass may prove feasible [137–139]. Sometimes the finding of reversible pulmonary hypertension at catheterization may suggest a response to vasodilators [89].

Multiple tumour embolism leading to pulmonary hypertension is a rare but well-described syndrome. The history may be quite short, the patient presenting with dyspnoea, and the radiograph may be normal. The primary tumour has most commonly arisen in breast, prostate, gastrointestinal tract or chorionic tissue [140–142]. Some such tumours, if recognized to be causing pulmonary hypertension early enough, may be susceptible to hormones or chemotherapy; a survivor of chorioncarcinoma embolism has been reported after such treatment [143]. In general, however, the syndrome is rapidly fatal.

#### Pulmonary veno-occlusive disease

##### Clinical features

In a small proportion of patients with obstructive pulmonary hypertension, the site of obstruction is found in the pulmonary veins. The patients present with progressive dyspnoea and eventually develop right-sided heart failure. The condition is no commoner in either sex, but is most usually seen in children and young adults [144–148]. In some there is a history of a preceding influenza-like illness and cases have been described in association with Hodgkin's disease [149], following chemotherapy with bleomycin and other drugs for neoplasms [150–152], and rarely after mantle radiation [153] and, in combination

with hepatic veno-occlusive disease, in bone marrow graft recipients [154]. It has also been described as one cause of pulmonary hypertension in human immunodeficiency virus (HIV) infection [155] (see below).

The clinical signs are those of pulmonary hypertension, although inspiratory crackles of pulmonary oedema and signs of pleural effusion may be present. Finger clubbing has been described but is not usual. The chest radiograph shows prominent proximal pulmonary arteries, Kerley's A and B lines and nodular opacities of pulmonary haemosiderosis (Fig. 26.8). The ECG shows evidence of right ventricular hypertrophy and the lung scan shows irregular diffuse areas of underperfusion. A bronchoscopic feature of intense hyperaemia of segmental and subsegmental bronchi has been described [156]. At catheterization, the pulmonary arterial pressure is high but the wedge pressure may be difficult to obtain and may be raised or normal.

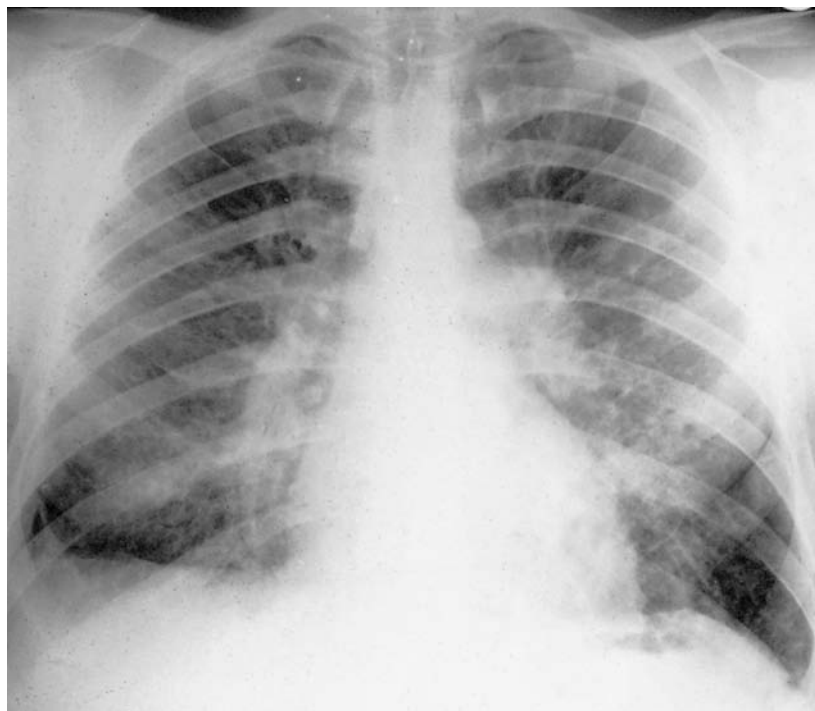
The clinical and radiographic signs are usually distinctive; if the radiograph is seen first, the physician will anticipate finding evidence of mitral stenosis and, in the absence of appropriate signs, this issue can be settled with echocardiography and right heart catheterization. On finding pulmonary hypertension, reversibility should be sought as described above. Open lung biopsy is usually necessary to confirm the diagnosis [146,149]. In one reported case, the clinical features of veno-occlusive disease were shown at postmortem to have been due to obliteration of the veins by sarcoid granulomas [157]. Sarcoidosis should therefore be included in the differential diagnosis.

The course of the disease is progressive and fatal. In many instances death occurs within 2 years of the onset of symptoms, although in some patients the illness has lasted up to 7 years [144,158]. Isolated reports have suggested the possibility of response to anticoagulants [159] and azathioprine [160]. Vasodilators have also been shown to produce improvement in a number of cases and should always be tried [149,161,162]. If this is unsuccessful, the option of lung transplantation should be considered [163].

#### *Pathology and pathogenesis*

The principal pathological lesion is partial obliteration of multiple pulmonary veins, from large ones to venules. The vessels contain acellular fibrous strands and organized thrombus showing different degrees of recanalization. Some medial hypertrophy occurs in the veins with internal and external elastic laminae [144,164,165]. The arteries show much less change, although some medial hypertrophy and intimal proliferation may occur and occasionally thromboses are also present. The changes in the veins are distributed throughout the lung, though this distribution may be patchy. The lungs themselves show congestion, with haemosiderosis and patchy interstitial pneumonitis with leucocytes, monocytes and plasma cells [158,164,166], with possible development into pulmonary fibrosis. The right chambers of the heart are dilated and hypertrophied.

The cause or causes of the syndrome are not known. The possibility that it is a reaction to viral infection has been referred to above, as has its relationship with bleomycin



**Fig. 26.8** Chest film of patient with pulmonary veno-occlusive disease, in this case thought to be secondary to Hodgkin's disease, showing pulmonary arterial dilatation, right basal effusion and Kerley's lines. (Courtesy of Dr David Ellis.)

and radiation therapy. Familial and congenital cases have suggested the possibility of intrauterine infection [167,168]. No obvious coagulation disorder has been described, although in one case evidence of an immune complex-mediated condition was adduced [169]. Finally, bush teas containing *Crotalaria* alkaloids have been described as causing veno-occlusive disease of the liver in West Indians [170]; however, these agents cause pulmonary arterial disease experimentally in rats and have not been shown to cause pulmonary venous obliteration in humans. It has been suggested that the common endpoint of a number of causative factors may be damage to the endothelium of the pulmonary veins, depleting its content of plasminogen activator and thus inhibiting normal clot lysis [171]; this remains speculative.

### ***HIV infection***

Since the late 1980s there have been a number of reports of cases of apparent primary pulmonary hypertension in patients with HIV infection [172–174]. It is very likely that this is a specific consequence of the infection itself rather than one of its infective complications [175]; in support of this, mild pulmonary hypertension has been produced in an experimental mouse model [176]. The clinical features and pathology do not differ from those of the idiopathic disease [175,177], and in some cases a response to vasodilators has been documented [177]. One report has documented pulmonary veno-occlusive disease [155], but in the other cases the pathological lesion has been on the arterial side. The virus has not been demonstrated in the vascular endothelium, suggesting that the mechanism may be related to more peripheral release of mediators.

### **Increased pulmonary venous pressure**

The causes of increased left atrial pressure are all, except one, cardiac conditions and are only mentioned here briefly; detailed descriptions can be found in cardiological textbooks. The exception is the very rare obstruction of the pulmonary veins by mediastinal fibrosis [178] (see Chapter 49). While a raised left atrial pressure of necessity causes a rise in pulmonary arterial pressure, this rise is often accentuated by reactive changes in the pulmonary vasculature. Thus the patient's likelihood of developing pulmonary oedema according to Starling's law (see Chapter 27) is reduced at the cost of the eventual development of right-sided heart failure. The pathological changes in the lungs of patients with pulmonary hypertension due to raised left atrial pressure are characteristic.

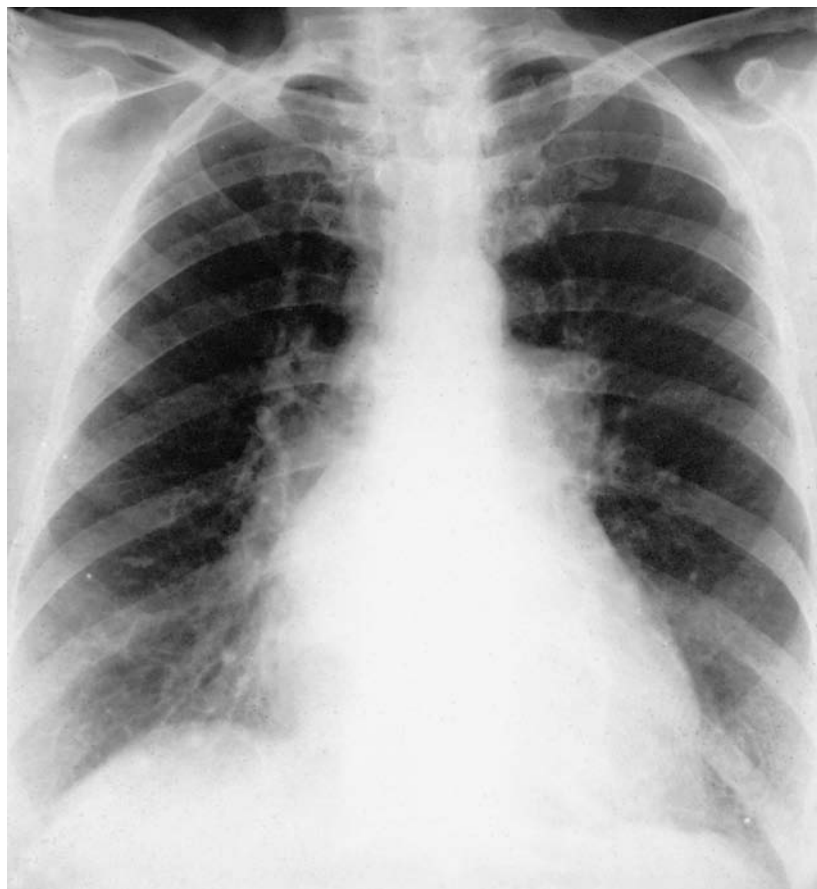
### **Mitral valve disease**

Mitral stenosis is usually caused by rheumatic disease and

is still a common condition in many subtropical parts of the world. Its importance to the respiratory physician is in differential diagnosis, since patients typically present with a history of increasing breathlessness, cough and sputum production [179]. Since winter exacerbations of bronchitis and haemoptysis are common symptoms, such patients are not infrequently referred to chest physicians. Diagnosis may be complicated by the frequent occurrence of airflow obstruction in the condition. The physical signs are characteristic, with tapping apex beat (due to a palpable first heart sound), right ventricular lift, accentuated first sound, opening snap and apical diastolic murmur. The ECG often shows right ventricular hypertrophy and P mitrale in pure stenosis, while the chest radiograph shows enlarged left atrium and pulmonary arteries, diversion of pulmonary perfusion to the upper zones (a feature well shown on xenon lung scans) and often signs of pulmonary oedema and Kerley's lines (Fig. 26.9). These classical features may be less obvious when severe pulmonary hypertension and right ventricular hypertrophy supervene and when there is a rigid calcified valve, when the auscultatory signs may disappear. However, echocardiography is a simple and reliable way of making the diagnosis and should always be used if the disease is suspected [180].

Mitral regurgitation often accompanies rheumatic mitral stenosis but may occur alone as a result of left ventricular disease, papillary muscle dysfunction or rupture of chordae tendineae. Regurgitation causes both pulmonary hypertension, secondary to raised left atrial pressure, and left ventricular hypertrophy and, eventually, failure.

Rare causes of mitral valve disease include congenital stenosis, often associated with congenital left-sided obstructive defects, congenital regurgitation in association with endocardial cushion defects (ostium primum atrial septal defect), Libman-Sacks endocarditis, and the hyper-eosinophilic syndrome [181,182]. An abnormal mitral valve may also be the site of bacterial endocarditis. The pathological changes in the lung in mitral valve disease include dilatation of proximal pulmonary arteries and narrowing of the lower zone elastic arteries with intimal fibrosis and often atheroma [183,184]. Medial hypertrophy of muscular pulmonary arteries is also most marked in the lower zone vessels. Arterioles show a muscular media and intimal thickening, capillaries and lymphatics are much dilated, and veins show medial thickening and appearances that make them difficult to distinguish from muscular arteries. Pulmonary haemosiderosis and sometimes ossification may be seen. All changes are most marked in the lower zones, where vascular obliteration and *in situ* thrombosis may occur, but plexiform lesions are not seen.



**Fig. 26.9** Chest film of patient with mitral stenosis showing left atrial shadow behind right atrium and Kerley's B lines.

#### Other causes of raised left atrial pressure

Any cause of left ventricular dysfunction raises left atrial and therefore pulmonary arterial pressure. These diseases are rarely sufficiently chronic for the pulmonary hypertension ever to become more than an incidental feature and reactive changes in the pulmonary vessels are rare. However, two conditions may mimic mitral stenosis in pathophysiological effects, left atrial myxoma and cor triatriatum.

Myxoma is a rare non-malignant cardiac tumour arising from the atrial septum, in most cases in the left atrium [185]. It is pedunculated and may present by causing symptoms and signs identical to those of mitral valve disease, including systemic embolization, or by producing systemic symptoms such as fever and weight loss mimicking bacterial endocarditis. It may cause prolonged mitral valve obstruction and lead to pulmonary hypertension but this is unusual. It is diagnosed by echocardiography. Cor triatriatum is a congenital anomaly in which the left atrium is divided by a membrane into two chambers, one receiving the pulmonary veins and the other connecting with the mitral valve [186]. The passage through the membrane may be very small, causing severe pulmonary venous hypertension from birth. Again, diagnosis is by echocardiography.

#### Increased pulmonary blood flow

As stated above, pulmonary blood flow may increase considerably without increase in the pressure in the circuit because of the spare capacity of the capillary bed. The conditions associated with increased flow, i.e. congenital and occasionally acquired left-to-right shunts, do not cause a serious rise in pulmonary pressures until reactive changes occur in the vessels. Once this happens, the pulmonary pressure may rise to systemic levels and the shunt reverse. These conditions rarely present initially to the chest physician, although most do see occasional examples presenting as pneumonia with right-sided endocarditis.

#### Atrial septal defect

The more common ostium secundum defect may remain undiscovered until adult life, when the clinical features may be confused with those of cor pulmonale [187]. Symptoms of breathlessness, cough and palpitations do not usually occur until the fourth and fifth decades. The physical signs include a systolic click and pulmonary flow murmur, with a fixed split of the second heart sound. The ECG shows partial right bundle branch block and P pulmonale. The chest radiograph shows plethoric lungs, big pulmonary arteries and large right atrium and ventricle.

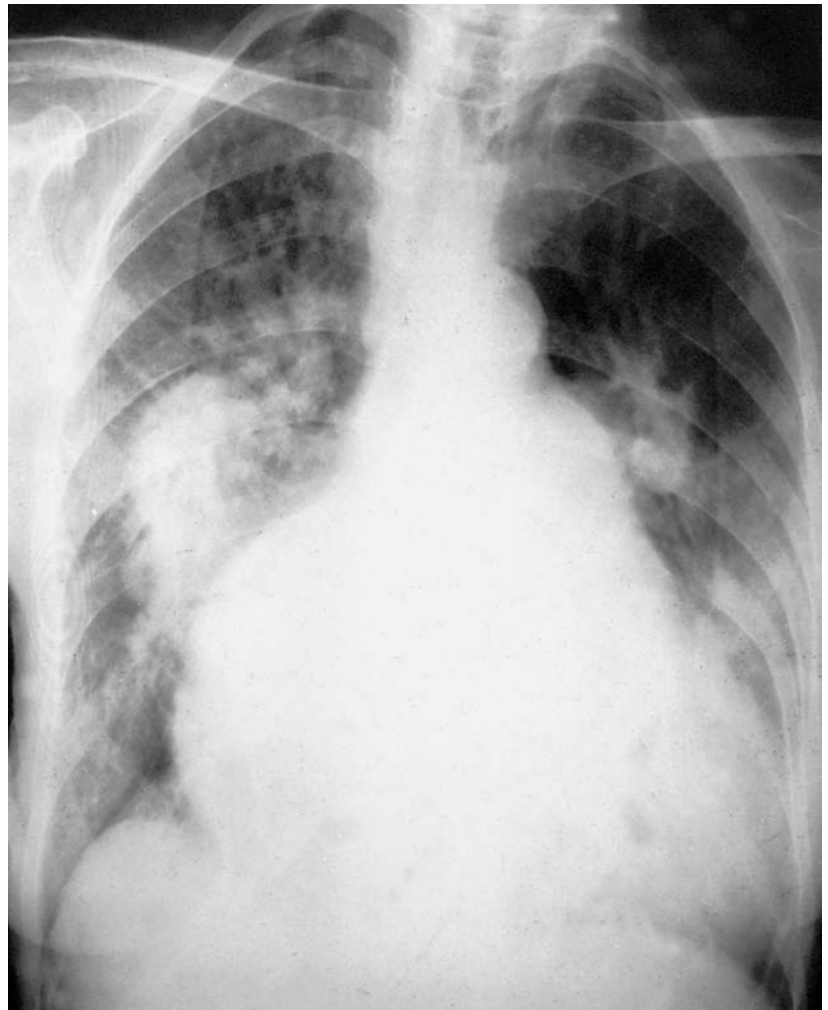
(Fig. 26.10). The increased pulmonary blood volume is reflected by a raised diffusing capacity on lung function testing. Ostium primum defects involve the mitral and tricuspid valves as well as the atrial septum; they usually present earlier in life and have additional signs of mitral regurgitation. The ECG shows a characteristic left axis deviation with partial right bundle branch block.

Both conditions may progress to cause pulmonary hypertension and eventually reversal of the shunt, the Eisenmenger syndrome. Before this occurs the pathological changes in the vascular bed are minimal, but with more severe hypertension muscularization of arterioles, medial hypertrophy of muscular arteries and marked endothelial proliferation are seen [188]. Very severe hypertension may be associated with secondary arterial and arteriolar dilatation and the development of plexiform lesions. Characteristic intimal fibrosis of pulmonary veins is seen.

### Post-tricuspid shunts

The two important post-tricuspid shunts that persist into

adult life are ventricular septal defect and patent ductus arteriosus. Ventricular septal defect may be acquired following infarction of the septum, although this causes acute pulmonary oedema rather than chronic pulmonary hypertension. Usually, the lesion is congenital and left-to-right shunting occurs when the pulmonary resistance drops naturally at birth. The increased pulmonary flow may result in pulmonary oedema in the first few weeks of life, but in many patients this is prevented by cessation of the normal involution of medial muscle in the muscular pulmonary arteries and therefore an increase in vascular resistance. In about 25% of patients the defect may close naturally as a result of muscular growth of the septum; in about 5% the shunt may be reduced by progressive stenosis of the infundibulum of the right ventricle. About 5% of patients go on to develop irreversible pulmonary hypertension and shunt reversal, usually in the second and third decades of life [189]. The symptoms are increasing exertional dyspnoea, faints, haemoptysis and, ultimately, cyanosis and clubbing. Before symptoms develop, the characteristic loud, left parasternal murmur obscuring the



**Fig. 26.10** Atrial septal defect before shunt reversal showing huge proximal pulmonary arteries, plethoric lungs and enlarged right atrium.

heart sounds and a mid-diastolic apical flow murmur are heard. The ECG may show left or right ventricular hypertrophy, depending on the stage of the disease, while the chest radiograph may show biventricular enlargement and pulmonary plethora. Before pulmonary hypertension supervenes, the carbon monoxide diffusing capacity is raised, reflecting the increased pulmonary blood volume.

It should be pointed out that in about half of all patients with persistent ventricular septal defect the shunt is small and the patient symptomless. The main hazard of this condition is bacterial endocarditis and precautions to prevent this are necessary. Most other patients are now operated on in infancy or childhood and shunt reversal is seen only rarely in the West.

The pathological changes in the pulmonary vessels reflect the stage and severity of the disease. In patients with pulmonary hypertension there is persistence of the

fetal pattern of muscle in the muscular pulmonary arteries [188]. Further progression is accompanied by medial hypertrophy and intimal proliferation, leading to progressive occlusion of muscular arteries and arterioles and the development of plexiform lesions [188].

Patent ductus arteriosus may present at any age, although left ventricular failure in infancy or childhood is most usual. The characteristic machinery murmur maximal in the second left intercostal space, together with a high-volume water-hammer pulse and radiographic changes of pulmonary plethora and left ventricular hypertrophy, usually make the diagnosis easy. Treatment is by surgery and few patients now go on to develop bacterial endarteritis or pulmonary hypertension. The latter outcome is associated with shunt reversal and clinical and pathological features like those occurring at the same stage of ventricular septal defect.

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# PULMONARY OEDEMA AND ADULT RESPIRATORY DISTRESS SYNDROME

CHRISTOPHER HASLETT

Pulmonary oedema is defined as an excess of extravascular water within the lung. This fluid may accumulate within the interstitial tissues, in alveolar walls and around vessels (interstitial oedema), within alveoli (alveolar oedema), or commonly both. Oedema may accumulate as a consequence of increased permeability of small vessels and alveolar walls or because of increased hydrostatic pressure in the small pulmonary vessels; blockage of lung lymphatics and reduction of plasma protein concentrations may also contribute occasionally. Thus two essentially different types of pulmonary oedema may be recognized clinically, high-pressure oedema and increased permeability oedema. The latter type has been called the adult respiratory distress syndrome (ARDS) [1,2].

## Anatomy and physiology

The alveolar epithelium is lined by flat type I pneumocytes that, although less frequent than the type II cells, constitute most of the alveolar surface area. These epithelial cells are connected by tight junctions, normally impermeable to fluid, and are coated on their alveolar surface by a waterproofing layer of surfactant. They are adherent to a basement membrane, which fuses in places with that of the capillary endothelial cells. The alveolar capillary is lined throughout with thin, flattened endothelial cells. The junctions between these cells are much less tight than those between the epithelial cells, thus allowing some permeation of fluid and solutes between them.

The fusion of epithelial and endothelial basement membranes is incomplete, and there is a thinner and a thicker side of the alveolar wall in relation to the capillary (Fig. 27.1). On the thin side, the membranes are fused and there is a minimal distance for gas diffusion, whereas on the thicker side the membranes are separated by an interstitial space. This space is in continuity with the spaces around the bronchovascular bundles, in the interlobular septa and under the visceral pleura, and leads therefore to the lymphatic drainage system of the lung.

As in other tissues and organs, so in the lung there is net movement of fluid from the capillaries and small precapillary and postcapillary vessels into interstitial tissue and thence via lymphatics back into the vascular compartment. This flow out of the microvasculature is determined by forces described in the Starling equation:

$$Q = K(P_{mv} - P_{pmv}) - \sigma(\pi_{mv} - \pi_{pmv}) \quad [27.1]$$

where  $Q$  represents the rate of flow of liquid,  $K$  the conductance of fluid across the barrier,  $\sigma$  the resistance of the barrier to passage of proteins,  $P_{mv}$  and  $P_{pmv}$  the microvascular and perimicrovascular hydrostatic pressures and  $\pi_{mv}$  and  $\pi_{pmv}$  the microvascular and perimicrovascular protein osmotic pressures. Under normal circumstances there is a small net flow of fluid with low protein content through the microvascular endothelium. This fluid is then transferred in the interstitial space towards the lymphatics and the peribronchovascular connective tissue space, the extra-alveolar interstitial tissue. It has been shown that a pressure gradient exists between this and the alveolar interstitial tissue [3], which together with the pumping action of respiration sucks fluid away from the alveoli. At the same time, fluid flow into the alveolar space is prevented by the tight junctions between epithelial cells and by the waterproofing action of surfactant. It has been estimated that every hour approximately 10–20 mL of fluid are removed by the lymphatics from the alveolar interstitial tissue in the normal human [4].

From this account, it can be seen that fluid accumulation occurs in the alveolar interstitial space if the hydrostatic pressure in the pulmonary capillaries is raised or if the endothelium of the capillaries becomes excessively leaky. In either case, lymphatic flow increases and excess fluid is also propelled into the extra-alveolar interstitial tissues, where it forms cuffs around bronchi and vessels. In the case of high-pressure oedema, the fluid has a low protein content and accordingly there is an increased osmotic force tending to reduce the rate of outflow. In the case of increased permeability oedema, the fluid is of relatively high protein content and this mechanism is less effective.

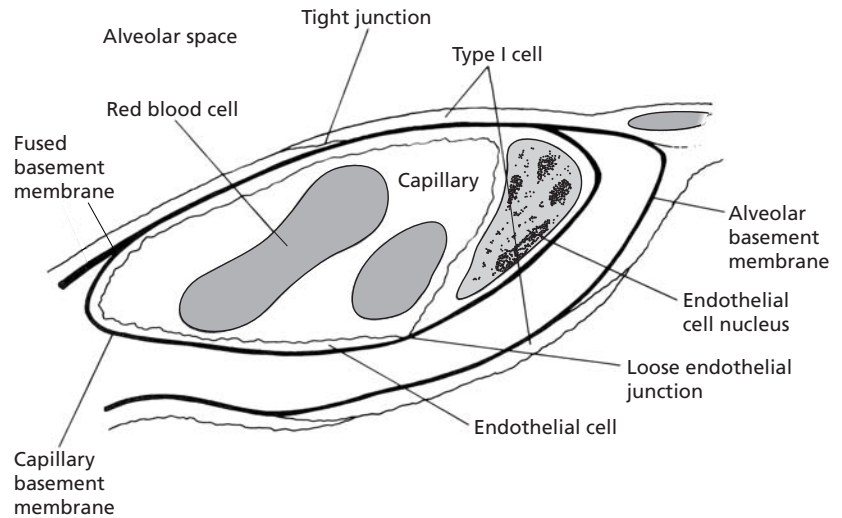


Fig. 27.1 The alveolar–capillary structures.

Translation of fluid from the alveolar interstitium to the alveolar airspaces is somewhat less easy to understand. It probably occurs because of leakage through the tight junctions resulting from the increasing interstitial pressure; it has been shown both in humans with disease and in experimental animals that the protein content of alveolar and interstitial fluid in these circumstances is identical and that the oedema fluid in left ventricular failure has a protein content about half that of plasma, suggesting that the normally impermeable membrane has lost its integrity [5–8]. It has been argued cogently that the normal alveolar surface lining is free of fluid and that the surfactant acts as a waterproofing layer, exerting a powerful force from within the airspaces to prevent ingress of water [9,10]. A rise in interstitial pressure, producing a gradient of above 2.7 kPa (20 mmHg) [11], may overcome these forces, allowing drops of water to seep through the otherwise tight junctions; sufficient drops would then merge to line the alveoli and the concave surface adopted would create a powerful force attracting more water. Alternatively, or perhaps in addition, the predominant site of leakage may be from extra-alveolar interstitial tissue through the rather more permeable bronchiolar epithelium and thence down into alveoli [12].

From Eqn 27.1 it can be seen that a fall in plasma osmotic pressure due to hypoproteinaemia may contribute to pulmonary oedema. This may occasionally be of relevance in humans, usually in association with other factors that tend to increase net outflow of fluid from the capillaries [13]. Other factors not considered by this equation may also make a contribution to the accumulation of oedema fluid in the lung. Clearly lymphatic blockage, as may occur in malignant infiltration [14], is potentially important. However pleural effusions rather than pulmonary oedema are more characteristic of the lymphatic abnormalities that occur in the yellow nails syndrome [15]. Less obviously, the perfused alveolar surface area may be rele-

vant, in that a greater area implies a greater total amount of fluid flow. Pulmonary lymphatic flow has been shown to increase in exercising sheep, presumably in relation to increased pulmonary capillary perfusion [16]. The relevance of this, if any, to human disease is unclear.

Clearance of excess fluid from the interstitial space depends on increased lymphatic flow once leakage has been reduced by appropriate therapeutic measures. However, clearance from the alveolar spaces is less easy to envisage. Some fluid may be transported into the airways and cleared by cough, as witnessed by the frothy sputum produced in left ventricular failure. Some, probably the majority in most cases, appears to be reabsorbed into the interstitial space. That this occurs despite the apparently tight junctions between epithelial cells suggests some active mechanism, and it has been suggested that water and electrolytes may be pumped actively back through the epithelial cells [17]. However, there is also evidence of some return of protein from alveoli [18], and consideration of the likely physical factors involved has led to the suggestion that surface tension may well provide sufficient force to impel fluid back between the cells, just as increased interstitial pressure forced it out originally [10]. This theory suggests that while a thin continuous layer of fluid in alveoli produces a force attracting more fluid in, if this layer is broken up (e.g. by stretching due to positive end-expiratory pressure ventilation) the presence of the hydrophobic surfactant coating beneath the fluid layer results in the formation of bubbles, rather like drops of water on a non-stick frying pan. These drops form in corners of alveoli where their surfaces generate powerful positive pressures, up to several hundred mmHg; this can be sufficient to overcome the resistance of the epithelium together with the negative oncotic force exerted by protein in the oedema fluid. Some morphological evidence that such droplets might form in the smallest airways was published 30 years ago [19].

While water and electrolytes seem able to be removed relatively easily from alveoli, proteins are clearly removed more slowly and less efficiently. The transudate of high-pressure pulmonary oedema presents less of a problem than the higher-protein fluid of increased permeability oedema, and experimental studies have shown increasing protein concentration (and therefore osmotic pressure) as the fluid is removed [20,21]. In such circumstances, the remaining protein may well contribute to the hyaline membranes frequently found lining the alveoli at autopsy [21].

High-pressure oedema

Cardiogenic pulmonary oedema is a syndrome familiar to all doctors. In brief, the important clinical features are shortness of breath, orthopnoea, paroxysmal nocturnal dyspnoea and cough. The condition may present with an acute episode, which commonly starts with cough and tachypnoea and is often associated with wheezing or with steadily increasing exertional dyspnoea and orthopnoea. In acute attacks, frothy (sometimes pink) sputum may be produced. The patient is anxious and cyanosed, and signs of the primary cardiac lesion together with bilateral basal repetitive inspiratory crackles and sometimes wheezes are found. In chronic disease, repetitive basal crackles are usually the only pulmonary sign.

The most common causes are shown in Table 27.1. Acute cardiogenic pulmonary oedema is usually due to myocardial infarction or hypertensive heart disease, and less frequently to rupture of the aortic valve or left ventricular

Table 27.1 Causes of increased pressure pulmonary oedema.

Left-sided heart failure due to:	
Coronary artery disease	
Aortic valve disease	
Hypertension	
Mitral regurgitation	
Cardiomyopathy	
Thyrotoxicosis	
Acromegaly	
Myxoedema	
Coarctation	
Patent ductus arteriosus	
Ventricular septal defect	
Supraventricular and ventricular tachycardias	
Pulmonary venous hypertension	
Mitral stenosis	
Left atrial myxoma	
Cor triatriatum	
Veno-occlusive disease	
Constrictive pericarditis, pericardial effusion	
Severe anaemia	
Fluid overload	
Cerebral injury	
Renal failure	} (in part also increased permeability)
High altitude	

septum, cardiomyopathy or left atrial myxoma. Acute episodes may also occur as a consequence of acute dysrhythmias and because of fluid overload, due to either overzealous infusion or renal failure. Chronic pulmonary oedema is most usually seen with aortic and mitral valve disease, cardiomyopathy and ischaemic myocardial disease. Veno-occlusive disease is a rare cause [22]. Pulmonary oedema of high altitude and that related to acute neurological disease are also probably in part mediated by a high pulmonary capillary pressure.

Radiological features

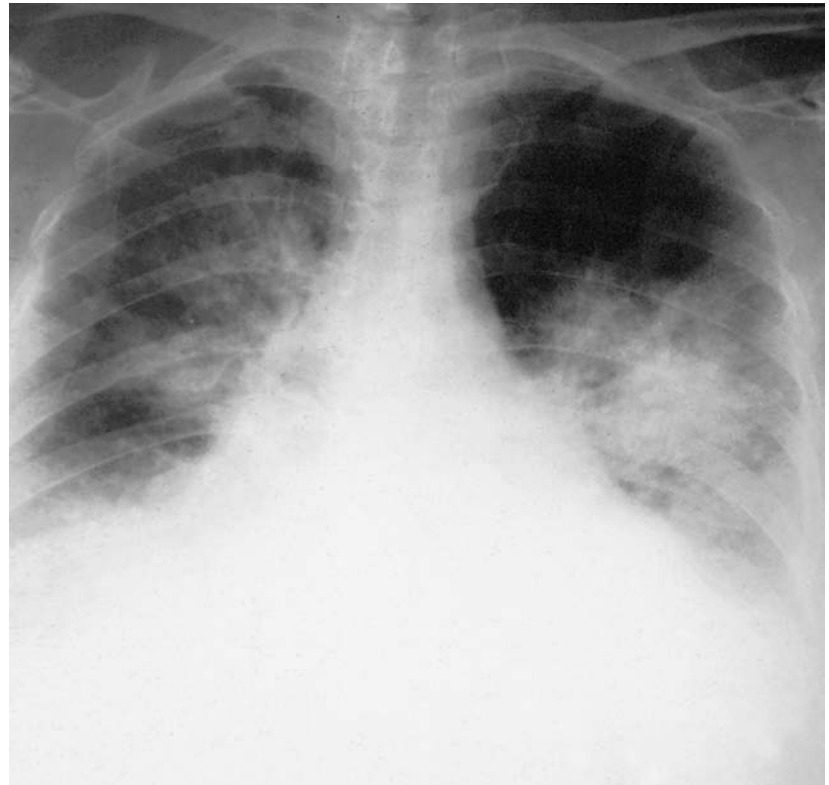
The radiological signs of interstitial oedema usually appear before clinical signs of pulmonary oedema are obvious [23,24]. The early signs are blurring of the normally clear outlines of the main pulmonary vessels, diffuse pulmonary clouding and the presence of Kerley's A and B lines (see Figs 7.46 & 7.47). The vascular blurring relates to the presence of perivascular interstitial fluid; cuffing of vessels and bronchi seen *en face* may also result from the same mechanism. Kerley's lines relate to fluid accumulation in and around lymphatics in interlobular septa. As the oedema increases, nodular opacities and ultimately signs of alveolar consolidation appear (Fig. 27.2). While increased density at the hila, the so-called 'bat's-wing' appearance, is characteristic, other patterns may be present and lateral asymmetry is not uncommon.

Other radiological signs may accompany those of the pulmonary oedema. Evidence of the primary cardiac disease, usually with left ventricular enlargement, is often present. Increased left atrial pressure and pulmonary interstitial pressure cause reduction of pulmonary arterial perfusion to the dependent part of the lung and thus diversion of flow through the upper zones; the upper zone vessels therefore appear relatively enlarged. Pleural effusion is also a frequent accompaniment of left ventricular failure. It is usually predominantly right-sided; in the absence of right-sided pleural obliteration, a unilateral left pleural effusion in heart failure should alert the physician to the presence of other disease such as pulmonary embolism. Finally, an increased intravascular blood volume may be detected by widening of the vascular pedicle, measured from a perpendicular dropped from the lateral origin of the left subclavian artery across to the lateral margin of the superior cava as it crosses the right main bronchus. The normal distance in the upright adult is 48±5 mm (26).

Diagnosis and management

Investigation of high-pressure pulmonary oedema consists essentially of differentiating it from other causes of similar clinical and radiological signs and then investigating the primary cause. Difficulties arise in early cases or





**Fig. 27.2** Severe bilateral cardiogenic pulmonary oedema showing 'bat's-wing' appearance. (From Simon & Wightman [25] with permission.)

when several conditions coexist, a frequent problem in the elderly. An abnormal ECG is almost invariably present in acute cardiogenic pulmonary oedema, together with clinical signs of the cardiac disorder. In patients in whom both cardiac failure and increased permeability oedema are serious possibilities, as with postoperative complications, extensive trauma and overwhelming infection, a percutaneous catheter floated through the pulmonary artery to record the wedge pressure is invaluable. Some points helpful in differentiating high-pressure and increased permeability oedema on the chest radiograph are listed in Table 27.2. These signs are not, of course, absolute, but taken together often allow a reasonably confident radiological diagnosis of the type of oedema.

As would be expected, the functional effects of high-pressure oedema are a reduction in lung compliance and lung volumes. Hypoxaemia is an invariable feature and this may be accompanied by hypocapnia; a metabolic acidosis may occur simultaneously because of reduced tissue oxygenation. Not infrequently, however, especially in the elderly, arterial hypercapnia may supervene in relation to increased lung stiffness and failing respiratory effort [27,28].

The management of high-pressure oedema is essentially that of the primary condition together with administration of diuretics and oxygen. The traditional therapy with morphine still has a place in acute left ventricular failure, although venesection and the use of cuffs have given way

**Table 27.2** Radiological differentiation of high-pressure and increased permeability pulmonary oedema.

	High-pressure	Acute lung injury
Cardiac size	Enlarged	Normal
Upper lobe vessels	Dilated	Normal
Kerley's lines	Present	Absent
Lung shadowing	Central, hazy	Peripheral, patchy
Air bronchograms	Unusual	Frequent

to peripheral vasodilators. Furosemide (frusemide) is the diuretic of choice because of its rapid action and its ability to increase the capacitance of the venous bed, diverting blood from the pulmonary circuit. This explains why relief of symptoms and fall in pulmonary wedge pressure may take place following intravenous administration before diuresis occurs. The positive inotropic effect of digitalis should not be forgotten in treating left ventricular failure; together with its antiarrhythmic effect this ensures that it remains a valuable drug when given in adequate digitalizing dosage. However, care must be exerted in its use following acute myocardial infarction when it may induce ventricular dysrhythmias.

High flow rates of oxygen are essential in the management of high-pressure oedema and these are safe even if the  $\text{Paco}_2$  is raised (unless there is evidence of severe airflow obstruction as well). Positive-pressure ventilation



is rarely necessary in this type of pulmonary oedema, in contrast to the situation with increased permeability oedema; it is effective in improving oxygenation, although it may impair venous return and further depress cardiac output.

### Adult respiratory distress syndrome

The first detailed clinicopathological description of ARDS was provided by Ashbaugh and colleagues [1], who in 1967 identified a subgroup of patients who could be differentiated from the majority of patients requiring intensive care management for severe respiratory failure using the following features:

- 1 tachypnoea and cyanosis refractory to oxygen treatment;
- 2 markedly reduced lung compliance on mechanical ventilation;
- 3 diffuse alveolar shadowing on the chest radiograph (Fig. 27.3);
- 4 pulmonary oedema, congestion and hyaline membranes on histological examination of necropsy specimens.

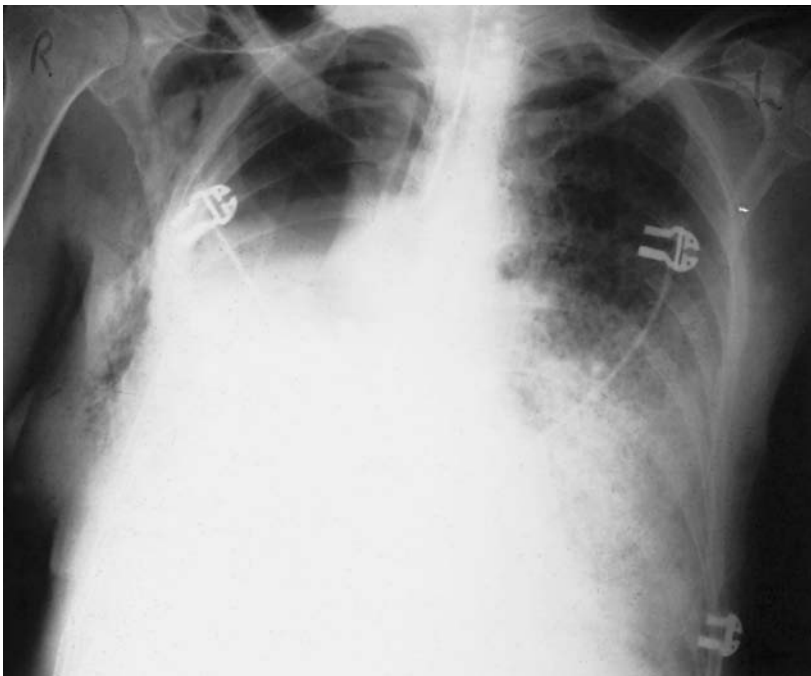
The syndrome was described as 'acute respiratory distress in adults' [1], and later in a more detailed analysis as 'adult respiratory distress syndrome' to distinguish it from a similar pathological condition in premature neonates [2]. However, it is likely that acute lung injury as a complication of severe trauma was recognized in both world wars and perhaps before [29]. In the tenth edition of his classic text *The Principles and Practice of Medicine* published in 1927

[30], William Osler remarked that 'uncontrolled septicaemia leads to a frothy pulmonary oedema that resembles serum, not the sanguineous transudative oedema fluid of...congestive cardiac failure'. Military surgeons in both world wars observed that previously healthy young men sometimes developed pulmonary oedema as a grave and usually fatal complication of non-pulmonary trauma. Indeed, this extract from the poem 'Dulce et decorum est' by the First World War poet Wilfred Owen refers to just such a case of toxic gas inhalation:

And watch the white eyes writhing in his face,  
His hanging face, like a devil's sick of sin;  
If you could hear, at every jolt, the blood  
Come gargling from the froth-corrupted lungs

The link between pulmonary oedema and severe head injury was made in the First World War. During the Second World War the association between 'wet lung' and injury of the long bones and abdomen was also increasingly recognized [31]. As observed by a modern authority on ARDS, John Murray [32], it is likely that the increasingly heroic and effective battlefield surgery in the Second World War and the use of 'Medevac' in the Vietnam War to transport the severely wounded rapidly to base hospital were factors in the increased recognition of this catastrophic complication, often called 'shock lung', in patients who hitherto would have died from their injuries. It must have been extremely distressing for the surgeons to perform life-saving surgery only to find that a significant subgroup of otherwise healthy individuals subsequently died from this late complication.

It is now widely accepted that ARDS is a syndrome of



**Fig. 27.3** Adult respiratory distress syndrome occurring in the left lung after right pneumonectomy for bronchial carcinoma.

acute inflammatory lung injury that can be initiated in pulmonary microvessels as a result of a wide variety of insults to the lung, either directly (such as toxic gas inhalation) or indirectly (such as multiple trauma and sepsis) (see Tables 27.3 & 27.4). It is also clear that in most cases ARDS is part of a systemic syndrome of acute microvascular injury, now called multiple organ failure, in which the lung features heavily but which may also include renal failure and injury to the liver, gut and skin [33]. It occurs in an unpredictable fashion, often after a latent period of several hours or days. Despite the varied causes there appears to be a common histopathological picture, characterized as 'diffuse alveolar damage' (DAD). Full-blown ARDS is a devastating condition with a mortality of 50–70%, although recent data suggest that the mortality may be reducing somewhat, probably as a result of improvement in intensive care management [34]. Some of those who remain on a mechanical ventilator enter a chronic phase, with a strikingly early and dramatic fibroproliferative response and rapidly progressive scarring. Nevertheless, in the 30–50% who survive, there is often remarkable recovery of lung function [35]. Great strides are now being made in our understanding of the inflammatory mechanisms that lead to acute lung injury and it is hoped that this will generate incisive new mechanism-based therapies that could be applied during the latent period in the hope of abrogating or aborting full-blown lung injury.

### Definition

Now it is clear that ARDS embraces a spectrum of disease severity, i.e. a continuum rather than an all-or-nothing

event, it is perhaps not surprising that it has been difficult to set the limits for a stringent diagnosis. This difficulty is further compounded by the wide range of predisposing events that appear to initiate a common clinicopathological picture (Fig. 27.4). The original Murray definition rested on the following principles:

- 1 severe dyspnoea and hypoxaemia refractory to oxygen therapy because of marked right-to-left pulmonary shunting;
- 2 widespread shadowing on the chest radiograph indicative of alveolar oedema in the absence of cardiac failure (normal pulmonary capillary wedge pressure);
- 3 decreased lung compliance on mechanical ventilation.

This definition was, and still is, valuable particularly in identifying the cast-iron case of severe ARDS. However, it has always been recognized that there are many other patients who display the classic radiographic appearances and hypoxaemia but who are not sufficiently ill or whose illness is sufficiently transient not to require mechanical ventilation. There has been additional difficulty in setting appropriate limits for pulmonary wedge pressure, particularly as patients with ARDS could easily become overloaded with fluid during their initial management or could develop an additional element of cardiac failure. There is also a relationship between certain precipitating causes and outcome, for example sepsis-provoked ARDS is often associated with multiple organ failure and has a poor prognosis, whereas many patients who develop ARDS after near-drowning or opiate overdose appear to have a more benign, self-limited form of the disease [36]. Finally, some cases of established, full-blown ARDS may progress in an unpredictable fashion to a chronic fibroproliferative phase with rapid onset of scarring, sometimes

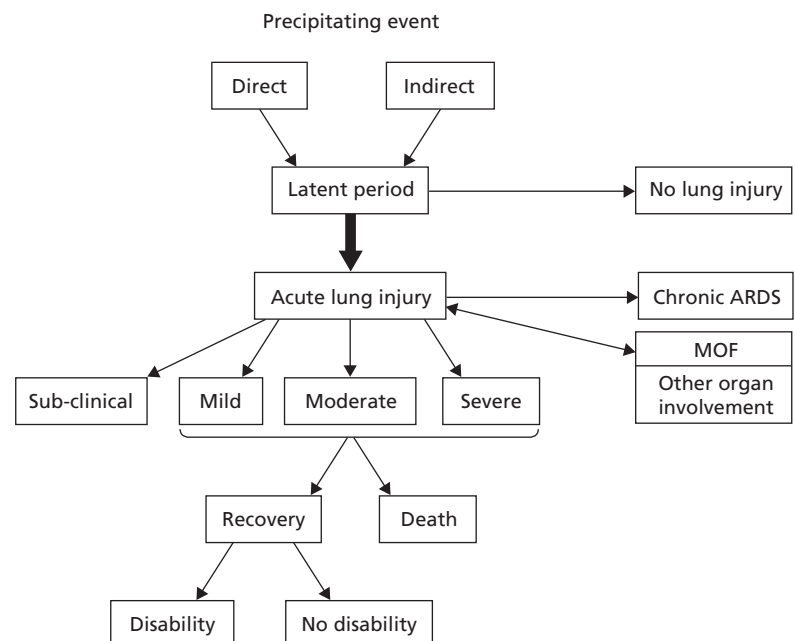


Fig. 27.4 The clinical spectrum of ARDS. MOF, Multiple organ failure.

within days. The recognition of this form of ARDS may have therapeutic implications (see below). A useful clinical definition of ARDS needs to account for these additional observations.

In order to take account of the variation in severity of lung injury, Murray's expanded definition includes a lung injury score that is now widely used [37] (Table 27.3). In 1992, an American–European conference was held to reach consensus on the clinical definition of ARDS. It was agreed that 'acute' should be substituted for 'adult' to account for the fact that this disorder can occur in children. However, the limitation to 'acute' fails to incorporate those patients who enter a chronic phase, recognition of which may be important since there could be additional therapeutic implications (see below). In the consensus criteria the Murray scoring system is simplified such that all patients with a  $P_{aO_2}/F_{iO_2}$  ratio of less than 200 are diagnosed as having ARDS (although this does not take into account any complicating effects of positive end-expiratory pressure)

**Table 27.3** Murray's lung injury score.

	Value
<i>Chest X-ray score</i>	
No alveolar shadowing	0
Alveolar consolidation confined to one quadrant	1
Alveolar consolidation confined to two quadrants	2
Alveolar consolidation confined to three quadrants	3
Alveolar consolidation confined to four quadrants	4
<i>Hypoxaemia score</i>	
$P_{aO_2}/F_{iO_2} \geq 300$	0
$P_{aO_2}/F_{iO_2}$ 225–299	1
$P_{aO_2}/F_{iO_2}$ 175–224	2
$P_{aO_2}/F_{iO_2}$ 100–174	3
$P_{aO_2}/F_{iO_2} < 100$	4
<i>PEEP score (when ventilated)</i>	
PEEP $\geq 5$ cmH <sub>2</sub> O	0
PEEP 6–8 cmH <sub>2</sub> O	1
PEEP 9–11 cmH <sub>2</sub> O	2
PEEP 12–14 cmH <sub>2</sub> O	3
PEEP $\leq 15$ cmH <sub>2</sub> O	4
<i>Respiratory compliance score (if available)</i>	
Compliance $\geq 80$ mL/cmH <sub>2</sub> O	0
Compliance 60–79 mL/cmH <sub>2</sub> O	1
Compliance 40–59 mL/cmH <sub>2</sub> O	2
Compliance 20–39 mL/cmH <sub>2</sub> O	3
Compliance $\leq 19$ mL/cmH <sub>2</sub> O	4
The final score is obtained by dividing the aggregate sum by the number of components that were included:	
No lung injury	0
Mild/moderate lung injury	0.1–2.25
Severe lung injury (ARDS)	$> 2.5$

ARDS, adult respiratory distress syndrome; PEEP, positive end-expiratory pressure.

and it was recommended that the definition should also be linked to the precipitating cause.

**Causes**

A very large number of widely diverse conditions have been implicated as causes of ARDS. It has been suggested [37,39] that these can be usefully segregated into *direct* precipitating events, for example certain pneumonias, toxic gas inhalation, etc. (Table 27.4) and *indirect* causes where the initiating insult is systemic or distant from the lung, for example pancreatitis, sepsis, etc. (Table 27.5). It is not yet possible to subclassify ARDS patients with regard to their pathogenesis since it seems, despite the diversity of precipitating events and sometimes different outcomes, that once lung injury begins there is a common pathological pattern of DAD. The segregation of precipitating events into direct and indirect has led to helpful insights into the circumstances and mechanisms by which insults distant from the lung, such as pancreatitis and severe burns, generate mediators and activate inflammatory cells that impinge on the lung and initiate the processes of endothelial and epithelial injury. Furthermore, direct causes such as inhalation of gastric acid are more likely to result in rapid onset of acute lung injury, whereas in multiple trauma or sepsis for example there is often a gap or latent period of several hours to 2 or 3 days before the patient develops clinically overt lung injury.

**Clinical spectrum**

The definition of ARDS thus includes patients at high risk

**Table 27.4** Direct causes of adult respiratory distress syndrome.

Infections
<i>Pneumocystis carinii</i> pneumonia
Influenza pneumonia
Falciparum malaria
Thoracic trauma
Lung contusion
Blast injury
Toxic gas inhalation
Phosgene
Smoke inhalation
Pulmonary embolization
Air embolism
Fat embolism
Amniotic fluid embolism
Aspiration of gastric contents (Mendelson's syndrome)
Drugs
Salicylate overdose
Opiate overdose
Bleomycin and other cytotoxic drugs
Paraquat poisoning
Near-drowning
Radiation

**Table 27.5** Indirect causes of adult respiratory distress syndrome.

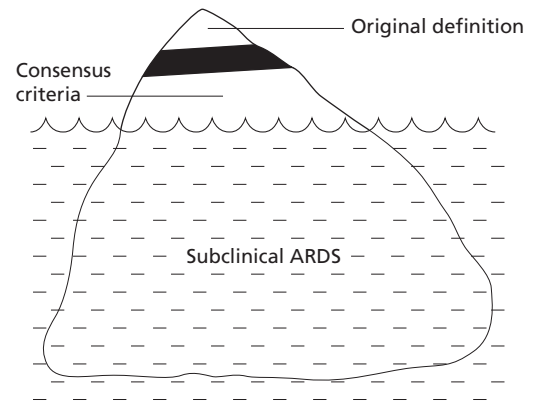
Sepsis (particularly Gram-negative septicaemia)
Multiple trauma
Acute pancreatitis
Severe burns
Multiple blood transfusions
Disseminated intravascular coagulation
Cardiopulmonary bypass
Anaphylaxis
Goodpasture's disease

who, after variable latent periods, develop acute lung injury that may be mild or severe. However, if the concept of a continuum of disease is accepted it is likely that among those at risk there will be a large number of patients with subclinical lung injury, some of whom might be detected by sophisticated imaging techniques for disclosing lung oedema whereas others may not be detectable by methods currently available (Fig. 27.4). Nevertheless the kinetic relationship between the subclinical disease group and the clinically overt group is important to our understanding of the pathogenesis of acute lung injury and also for planning clinical management. Thus the original Murray definition would include only those in the severest category, while the consensus criteria would include many more. However, if we think of ARDS as an iceberg, the concept of a continuum of lung injury suggests that the largest proportion may well be hidden beneath the surface (Fig. 27.5).

### Epidemiology

The prosecution of high-quality epidemiological research has been dogged by the vexed question of clinical definition, not only the diagnosis of ARDS but also the difficulty of achieving stringent diagnostic criteria for some of the most important predisposing conditions, such as 'sepsis syndrome'. Furthermore, the diagnosis of ARDS and its recording as a cause of death are likely to vary considerably between centres and particularly between different countries. Therefore, it is perhaps not surprising that the recorded incidence of ARDS even from the same precipitant cause may vary widely. Recent studies suggest an incidence of about 5–7 per 100 000 population per annum worldwide [40], 4.5 per 100 000 in England [41] but as low as 2 per 100 000 in the Canary Islands [42]. The latter study is likely to be an underestimate since patients under the age of 15 were excluded. It is generally held that the worldwide annual incidence of ARDS is about 5–7 per 100 000.

Studies in the USA suggest that the average patient is 49±2 years, white (2:1 white/black), male (3:2 male/female) and a non-smoker (2:1 non-smoker/smoker)

**Fig. 27.5** The ARDS iceberg; for explanation see text.

[43–45]. Established ARDS clearly represents a major demand on intensive care and rehabilitation resources. One North American study indicated that in fatalities the average time from diagnosis to death was 16 days, whereas in survivors the average time to discharge was 47 days [43].

### Predisposing events and predictive factors

It is generally held that about 40–60% of ARDS cases are associated with sepsis, 20–35% with multiple trauma, 20–35% with pneumonias and gastric aspiration, 9% with multiple massive transfusions and 7% with acute severe pancreatitis [43,46,47], although there is considerable variation between clinical studies. One clear message is that patients with several risk factors have a much higher incidence (45%) compared to those with a single factor (6%) [46]. Sepsis, particularly Gram-negative septicaemia, is clearly a major problem [46]. Bacteraemia alone is associated with a comparatively low risk of developing full-blown ARDS, but when a systemic response or organ failure occurs up to 40% may develop the condition.

Even if better clinical definitions are achieved and result in an improved overall indication of risk for a particular predisposing condition, it is currently impossible to predict which individual patients in a given risk group are most, or least, likely to develop full-blown ARDS. The ability to do this would be not only of great value in epidemiological studies and in planning management but might also highlight key mechanisms that could be targeted in those patients at the highest risk, perhaps before the onset of full-blown disease.

The recognition that ARDS in its early stages is a form of acute inflammatory microvascular injury (see below) has led to a number of attempts to identify markers of inflammatory events as important predictors of the subsequent development of full-blown disease. However, many of these studies have been disappointing, perhaps because they were carried out at varying times after insult, often in

the late risk period or when patients were established in the intensive therapy unit (ITU), by which time the inflammatory response is likely to be advanced and complex. Furthermore most included either a variety of risk groups or conditions such as 'sepsis syndrome' that make it difficult to apply an accepted stringent definition and to determine the time of onset. Early attempts were made to implicate the complement product C5a as a final common pathway, since it is activated in sepsis and multiple trauma and is known to activate neutrophils and other inflammatory cells. Yet in experimental models, complement activation alone was not sufficient to cause lung injury [48] and it has been demonstrated that there is no relationship between blood C5a levels and the development of ARDS [49]. This is not to suggest that C5a is not an important mediator, particularly in combination with other agents. In this regard it has been shown that C5a and other neutrophil-activating agents need to be combined with a priming agent such as endotoxin (the active agent on the surface of Gram-negative organisms) in order to cause either a maximal inflammatory cell secretory response [50] or neutrophil-mediated injury *in vitro* and *in vivo* [51,52]. In the late risk period it is perhaps unreasonable, given the vast redundancy of mediators inherent in the inflammatory response, to expect a single mediator to predict the onset or severity of ARDS. Nevertheless, attempts have been made to link other powerful mediators, such as tumour necrosis factor (TNF)- $\alpha$ , with ARDS in this fashion. TNF- $\alpha$  is undoubtedly centrally important in the initiation of inflammatory responses and when infused in animals causes many of the features of endotoxic shock [53], but in patients no relationship has been found between TNF- $\alpha$  levels and the onset or severity of ARDS [54,55]. In this example timing may perhaps have been an issue, since TNF- $\alpha$  is likely to exert important effects in the early stages of the initiation of the inflammatory response (see later), while measurements late in the risk period when the subclinical inflammatory response is likely to be well advanced may not be of predictive value.

An alternative approach, taken by the author, has been to investigate well-defined subgroups of patients at risk of ARDS (e.g. due to multiple trauma, in which the initiating event can usually be fairly well timed) during the earliest possible stage of the latent period, usually within 2 h of the episode. In these patients we studied events relating to inflammatory cell recruitment, adhesion, activation and secretion, and correlated markers of these with the subsequent development (or not) of ARDS using Murray's original stringent definition. Under the circumstances of our studies there was a strong statistical relationship between levels of neutrophil elastase in peripheral blood at the early stage of the risk period and subsequent progression to ARDS [56], although specificity was low and the overlap between the groups suggested that neutrophil

elastase alone is unlikely to be a valuable predictor of ARDS. In another study of other potentially damaging neutrophil mechanisms in the ARDS risk period, Parsons and colleagues [57] found in patients with sepsis that levels of superoxide dismutase and catalase activity were related to the development of ARDS.

Although a plethora of inflammatory mediators may be involved in recruiting neutrophils and other inflammatory cells to inflamed tissues, the author's studies have identified no relationship between levels of any circulating mediators and progression of ARDS. However, studies of the appearance of inflammatory mediators in bronchoalveolar lavage (BAL) fluid obtained within 2 h of the provocative event in well-defined subgroups of patients at risk of ARDS have found a strong correlation between concentrations of the neutrophil chemokine interleukin (IL)-8 and subsequent development of ARDS [58]. This relationship was not seen with any other cytokine or chemokine. While it is reasonable to be sceptical about the predictive value of a single inflammatory mediator in a complex inflammatory disease, it is possible that in the early stages of the initiation of inflammation a single mediator or perhaps a small group of mediators may be crucially important. An increase in bronchoalveolar IL-8 has also been found in premature neonates at risk of respiratory distress syndrome [59] and in infants with the cystic fibrosis gene, in whom increased levels in BAL fluid appeared to herald or precede the onset of clinically overt lung disease. Thus IL-8 may become a valuable predictor of the development of ARDS and even an important therapeutic target.

In studies of molecules on the surface of neutrophils that are important in their adhesion to endothelial cells (a prerequisite for cell sequestration/emigration), no relationship has been found between the level of expression of a range of integrin and selectin molecules on *circulating* neutrophils and the subsequent development of ARDS. Once again this is perhaps not surprising, since neutrophils that are 'sticky' are likely to be sequestered in pulmonary microvessels and therefore inaccessible to peripheral blood studies. However, a strong inverse relationship between peripheral blood levels of the cleaved, soluble form of L-selectin (sL-selectin) and the development of ARDS has been found [60]. This molecule is cleaved from the neutrophil surface during the transition from transient adhesion to firm adhesion necessary for neutrophil transmigration of the endothelium, and therefore could provide a blood marker of neutrophil-endothelial interactions in the normally inaccessible pulmonary microvasculature. sL-selectin is known to bind to activated endothelial cells and it is speculated that the low levels that correlate strongly with development of ARDS reflect widespread endothelial activation and/or incipient injury. The inverse relationship between sL-selectin levels and increasing recruitment of other injured organs in the

development of multiple organ failure in these patients lends credence to this hypothesis [60] (Fig. 27.6).

Clearly this work in the early risk period of ARDS must be confirmed and extended. While there is not a reliable prognostic indicator for ARDS currently, it is likely that one, or perhaps a small group, of these markers may serve this function.

### Pathology

The non-specific acute alveolar injury that characterizes ARDS was first described in detail in 1976 and assigned the term 'diffuse alveolar damage' (DAD) [61] (Fig. 27.7). Like the clinical situations in which diverse predisposing condi-

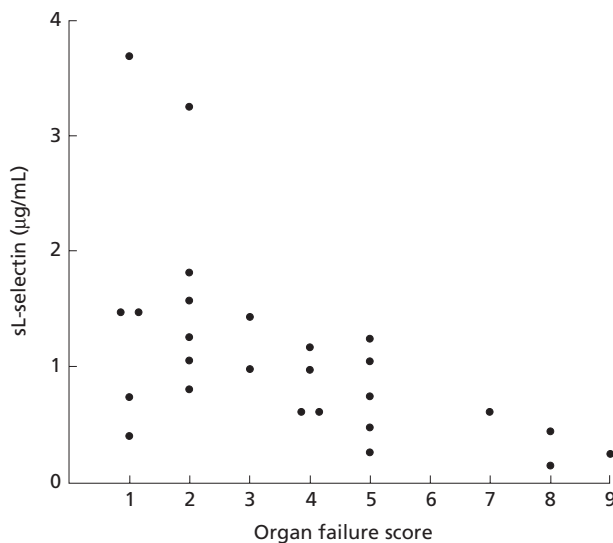


Fig. 27.6 Relationship between plasma sL-selectin levels and subsequent multiple organ failure score.

tions appear to result in the common clinical picture described by Ashbaugh and colleagues [1], DAD can be induced by a wide variety of noxious stimuli [62]. In its early stages the alveoli may show evidence of atelectasis and the lung microvessels may appear engorged. The alveolar septa are oedematous, with inflammatory exudate and extravasated erythrocytes, and a proteinaceous inflammatory exudate may flood the alveoli in some areas of the lung (see Plate 27.1a, facing p. 630). Increased numbers of neutrophils may be seen in capillaries and in the interstitial spaces and, if obtained at the earliest stages, BAL fluid shows large numbers of neutrophils (Plate 27.1b, facing p. 630). It has been shown that neutrophil numbers and the concentration of neutrophil-secreted products in BAL fluid appear to correlate with ARDS and its severity. The initiation of lung injury is likely to occur within the pulmonary capillaries (see below) and these observations draw attention to the likely role of neutrophils early in pathogenesis. On ultrastructural examination there is clear evidence of endothelial and epithelial injury, and this may be extensive. Hyaline membranes, the light microscopical hallmark of DAD, are likely to be derived from layers of necrotic epithelial cells (see Fig. 27.7).

It is important to recognize that these pathological events do not occur in a strictly ordered sequence and may appear to have reached different stages in different parts of the lungs. It is not unusual to find evidence of continued inflammatory injury at the same time as alveolar type II cell proliferation or other evidence of attempts at repair. In those patients who die after just a few days of mechanical ventilation there is often evidence of a pronounced fibroproliferative response (Plate 27.1c, facing p. 630), including fibroblast migration into injured alveoli and fibroblast proliferation and collagen deposition that within 2 weeks can be quite remarkable (Plate 27.1d, facing p. 630). Never-

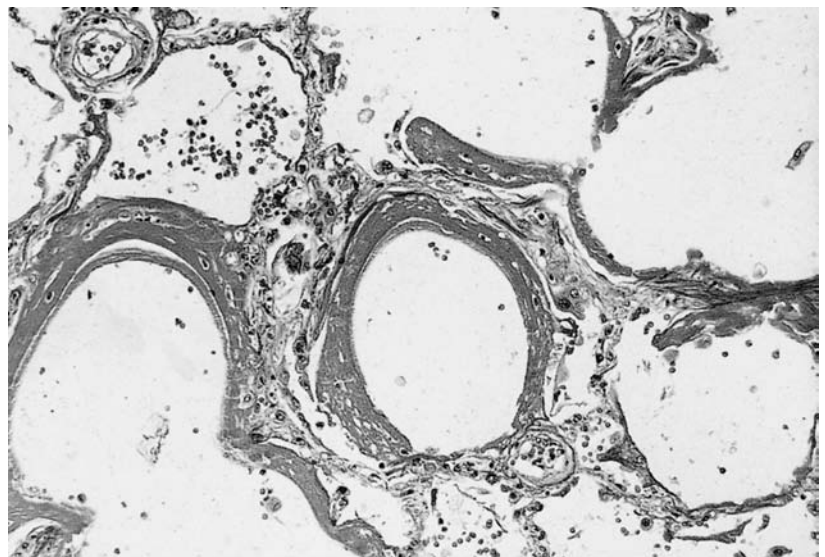


Fig. 27.7 Necropsy specimen from a patient who died of ARDS following pneumonectomy showing an alveolar duct (left) and several alveoli containing prominent proteinaceous hyaline membranes (haematoxylin & eosin  $\times 85$ ).



theless in those patients who survive the initiating condition and who are mechanically ventilated, death is not usually due to progressive respiratory failure but to failure of other organs less easy to support than the lung, to septicaemia or to secondary noscomial infections in the injured lung. However, barotrauma from mechanical ventilation of poorly compliant lungs can be a major problem in some patients.

Very little is known about the pathology of the recovery phase of ARDS since there are few case reports describing lung biopsies that have been repeated for clinical indications; these have suggested that some pulmonary remodelling may occur. Intuitively, however, the examples of occasional patients with severe ARDS who may have been ventilated for many days yet who nevertheless appear to regain virtually normal lung function suggest that some forms of inflammatory lung injury and perhaps even fibrosis have the capacity to resolve and/or become remodelled.

## Pathogenesis: cellular and humoral mechanisms

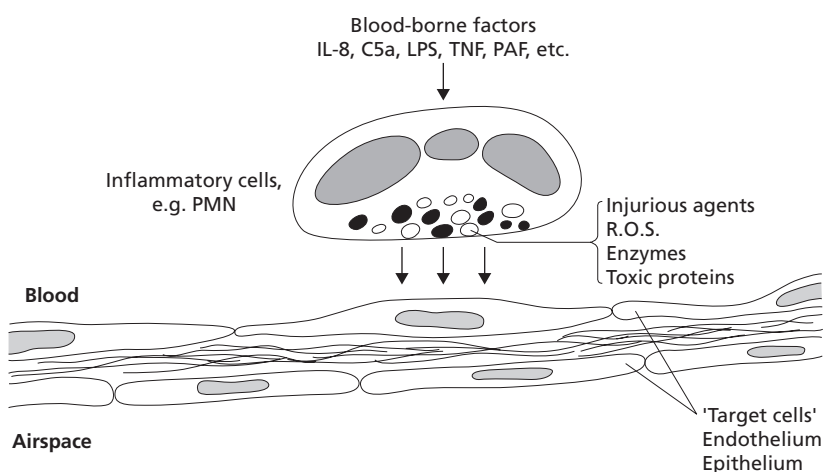
### Neutrophils and other inflammatory cells

Neutrophils have long been recognized in the lung tissues of necropsy specimens obtained early in the natural history of ARDS [63]; similarly, cytology of BAL fluid shows a high percentage of neutrophils (see Plate 27.1b, facing p. 630) and their products such as myeloperoxidase, which correlate with the development and severity of the condition. Other potentially injurious neutrophil products, including elastase and collagenase, are also found [64,65]. Of particular importance, peripheral blood levels of neutrophil elastase in patients at risk of ARDS correlate with subsequent development of the condition [56]. External imaging of radiolabelled neutrophils has demonstrated neutrophil accumulation in the lungs of patients with ARDS [66], and recent studies have suggested that

the specific neutrophil chemokine IL-8 may be critically related to the development of the condition [58]. Studies in animal models of acute lung injury using stimuli relevant to the pathogenesis of ARDS specifically implicate the neutrophil. In a sheep model, neutrophil depletion abrogated endotoxin-induced lung injury [67]; in a rabbit model of lung injury induced by a combination of endotoxin and C5a, the injury was abolished by neutrophil depletion and reconstituted by replenishment of neutrophils [52]. This body of evidence has led a number of observers to implicate the neutrophil as centrally important in the pathogenesis of ARDS [63,68,69].

This is not to suggest that other inflammatory cells are unimportant in the pathogenesis of this condition. In fact ARDS has been described in neutropenic patients [70], although histology does show the presence of some neutrophils in the lungs and it is uncertain how much of a neutrophil load may be required; certainly neutrophil replenishment experiments in neutropenic animals replace only a small proportion of the total neutrophil complement. Nevertheless, these studies of neutropenic patients raise the possibility that other cells, perhaps monocytes (which possess most, if not all, of the potentially injurious mechanisms and capacity of neutrophils), play an important ancillary role or may even substitute for granulocytes under some circumstances.

In summary, it is widely accepted that in the pathogenesis of most cases of ARDS a key role is played by the neutrophil, which is able to generate a range of reactive oxygen intermediates (ROI) and potentially histotoxic granule contents such as elastase and collagenase [71,72]. It is now generally believed that one of the earliest initiation mechanisms is damage to the capillary endothelial cells and airway epithelial cells that form the delicate alveolar gas-exchange membrane caused by toxic products of inflammatory cells that have become sequestered and activated as a result of inflammatory mediators generated as a consequence of the initiating insult (Fig. 27.8). It is uncer-



**Fig. 27.8** Early events in acute lung injury.



tain why lung injury is so prominent and is often the first clinically obvious event in the multisystem microvascular injury of multiple organ failure. However, this may be partly due to the fact that the major part of the marginating pool of neutrophils resides in lung capillaries; even in the healthy state, neutrophils (average diameter 7.5  $\mu\text{m}$ ) have to squeeze through lung capillaries (mean diameter 5.5  $\mu\text{m}$ ), thus presenting a massive surface area of contact between this potentially injurious cell and the vulnerable gas-exchange membrane (Fig. 27.9). With regard to this interaction, it is now clear that neutrophils cannot injure cells or degrade matrix proteins without being extremely closely apposed, and an understanding of the kinetics and adhesion mechanisms involved are essential in order to appreciate the pathogenesis of acute lung injury. Finally, it is now clear that neutrophil secretion is not necessarily an all-or-nothing phenomenon; it is likely to be tightly controlled and, for maximum release of ROI or granule enzymes, the neutrophil has to be exposed to agents that prime the cell (see below) together with those that trigger the cell. In order to simplify the complex mechanisms likely to be involved in neutrophil-mediated injury the discussion is divided as follows:

- 1 involvement of mediators, particularly those involved in inflammatory cell sequestration and activation in the lung;
- 2 neutrophil-endothelial interaction and the creation of an injury-favouring microenvironment;
- 3 potentially injurious neutrophil products released from primed and triggered neutrophils.

### Mediators

A very large number of mediators, indeed several media-

tor cascades, have been implicated in the pathogenesis of ARDS.

### Endotoxic lipopolysaccharide

Endotoxic lipopolysaccharide (LPS) is the main 'active' ingredient of the cell walls of *Escherichia coli* and other Gram-negative organisms that cause sepsis syndrome, septic shock and ARDS. When injected into animals, LPS causes many of the pathophysiological features of septic shock and, in some animals such as the sheep, acute lung injury [67]. Low concentrations of LPS may also enter the circulation of patients with circulatory shock by the process of translocation across the compromised gut lining [73–75]. LPS exerts a number of direct influences on neutrophils and very low concentrations (pg/mL) are required in the presence of serum when LPS interacts with a protein called LPS-binding protein to ligate CD14 on the neutrophil surface [76–78]. LPS alone is not a good neutrophil secretagogue but causes enhanced expression of neutrophil surface adhesion molecules that bind the activated endothelium [79] (see Table 27.6) and causes a direct reduction in neutrophil deformability [80], both of these events being critical for neutrophil sequestration in pulmonary microvessels. LPS also causes macrophages to release cytokines (including IL-1 and TNF- $\alpha$  which play key roles in the initiation of inflammation), activates other cascades including the complement, coagulation and kinin cascades, and generates systemic cytokines (including IL-6) that regulate the acute-phase response.

While endotoxin probably plays a key early role in the pathogenesis of ARDS [81] and can be detected in patients both with and at risk of ARDS [82–84], so far antiendotoxin therapeutic strategies have proved disappointing. In

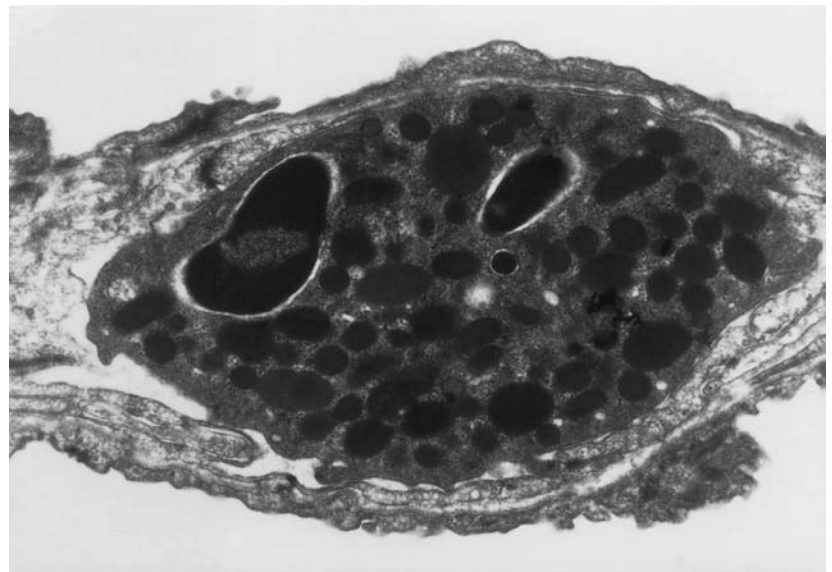


Fig. 27.9 Electron micrograph of neutrophil in pulmonary capillary.

part this may have been because the trials were carried out in patients with established sepsis syndrome when the mediator cascades induced by LPS were probably already well established, and the time may have passed when LPS might have played a critical role. Other studies suggest that while LPS alone exerts some important effects, for induction of lung injury it needs to be combined with other inflammatory mediators such as C5a [52].

#### *Peptide mediators*

Endotoxin is a potent activator of the complement cascade and for some years the peptide C5a was assumed to be centrally involved in neutrophil attraction to the lung in ARDS, since it is an effective neutrophil chemotaxin and secretagogue *in vitro* and is found in the blood of patients at risk of ARDS and of those with established disease [49]. However, lung macrophages do not produce C5a and levels of C5a in patients at risk do not correlate with the development of ARDS [49]. The current consensus is that chemokines, especially IL-8, play the key role in neutrophil chemoattraction to the lung in ARDS. However C5a, like many other mediators, probably exerts a number of powerful influences in the pathogenesis of ARDS, especially in combination with agents such as LPS [81].

There has been much less study of the role of the contact system that activates bradykinin and the clotting and fibrinolytic cascades, although these are likely to be important in the pathogenesis of ARDS. Activated kinins are vasoactive and cause increased vascular permeability. They can also act as secretagogues for neutrophils and other inflammatory cells.

#### *Cytokines*

Cytokines are a diverse group of soluble, hormone-like polypeptides produced by leucocytes and also by some constitutive tissue cells, especially macrophages, endothelial cells, epithelial cells and fibroblasts. It is likely that they play key roles at all stages of the evolution of ARDS. TNF- $\alpha$  and IL-1 are generated by alveolar macrophages on exposure to LPS and other stimuli of relevance to the pathogenesis of ARDS and are likely to play key roles in initiation [85–89]. These cytokines cause other resident cells, particularly epithelial and microvascular endothelial cells, to release IL-8 and other potent neutrophil chemokines. They also act on capillary endothelial cells to induce expression and activation of adhesion molecules necessary for neutrophil sequestration and for the creation of an injury-promoting microenvironment. Elevated levels of these agents have been found in association with ARDS [88,89]. TNF- $\alpha$  is not a good neutrophil secretagogue but like LPS it is a potent priming agent for subsequent neutrophil secretory responses.

Other cytokines, such as platelet-derived growth factor,

fibroblast growth factor and transforming growth factor  $\beta$ , are likely to play an important part in the vascular remodelling, fibroblast chemotaxis and fibroblast proliferation, and collagen synthesis that characterize the poorly understood fibroproliferative or chronic phase of ARDS.

#### *Chemokines*

This expanding family of small molecular weight peptides has received much recent attention. Depending on the position of cysteine in the molecule they have been subdivided into the C-X-C and C-C chemokines. The C-X-C subgroup contains a variety of peptides that are powerful neutrophil chemoattractants and activators, whereas the C-C group exert their chemotactic influences on monocytes and/or eosinophils. As discussed above it is now generally agreed that IL-8 and its family members are more likely to be responsible for neutrophil attraction to the lung in ARDS than C5a. IL-8 is an 8-kDa polypeptide that is a potent neutrophil chemoattractant and a powerful stimulus for endothelial cell chemotaxis and angiogenesis [90–92]. In personal studies of patients at the earliest stage of the risk period for ARDS, of a plethora of candidates studied IL-8 was the only mediator to correlate with development of ARDS [58]. Other chemokines are likely to play important roles in subsequent monocyte emigration but these are less well characterized.

#### *Membrane phospholipid derivatives*

Membrane phospholipid derivatives, including platelet-activating factor (PAF), leukotrienes, prostaglandins and prostacyclin, may influence inflammatory cells (PAF is an important neutrophil priming agent), but they also exert major influences on local blood vessels and promote the generation of oedema fluid. Thromboxanes can cause marked pulmonary vasoconstriction and may be partly responsible for the pulmonary hypertension that characterizes the early stages of ARDS.

#### ***An injury-promoting microenvironment between abnormally sequestered neutrophils and pulmonary capillary endothelial cells***

Neutrophils do not injure endothelial cells *in vitro* without direct contact, and it is likely that stimulated neutrophils interact with endothelium in such a way as to lead to the formation of a specialized intercellular microenvironment within which concentrations of histotoxic agents, such as enzymes and ROI, would reach high levels whereas their high molecular weight inhibitors would be relatively excluded. Furthermore, many potent neutrophil enzymes such as elastase are preferentially located on the leading surface of the cell and need close apposition in order to cause effects. Finally, some of the most active ROI are so

labile that they are able to act over very short tissue distances (Fig. 27.10). This concept of a restricted intercellular microenvironment necessary for neutrophil-mediated injury is supported by experiments showing that matrix degradation in areas where stimulated neutrophils are tightly adherent continues in the presence of the large molecular weight antiproteinase  $\alpha_1$ -proteinase inhibitor [93]. The creation of such a microenvironment between neutrophils and endothelial cells in lung capillaries is likely to occur because of a combination of adhesion mechanisms and alterations in neutrophil rheological properties, particularly reduction in deformability.

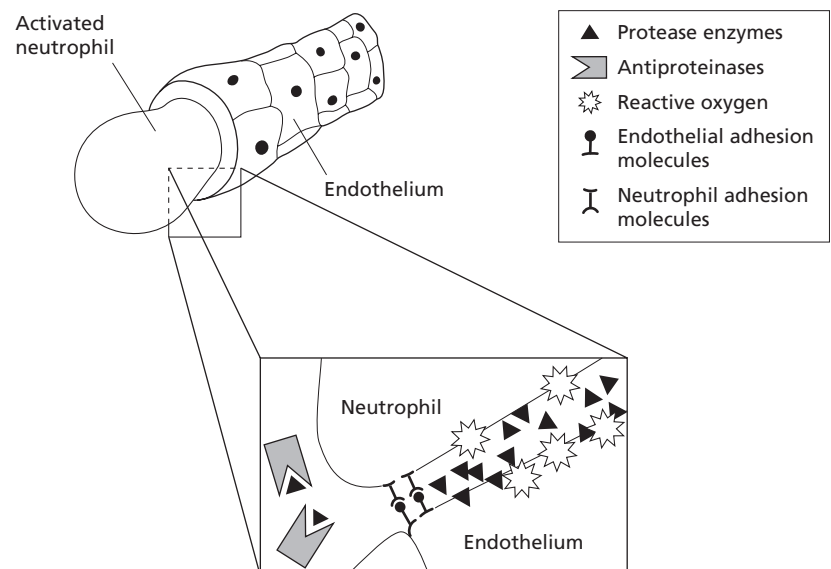
#### Neutrophil-endothelial surface adhesive molecules

Adhesion between neutrophils and endothelial cells *in vitro* is greatly enhanced within minutes of the addition of inflammatory mediators such as C5a or PAF [94]. Much of this enhanced adhesion can be abolished by monoclonal antibodies directed against the CD11/18 group of adhesive leucoproteins on the neutrophil surface. A number of inflammatory cytokines increase the expression of neutrophil adhesion molecules that are of relevance for their interaction with endothelial cells. Similarly, endothelial cells that have been activated by LPS or cytokines express adhesion molecules on their surface, and others that are already expressed become activated. *In vivo* it is likely that neutrophil adhesion to endothelial cells in microvessels occurs by a complex process involving at least two phases. In the first, transient phase of adhesion (which is nevertheless necessary for the second phase), interactions between molecules of the selectin family on neutrophils and endothelial cells are particularly important. In the second phase of tight adhesion, necessary for the creation of an injurious microenvironment and also for capillary trans-

migration of neutrophils, integrin molecules play the central role. In considering this pro-injury microenvironment it is also important to consider its kinetic aspects. For example, a neutrophil in contact with a pulmonary capillary endothelial cell for a few microseconds is a very different proposition to an activated secreting neutrophil in contact with the endothelium for several seconds. Experiments in which low concentrations of endotoxin and chemotactic peptides induce acute lung injury in the rabbit show that these agents, when combined, greatly enhance the time of contact of neutrophils with the lung microvessels [50,52].

#### Reduced neutrophil deformability

As discussed above, neutrophils are normally required to squeeze through the narrow lung capillaries, and any factors that reduce neutrophil deformability would significantly increase their time of sequestration and thereby increase the time of contact between activated or secreting neutrophils and the vulnerable gas-exchange membrane. Although it has been widely considered that abnormal sequestration occurs mainly via upregulation of neutrophil and endothelial surface adhesive molecules, alteration in neutrophil deformability is also likely to play an important role in the particular setting of the pulmonary circulation. It has been shown that neutrophils treated with relevant inflammatory mediators are retained abnormally on filters with a pore diameter of 5  $\mu\text{m}$  by a mechanism that does not involve CD11/18 but which is abolished by cytochalasin D, suggesting a role for the cytoskeleton [80,95]. Direct measurements showed that these cells had markedly reduced deformability *in vitro* and, when injected intravenously, had prolonged residence time in the pulmonary microcirculation [96]. The



**Fig. 27.10** Concept of a restricted pericellular microenvironment favouring tissue injury at the neutrophil-endothelial interface.

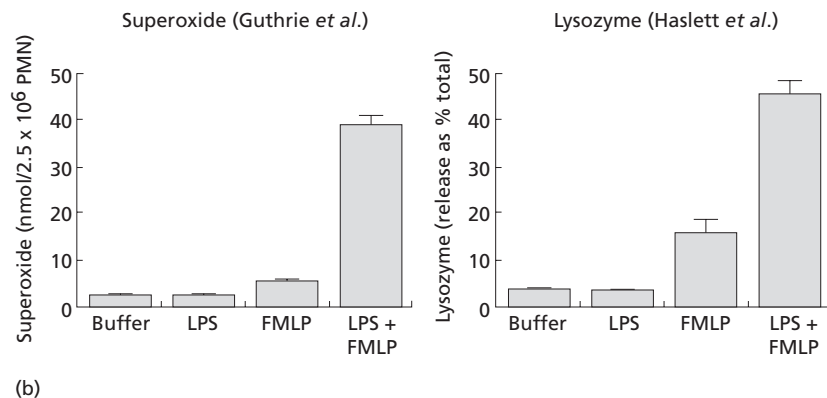
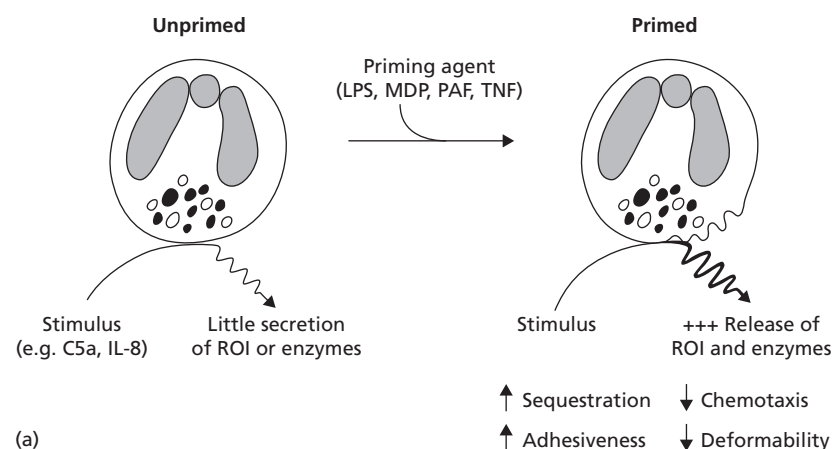
mechanisms involved in neutrophil deformability are much less well understood than the molecular mechanisms relating to the expression of adhesion molecules. However a full understanding of pathogenesis and its potential therapeutic manipulation requires that these mechanisms receive more research attention.

### Neutrophil priming, triggering and secretion of injurious products

Even when neutrophils are tightly apposed to matrix proteins or endothelial cells *in vitro*, the induction of neutrophil-mediated injury is not an all-or-nothing phenomenon. When neutrophils are prepared by stringent methods that avoid their exposure to ubiquitous LPS or other agents that might influence their function, stimulation with secretagogues such as C5a or formylmethionine leucyl-phenylalanine (fMLP) may cause little or no release of ROI or enzymes. However if these cells are previously exposed to low concentrations of LPS, which does not cause secretion itself, subsequent exposure to fMLP causes major release of ROI and granule enzymes [97,98]. These priming and triggering phenomena have a number of implications for tissue injury. Firstly, the presence *per se* of

neutrophils in tissue does not equate with injury and it is likely that they need to be primed and triggered to achieve a maximal secretory state. Secondly, when examined in this context, many of the mediators implicated in the pathogenesis of ARDS exert different effects, for example LPS, TNF- $\alpha$  and PAF are poor secretagogues but highly effective priming agents, whereas C5a, IL-8 and leukotriene B<sub>4</sub> and other neutrophil chemotaxins are potent secretagogues for primed cells [99,100]. Furthermore, in studies of neutrophil-mediated injury *in vitro* using stringently prepared neutrophils, it has been found that both LPS and C5a (or fMLP) are required for injury to occur, while *in vivo* this combination of agents is needed to induce neutrophil-mediated endothelial injury [51,52].

Therefore, rather than seeking a single common mediator it is perhaps more important to define how certain key mediators act together to influence critical mechanistic events such as neutrophil secretion. In this regard, the intracellular pathways responsible for neutrophil priming, activation and secretion are partially understood (Fig. 27.11) but little is known of how agents that prime neutrophils influence these events. While priming agents including LPS do not cause significant secretion they do exert other influences on neutrophil behaviour, including



**Fig. 27.11** (a) The concept of neutrophil priming. (b) Release of superoxide and lysozyme by neutrophils primed by lipopolysaccharide. (Data from Guthrie *et al.* [97] and Haslett *et al.* [98].)

reduction in deformability and increased adhesivity, which may be extremely important in determining the degree and longevity of neutrophil sequestration in pulmonary capillaries [95]. Indeed, in one of the *in vivo* studies mentioned above the addition of LPS, necessary for C5a-induced lung injury, greatly increased the time of contact between neutrophils (presumably primed and triggered) and pulmonary capillary endothelium [50].

When the vast array of potentially injurious neutrophil products (Table 27.6) is considered, it is clear that there is remarkable redundancy of the inflammatory response. Most of these products have probably evolved to assist the neutrophil in its rapid passage to the inflamed/infected site and in effective killing of bacteria; however, in neutrophil-mediated tissue injury and disease processes the difficulty of identifying centrally important toxic

agents cannot be exaggerated. Much circumstantial evidence has accrued to support a role for neutrophil-generated ROI in ARDS [72]. However, studies in the early risk period suggest that neutrophil elastase is also an important agent; in an *in vitro* study of neutrophil-mediated endothelial injury using neutrophil stimuli of relevance to the pathogenesis of ARDS, inhibitors of ROI alone were not effective in blocking injury, whereas a specific neutrophil elastase inhibitor exerted major inhibitory effects [51,56]. At present it seems that an effective therapeutic strategy directed against neutrophil toxic products would need to include both antiproteinase and antioxidant elements.

### Outcome of acute lung injury: resolution of inflammation and repair or progression of disease

Many of the 50% who survive ARDS appear to regain useful lung function, and it is implicit that there must be effective mechanisms whereby acute inflammation can resolve and injury can be repaired. However, by contrast with the amount of research devoted to the initiation mechanisms of inflammation, this topic has received comparatively little attention until recently. Thus the circumstances whereby the resolution and repair mechanisms fail and a chronic inflammatory phase develops, together with an excessive or inappropriate fibroproliferative response, remains a mystery not only for ARDS but for a whole spectrum of chronic inflammatory/scarring diseases in the lungs and other organs.

### Resolution of acute inflammation

For lung tissues to return to normal, all the processes that occur during the evolution of acute inflammation must be reversed, including removal of the inciting stimuli, dissipation of mediators, cessation of granulocyte emigration from blood vessels, restoration of normal microvascular permeability, cessation of monocyte emigration from blood vessels and their maturation into macrophages, removal of extravasated fluid, proteins, bacterial and cellular debris, removal of extravasated neutrophils and inflammatory macrophages, and replacement and repair of any damaged cells or tissues.

Factors involved in the cessation of inflammatory cell migration into tissues are poorly understood, although neutrophil emigration is known to cease very rapidly in the evolution of self-limited acute inflammatory responses in the lung and yet this mechanism for inhibition of neutrophil emigration appears to fail in chronic inflammatory conditions associated with lung fibrosis [101,102]. Whether the normal cessation of neutrophil emigration is due to dissipation of chemotaxins or the generation of chemotactic factor inhibitory agents remains uncertain. Similarly, the processes whereby neutrophils are removed from tissues have received little attention until recently.

**Table 27.6** A short list of neutrophil contents and products.

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<i>Azurophil granules</i>
Lysozyme
Peroxidase
Acid phosphatase
Neuraminidase
$\beta$ -Glucosaminidase
$\alpha$ -Fucosidase
Esterase
Cathepsin G
Cathepsin D
Elastase
Histonase
Defensins
Bacterial/permeability-inducing protein
Glycosaminoglycans
Chondroitin sulphate
Heparan sulphate
 <i>Specific granules</i>
Vitamin B <sub>12</sub> -binding protein
C3bi receptor
Formylmethionine leucyl-phenylalanine receptor
Lactoferrin
Cytochrome b
Lysozyme
Collagenase
 <i>Lipids</i>
Platelet-activating factor
Arachidonic acid
Thromboxane B <sub>2</sub>
Leukotriene B <sub>4</sub>
5-Hydroxyeicosatetraenoic acid
 <i>Oxidants and reductants</i>
Hydrogen ion (H <sup>+</sup> )
Superoxide anion (O <sub>2</sub> <sup>-</sup> )
Hydroxyl radical (OH <sup>•</sup> )
Singlet oxygen ( <sup>1</sup> O <sub>2</sub> )
Hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> )
Hypochlorous acid (HOCl)

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Because neutrophils and other inflammatory cells contain such a huge armamentarium of histotoxic agents and because the kinetics of their removal determines tissue residence time just as importantly as their rate of emigration, it is important that removal mechanisms and their influences are elucidated. It has been assumed that neutrophil granulocytes undergo necrosis and disintegrate at the inflamed site [103], although this would inevitably expose healthy tissue to large concentrations of potentially injurious neutrophil contents. However, an alternative tissue fate has been described, whereby extravasated neutrophils undergo apoptosis or programmed cell death [104,105]. This process is responsible for the physiological removal of unwanted cells in a whole range of tissues, including embryonic remodelling and the removal of cells from the gut crypts. In the granulocyte, apoptosis leads to shut-down of the secretory apparatus and removal of intact cells that retain their granule contents by inflammatory macrophages, which use a phagocytic recognition mechanism that fails to activate the macrophage or to provoke it to secrete proinflammatory mediators [105–110]. This ‘silent’ removal process is under a number of controls. The ‘suicide’ programme of the granulocyte can be inhibited by a range of important inflammatory mediators [111]; indeed it is likely that apoptosis is the major mechanism controlling the longevity of neutrophil and eosinophil granulocytes in inflamed tissues. Although the neutrophil and eosinophil are closely related developmentally, different mediators influence their apoptotic programme; for example both are inhibited by granulocyte-macrophage colony-stimulating factor, whereas IL-5 selectively inhibits eosinophil apoptosis and LPS selectively inhibits neutrophil apoptosis [112]. Furthermore it has been discovered that apoptosis can be induced by a variety of ‘death receptors’ that may be used differently by different cell types. For example, neutrophil apoptosis is promoted by TNF- $\alpha$  but not by corticosteroids whereas corticosteroids accelerate eosinophil apoptosis [110,113], while apoptosis in both granulocyte types is induced by ligation of the Fas surface receptor. It is possible that these different responses to death receptor ligation and the different survival factors could be employed therapeutically to remove certain cell types by the mechanism which nature intended (see below). It is also clear that macrophage clearance of apoptotic cells is under a series of controls; for example cationic proteins and low pH inhibit clearance, whereas certain cytokines, corticosteroids and CD44 ligation promote macrophage clearance of apoptotic cells [107,114].

### Repair

Even in ‘beneficial’ inflammation, as exemplified by the inflammatory response to the pneumococcus in the pathology of lobar pneumonia, there is evidence of

destruction of endothelial and epithelial cells; yet in the recovery phase of lobar pneumonia it is clear that the damaged epithelial–endothelial linings can be reconstituted with no significant evidence of a scarring response [101]. Individual cells are likely to be replaced by their neighbours but when significant numbers of cells are lost in more extensive injury there must be local cellular proliferation to reconstitute the cellular layer. Endothelial cell monolayers *in vitro* appear to be able to recover from hydrogen peroxide-mediated injury by a mechanism requiring protein synthesis [115]. Epithelial monolayers also display a remarkable capacity to regenerate, although after extensive type I epithelial cell injury it is the type II pneumocytes that proliferate to reconstitute the epithelial barrier. Type II cell proliferation is a common and often early finding in the natural history of ARDS [62], indicating that the evolution of the disease is a continuous balance between repeated injurious insults and attempts at repair.

Most pathologists agree that the extent of epithelial injury is critical in determining whether the lung attempts to heal by reconstitution of the epithelial lining or by fibrosis.

### Pathophysiology

Gas dilution studies have shown that only one-third to one-half of the total lung volume is filled with gas in patients with acute lung injury. The use of CT has revealed that most of the alveolar oedema fluid is distributed to the dependent parts of the lungs, and sometimes moving the patient to the prone position can improve gas exchange. Other studies have suggested that the distribution of oedema is more uniform in patients who are ventilated by high-frequency jet ventilation, which suggests that the mode of ventilation may also have an important influence.

Other pathophysiological consequences may result from surfactant production, which is disordered both in volume and quality, perhaps the result of dysfunctional type II cells in acute lung injury. Qualitative changes in surfactant may be sensitive markers of early alveolar injury and in some studies surfactant alterations in the risk period and early stages of ARDS correlate with the severity of lung function changes in full-blown disease. Progressive alterations in the percentage composition of certain phospholipids during the later stages of the natural history of ARDS have been observed but their functional significance is uncertain [116–119]. Surfactant function may also be detrimentally influenced by ROI and phospholipases released locally by neutrophils and other inflammatory cells; it is also likely that the high protein concentration in the inflammatory exudate markedly impairs surfactant function. These qualitative and quantitative changes in surfactant composition and the adverse influences on surfactant function undoubtedly make a

major contribution to the atelectasis, reduced functional residual capacity, reduced compliance and increased shunt found in established ARDS. However, there may be other changes in surfactant function that relate to other aspects of lung disease in ARDS. In particular much less is known about the changes in surfactant protein composition and function in ARDS. These proteins (Sp-A, Sp-B, Sp-C, Sp-D) have recently been subjected to more detailed study (see Chapter 4) and have been found to opsonize bacteria and to exert effects on inflammatory cells including macrophages [120,121]. It is possible that quantitative or qualitative changes in these proteins could have secondary influences particularly on host defence in the damaged lung, which is especially prone to secondary and often devastating infections with Gram-negative and other bacteria.

Pulmonary hypertension is a common complication of the early stages of ARDS. It contributes to pulmonary oedema and is associated with increased mortality [33,122]. In the early stages it is probably the result of vasoconstrictor mediator release. In the late stages it may occur as a result of pulmonary thromboembolism or remodelling of the injured lung. Pulmonary hypertension may also contribute to right ventricular dysfunction, although poorly characterized circulating factors also directly depress the myocardial contractility of both the right and left ventricles [123]. At different stages of ARDS augmented hypoxic pulmonary vasoconstriction and loss of the normal hypoxic vasoconstrictor response are thought to play a role in the development of pulmonary hypertension and increased right-to-left shunting respectively [124]. Decreased cardiac output in patients with ARDS may lead to impaired oxygen delivery to tissues, even in the presence of a normal  $P_{aO_2}$  [125,126]. This problem may be compounded by impaired tissue oxygen uptake, which is particularly common in patients with sepsis for example and which may occur as a result of tissue oedema, microembolization of capillaries and loss of local microvascular control mechanisms. Finally, to make matters worse, in many of these patients there is an increased tissue oxygen demand as a result of fever and tissue inflammation and repair processes.

### Clinical features and diagnosis

The patient develops progressive dyspnoea and often a non-productive cough, usually several hours or days after a recognized predisposing condition. Generally, clinically overt ARDS develops more rapidly (hours) after direct insults to the lung, such as inhalation of toxic gases or aspiration of gastric contents, than after indirect insults such as Gram-negative septicaemia or multiple trauma (24–48h). On examination the patient is tachypnoeic and often cyanosed and agitated. Tachycardia is likely to be present but the jugular pressure is not elevated [1,2]. Scat-

tered inspiratory crepitations may be heard on auscultation but this is not a constant feature.

The chest radiograph typically shows fluffy areas of opacification either throughout the lung (see Fig. 27.3) or predominantly peripherally [1,2,127]. Air bronchograms are common but Kerley's lines, pleural effusions and dilatation of upper zone vessels are rare. Thus there are a number of radiological features that can help differentiate ARDS from pulmonary oedema due to left ventricular failure (see Table 27.2), although the distinction is not always easy. Equally, distinguishing ARDS from diffuse pneumonia may be difficult: not only can the radiological features be virtually identical (e.g. in *Pneumocystis carinii* pneumonia) but pneumonia is also both a recognized cause and a complication of ARDS. Therefore, while patients can be categorized as suffering from ARDS according to the consensus criteria, it is often necessary for the clinical management to exclude cardiac failure and primary pneumonias. With regard to the former, it may be necessary to obtain a pulmonary capillary wedge pressure (normal or low in ARDS, elevated in left ventricular failure) and very occasionally a video-assisted thoracoscopic lung biopsy may be needed to exclude other causes of interstitial shadowing, especially pneumonia.

### Management

Although new therapeutic approaches may be on the horizon, the current treatment of ARDS remains supportive. The trend towards improvement in mortality has undoubtedly been the result of general advances in intensive care over the past decade or so. Because of the wide variation in patient subgroups, ventilatory techniques and other aspects of ITU management, there is as yet no widely accepted single protocol for managing ARDS. The general principles rest on the maintenance of mixed venous oxygen saturation and the function of other organs such as the kidneys, together with a readiness to diagnosis and treat potentially lethal infective complications.

### Respiratory support

Some of the technical aspects of the various approaches that have attempted to improve gas exchange and tissue oxygenation in patients with ARDS are discussed in Chapter 58, and the interested reader is referred to several excellent reviews of this topic [128–134]. One of the problems with conventional methods of respiratory support and oxygen delivery is that mechanical ventilation itself and the high concentrations of inspired oxygen necessary may both exacerbate lung injury, while the high airway pressures needed to ventilate these patients may result in barotrauma, reduced cardiac output and reduced oxygen delivery. The decision to place a patient with ARDS on mechanical ventilation, given these possible complica-



tions, depends on a variety of clinical factors including worsening gas exchange and impending exhaustion. Most patients are supported by intermittent positive pressure ventilation often combined with positive end-expiratory pressure (PEEP, 5–20 cmH<sub>2</sub>O), which may decrease shunt by reducing alveolar collapse, increasing compliance and functional residual capacity. However, there is no hard evidence that PEEP alters the clinical course of ARDS. High PEEP often leads to reduced cardiac output, and large tidal volumes may be required to counteract the increasing physiological dead space. Furthermore, the resultant high inflation pressures greatly increase the risk of barotrauma, including pneumothorax and pneumomediastinum.

A number of new ventilatory strategies have been used in an attempt to maintain airway pressures while at the same time limiting peak inspiratory pressures. These include high-frequency jet ventilation, which maximizes alveolar recruitment at lower peak inspiratory pressures [133], and inverse ratio ventilation, which works on the principle of prolonging the inspiratory time to the point of reversing the inspiratory–expiratory ratio, with similar effects on pathophysiology [134]. Temporary improvements in gas exchange may accrue by turning patients with acute lung injury to the prone position [135]. However, it is not yet established whether any of these techniques reduce mortality, since there have been few controlled trials comparing them with conventional respiratory support.

Because of the acknowledged limitations of mechanical ventilation with high  $F_{IO_2}$ , attempts have been made to develop methods of extrapulmonary gas exchange, such as extracorporeal membrane oxygenation [136,137]. However, these techniques are expensive, only available in specialist centres and associated with their own set of complications, including sepsis, coagulopathy and haemorrhage. Their benefits are still not fully established in clinical trials but because of their long-term potential for support of patients of this type there is considerable ongoing research.

## Non-respiratory support

### Infective complications

One of the gravest complications of ARDS is nosocomial infection of the injured lung, which has an associated mortality rate approaching 90% [138]. There are a number of reasons why this condition is very difficult to recognize, assess and treat in established ARDS: (i) pneumonia itself is a common risk factor for ARDS; (ii) by definition the chest film in ARDS already shows widespread pulmonary infiltrations; (iii) ARDS itself may lead to fever and leucocytosis in the absence of secondary infection; and (iv) colonization of the upper airways of intubated ventilated

patients increases with the duration of mechanical ventilation. While it is important to resist the temptation to treat all patients with broad-spectrum antibiotics based on clinical suspicion or cultures from tracheal aspirates alone, it is imperative that potentially fatal infections are recognized and treated promptly and aggressively. Most centres recommend sampling using the protected specimen bronchial brush via the fiberoptic bronchoscope or BAL via the fiberoptic bronchoscope [139,140]. The most common organisms implicated in nosocomial pneumonia are Gram negative, particularly *Pseudomonas aeruginosa* [141].

### Fluid balance

Expert management of fluid balance is critical in order to avoid causing an increase in capillary hydrostatic pressure and thus exacerbating pulmonary alveolar oedema. While the achievement of negative fluid balance can result in a reduction of alveolar oedema and improved outcome, it can also be complicated by a reduction in cardiac output, reduced oxygen delivery to tissues and renal failure. In order to maintain cardiac output and oxygen delivery to tissues and at the same time reduce pulmonary artery pressure, complex and often empirical manipulations of fluid balance, the use of loop diuretics and haemofiltration are often necessary. Early attention must be paid to nutritional support, particularly in septic patients, and feeding via a jejunal tube may help maintain gut mucosal integrity.

## Drug therapy

### Pulmonary vasodilators

Theoretically these should reduce right ventricular afterload and thereby improve cardiac output and tissue oxygen delivery. However, trials with nitrates failed to improve oxygen delivery and a multicentre trial of prostaglandin E<sub>1</sub> did not improve mortality rates [142–144]. One of the problems with intravenously delivered vasodilators is that they also dilate vessels supplying non-oxygenated lung, thus worsening the shunt problem. More recently, inhaled nitric oxide has been advocated as a therapy that should selectively dilate vessels supplying aerated lung, thereby improving ventilation–perfusion matching. Early experience has shown a prolonged haemodynamic benefit from this form of treatment with no evidence of toxicity [145,146], although whether these improvements in pathophysiology result in reduced mortality remains to be established.

### Exogenous surfactant therapy

Encouraged by trials suggesting that the intrapulmonary

instillation of exogenous bovine or synthetic surfactant improves outcome in neonatal respiratory distress syndrome [147], this approach has been recently applied to patients with ARDS. However, there are difficulties with the mode of administration in achieving widespread delivery to the small airspaces of the lung and trials so far have not been particularly encouraging [148].

#### *Anti-inflammatory therapy*

In the risk period and in the early stages of established ARDS, well-conducted multicentre trials have shown that despite their multiple effects in various inflammatory cascades, corticosteroids are of no benefit and may even have detrimental infective complications [149,150]. However, intriguing new studies, which require to be extended and confirmed, suggest that there may be a previously unsuspected role for corticosteroids in the treatment of ARDS. There are now several reports of their potential benefit in late ARDS, particularly in the fibroproliferative chronic stage [151–153]. As discussed above, antiendotoxin antibody therapy in patients with sepsis syndrome has no major overall benefit. Pentoxifylline, a methylxanthine derivative that reduces both the production of TNF- $\alpha$  and IL-1 and their biological effects on inflammatory cells, has proved beneficial in animal models, but its place in the clinical management of ARDS remains to be established.

So far, no attempt at manipulation of the inflammatory mechanisms involved in pathogenesis or of the pathophysiological events has proved to have a beneficial influence on the outcome in ARDS (Table 27.7). Nevertheless, as discussed above, recent advances in the understanding of the mechanisms of ARDS may lead to novel therapeutic strategies, and perhaps advances in the techniques of extracorporeal oxygenation may ultimately be clinically applicable. It is clear that multiple approaches could be taken against a whole range of cytokines, chemokines, adhesion molecules and inflammatory cell products, and

it is likely that many potential therapeutic candidates will emerge from the burgeoning biotechnology industry over the next decade. It is difficult to be certain which are the appropriate candidates to be tested in the large multicentre trials of well-defined subgroups of ARDS patients that will be required to establish efficacy without unacceptable detrimental effects on host defence, particularly against bacterial infection.

#### *Prospects for new mechanism-based therapy*

As discussed, most of the steady reduction in mortality over recent years is probably the result of gradual improvement in ITU management, and attempts at anti-inflammatory therapy have not been helpful so far (see Table 27.7). The use of corticosteroids in established disease and in the risk period has proved disappointing and has even been associated with detrimental effects; thus treatment remains supportive. However recent advances in our understanding of the early mechanisms of disease may provide an opportunity to develop new therapeutic approaches, which could be applied in high-risk subgroups of patients, particularly in the risk period before the full-blown complex disease is established. A number of approaches could be taken.

Certain key mediators could be targeted. However, it will be important to establish the stage of pathogenesis when that factor is most vulnerable, e.g. anti-LPS strategies have probably been applied too late in the pathogenesis of septic shock (see below). Based on recent evidence, it appears that IL-8 may be centrally important in the pathogenesis of ARDS but, again, it may need to be inhibited early in the risk period.

The processes whereby neutrophils sequester in pulmonary capillaries, including those involved in adherence to endothelial cells, could be manipulated. The mechanisms responsible for reduced deformability are poorly understood at present, although the molecular characterization of adhesion molecules required for neutrophil-

**Table 27.7** Specific therapies attempted in adult respiratory distress syndrome.

Methods	Results	Reference
<i>Pharmacological</i>		
Corticosteroids	No role in risk period or early disease; ? in chronic phase	Bernard <i>et al.</i> [149], Bone <i>et al.</i> [150]
Prostaglandin E <sub>1</sub>	Improved haemodynamics, no survival benefit	Bone <i>et al.</i> [154]
Inhaled nitric oxide	Reduces shunt, no survival benefit	Rossaint <i>et al.</i> [146]
Antiendotoxin antibodies	No overall benefit	Parrillo [84], Warren <i>et al.</i> [155]
Exogenous surfactant	No survival benefit	Lewis & Jobe [148], Weg <i>et al.</i> [156]
<i>Ventilation parameters</i>		
Inverse ratio ventilation	No proven survival benefit	Tharraz <i>et al.</i> [157]
Extracorporeal oxygenation	Role unclear, no proven survival benefit	Zapol <i>et al.</i> [136], Gattinoni [137]
High-frequency jet ventilation	Less barotrauma, but no proven survival benefit	Keogh <i>et al.</i> [133], MacIntyre <i>et al.</i> [158]

endothelial adherence are receiving much attention. The use of monoclonal antibodies that block adhesion molecules is an expensive approach and perhaps the antibody molecules may be too large for effective accessibility to the intercellular microenvironments. However, the molecular engineering of peptides that block key sites of adhesion molecule ligation may provide new drugs in the near future. There have been suggestions that different components of the adhesion molecule repertoire may be employed during different physiological processes in different organs [159]. This suggests the exciting possibility that in the longer term it may be possible to block neutrophil adhesion molecules needed for migration to sites where they are involved in disease pathogenesis, while perhaps retaining their ability to migrate to other sites for the purpose of host defence.

It may be possible to block key neutrophil injurious products. However, in this prime example of redundancy, which ones should be blocked? There is much circumstantial evidence that ROI generated by neutrophils and other inflammatory cells are centrally important in pathogenesis and there is increasing recent evidence that neutrophil elastase may be an important target.

By now, it should be appreciated that any approach (including all three mentioned above) that would effectively wipe out the neutrophil effector pathway has a major drawback, namely the loss of these highly effective mechanisms in host defence, particularly against bacteria. While this consideration may be more important in chronic inflammatory diseases and may represent less of a problem in acute tissue injury syndromes such as ARDS (in which patients could be supported during the application of such therapies for a few days), it must be remembered that injured, burned and septic patients are likely to be particularly at risk from potentially life-threatening infections; it is of interest that much of the increased morbidity and mortality observed in the multicentre studies of corticosteroid therapy in ARDS were associated with infective complications [149,150]. As we learn more about the inflammatory response it seems clear that the very same mechanisms that evolved to protect the host against bacterial invasion are turned against the host in the pathogenesis of inflammatory diseases, and it is unlikely that we will be able to dissect the mainly detrimental mechanisms from those crucially involved in host defence. Thus inflammation is a double-edged sword, and this paradox, together with the very many redundant mechanisms, are perhaps the biggest problems in the design of anti-inflammatory strategies.

Nevertheless, other approaches could be taken which might not have the same implications for host defence. It has become clear that epithelial cells and endothelial cells *in vitro* and *in vivo* have the capacity to resist a certain amount of oxidative and/or protease-mediated damage. We are beginning to learn more about these cytoprotective

mechanisms, for example the role of glutathione and small molecular weight antiproteinases such as secretory leuko-proteinase inhibitor and elafin. In the future it may be possible, in the ARDS risk period for example, to augment the production of such protective mechanisms by the endothelial and epithelial cells themselves using pharmacological or gene-therapeutic approaches [160].

It may also be possible to harness the poorly understood mechanisms whereby acute inflammation normally resolves spontaneously. By contrast with initiation mechanisms, this side of the inflammatory equation has been subjected to far less research. However, it now seems clear that apoptosis is a key mechanism controlling the functional longevity of neutrophils and other granulocytes at the inflamed sites. As discussed above, in granulocytes apoptosis leads to cessation of secretion and to their silent removal by local macrophages. When more is known about the selective use of different death receptors or the induction of apoptosis in different cell types it may be possible to induce the selective removal of neutrophil granulocytes at an appropriate stage in the pathogenesis of ARDS. Finally, recent studies have suggested that anti-inflammatory cytokines may be important in the outcome of established ARDS. In studies of the risk period it appears that while IL-8 is a key predictive and mechanistic factor involved in whether patients progress to full-blown disease, once the diagnosis of ARDS is established the levels of IL-8 in blood or BAL fluid or of any other proinflammatory mediator are related to outcome. This has led to speculation that in established disease certain anti-inflammatory cytokines, such as IL-1 receptor antagonist or IL-10, may dictate outcome. Indeed, research on patients with established ARDS shows that mortality appears to be associated with lower levels of IL-1 receptor antagonist and IL-10 in BAL fluid compared with those who survive [161]. Thus it is possible that outcome is more related to the patient's ability to mount an effective anti-inflammatory cytokine response, which might then permit resolution and repair processes to take over. These studies need to be confirmed and extended but, if correct, suggest a future therapeutic strategy whereby an ineffective anti-inflammatory cytokine response could be remedied, perhaps by genetic augmentation of their production in the lung tissues of ARDS patients.

## **Outcome of ARDS: its natural history and sequelae**

### **Mortality**

Most studies have indicated a mortality rate of 50–70% [162–164], with little change since the syndrome was first described 30 years ago. However, some recent longitudinal studies suggest a fall in mortality. In one single-centre study there was a reduction in mortality from 54% to 40%

between 1983 and 1992, a trend that was confirmed in a recent multicentre report [34,165]. These observations were not accounted for by changes in the patient population in terms of age, sex, injury severity score (in trauma) or risk subgroups. Factors associated with mortality include the following.

1 Development of acute multiple organ failure: in patients who develop non-pulmonary organ dysfunction between hospital and ITU admission the mortality approaches 90%, whereas it is about 50% in those patients with respiratory failure only [166].

2 Severity of ARDS and early response to treatment: those patients with the best static lung compliance and major rapid improvement in arterial oxygenation are most likely to recover [167].

3 Predisposing condition: 20–45% of patients with sepsis syndrome develop ARDS and 70–90% of these die, compared with a mortality rate of about 10% in ARDS due to fat embolism [167–171].

4 Presence of underlying disease, for example cirrhosis or malignancy, is associated with a worse prognosis [172].

5 Age: in patients who are aged over 60 mortality is about 75%, in those aged 50–59 it is 62% and in those aged 16–49 it is 37% [165,173].

6 Markers of inflammation and injury: in general the presence of inflammatory mediators in the lungs and their concentration therein have not been helpful in predicting the outcome of established ARDS. These include TNF- $\alpha$ , IL-1, IL-8 and a range of other chemokines and circulating soluble endothelial adhesion molecules, including von Willebrand factor antigen and E-selectin. It may seem surprising that there appears to be no relationship between a wide range of proinflammatory mediators and disease outcome. However, the recent observation that low levels of anti-inflammatory agents, such as IL-1 receptor antagonist and IL-10, correlate closely with mortality suggests that an effective anti-inflammatory cytokine response may be a more important determinant of recovery [161]. Markers that relate to an effective inflammatory resolution and repair response, such as pro-apoptotic factors, remain to be evaluated.

Death in most patients with ARDS is due to the development of multiple organ failure or nosocomial pneumonia and further episodes of sepsis rather than to intractable respiratory failure *per se*. As discussed above there is no evidence that any pharmacological intervention over and above high-quality intensive care has any influence on outcome. There is a great need for better indicators of outcome, whether these relate directly to the disease process or are surrogate markers. Because the number of ARDS patients in any single centre is small, these indicators will need to be established by consensus in multicentre cooperative groups. Reliable outcome data are critical not only for the assessment of new forms of therapy but also for identifying those patients likely to benefit from

intensive care as against those in whom the outlook is presently hopeless.

### Sequelae

One study of pulmonary function in ARDS survivors showed that 4% of patients were severely impaired and 15% were moderately impaired a year later; remarkably, particularly when the histopathology of this condition is considered, around 50% of patients showed only mild impairment and 30% returned to apparently normal function [174]. Long-term pulmonary dysfunction is associated with a high  $F_{IO_2}$  and severe hypoxaemia during the ARDS episode as well as with the patient's age and smoking history [175].

The remarkable recovery of pulmonary function demonstrated by most survivors suggests that when the natural processes of resolution of inflammation and repair are better understood we should gain new therapeutic insights that could be applied to patients with established ARDS. The promotion of naturally available resolution and repair mechanisms should have no potential detriment to host defence against bacterial infection.

### Neurogenic pulmonary oedema

Pulmonary oedema occasionally occurs as a sequel to intracerebral disease [176]. Described initially following epileptic seizures, it is now known to occur after head trauma, intracerebral and subarachnoid haemorrhage and neurosurgery. The common aetiological factor seems to be an acute rise in intracranial pressure. This may be followed immediately or within a few hours by acute pulmonary oedema, though occasionally the onset of oedema is slowly progressive over several days. In the former case it is often relatively benign and short-lived, resolving spontaneously within 48h. However, sometimes it may be severe and fatal. Studies of lung water, carried out prospectively in patients with serious head injuries and subarachnoid haemorrhage, have shown that accumulation of fluid is a frequent event, occurring in up to 50% of patients [177].

The condition presents with breathlessness, cough and sometimes haemoptysis some hours after the cerebral episode. In most cases it reduces spontaneously, requiring only supplemental oxygen. Sometimes assisted ventilation is necessary to overcome hypoxaemia, although PEEP should be avoided as it increases intracranial pressures and decreases cerebral perfusion. As far as possible, attention should be directed to alleviating the primary cause and reducing intracranial pressure.

Neurogenic pulmonary oedema is considered separately because there is evidence that both hydrostatic factors and increased permeability play a part in its aetiology. An acute rise in intracranial pressure may cause

increased sympathetic discharge and a rise in levels of circulating catecholamines in the blood. This may cause acute left ventricular failure as a result of increased venous return, shortened contraction time and systemic vasoconstriction, probably due to  $\alpha$ -adrenergic stimulation. Pulmonary vasoconstriction may also occur in these circumstances, and this has been shown to be a response to catecholamine release following raised intracranial pressure in animal models [178,179]. These changes may combine to alter the balance of the Starling equation towards oedema formation. However, there is clinical evidence that the oedema fluid may contain relatively high levels of protein and that oedema can occur in the absence of raised pulmonary pressures [6,180]. This evidence of increased vascular permeability in humans is consistent with findings in animal studies [181], and suggests that other factors must be, at least in some cases, acting directly on the endothelium. What these are remain a mystery. Sometimes they may be related to a sudden acute rise in capillary pressure causing a type of 'blast injury' [178]; or they may be other humoral mediators and, again,  $\alpha$ -adrenergic agents may be responsible [182].

### High-altitude pulmonary oedema

A proportion of people ascending to high altitudes develop acute mountain sickness, a syndrome in which the traveller or climber feels generally unwell, nauseated, anorexic, lethargic and dizzy [183–185]. Headache and vomiting are common symptoms. While this condition usually settles spontaneously with rest in a few days, a few develop high-altitude pulmonary oedema. This usually starts within 3–96 h of ascent [185,186] and is rare below about 3000 m. It is more common in younger people and seems to occur in proportion to the rate of ascent, the exertion required to ascend and the altitude reached. There is anecdotal evidence that people who have experienced acute mountain sickness are liable to suffer from it again, and some are clearly so susceptible that they should avoid high altitudes altogether. It is particularly common in high-altitude dwellers returning home after a spell at sea level [187,188].

The condition may be accompanied by cerebral oedema, in which case the patient becomes confused and stuporose, eventually lapsing into coma [189]; it seems likely that the three components of high-altitude sickness, acute mountain sickness and pulmonary and cerebral oedema, are closely associated. Increases in cerebral and retinal blood flow and retinal haemorrhages occur very commonly at high altitudes [190–192], and papilloedema occurs in patients with the cerebral syndrome.

Pathological studies of fatal cases of high-altitude pulmonary oedema are sparse. They have shown the expected congestion of the lungs, with pink froth in the airways, proteinaceous alveolar fluid and hyaline mem-

branes [193,194]. Pulmonary arterial thromboses and bronchopneumonia are frequent features of fatal cases, most of whom also have well-marked cerebral oedema.

The aetiology of high-altitude pulmonary oedema is obscure. It is clearly related to hypoxia and may also be exacerbated by the cold conditions and exertion invariably associated with altitude. One physiological response to hypoxia and to exercise is fluid retention, with a shift of fluid from the systemic to the pulmonary circulation and an increase in pulmonary arterial pressure. The mechanisms of this are not understood, although it has been suggested that there are alterations in the renin–aldosterone response, perhaps as a result of hypoxia interfering with the production of angiotensin-converting enzyme in susceptible individuals [195,196]. Studies of pulmonary oedema fluid and BAL specimens have shown that the fluid from the lungs contains red blood cells and has a high protein content, indicating that the oedema is of the increased permeability type [183]. On the other hand, there is little evidence that an inflammatory reaction has occurred in the lungs, suggesting a similar mechanism to that of neurogenic pulmonary oedema. One hypothesis proposes that hypoxic vasoconstriction in some parts of the lung results in much increased flow and pressure in other parts, resulting in high-pressure damage to capillary endothelium. Why some people develop the disease and others do not may be related to different responses of the medullary respiratory centres to hypoxic stimuli; studies have shown that individuals who have had high-altitude pulmonary oedema have a reduced ventilatory response to hypoxia [183].

Whatever the aetiological mechanisms, the condition usually responds promptly to the increased oxygen tensions of lower altitudes and thus appropriate treatment is immediate removal to such altitudes. Because of the difficulties of transportation of severely ill patients in the circumstances normally prevailing on high mountains, removal should take place as soon as the diagnosis is suspected rather than when the patient is severely dyspnoeic. If oxygen is available, it should be given at high flow rates. Acetazolamide, a carbonic anhydrase inhibitor that acts as a diuretic and a respiratory stimulant, is a reasonably effective prophylactic against acute mountain sickness and may help to prevent pulmonary oedema [197–199]. However, the primary preventive measures are to take time over ascent, to return to lower altitude at night after climbing in the day, and to avoid taking people who have previously suffered from the condition on future expeditions.

### Near-drowning

Strictly speaking, drowning results from inhalation of water, although the terms 'dry drowning' and 'secondary drowning' are applied, respectively, to death due to

immersion without water inhalation (perhaps as a result of cold-induced vagal activity and apnoea) and to pulmonary oedema occurring up to 72 h after an immersion accident. In freshwater drowning, there is absorption of water from the lungs into blood, haemolysis and hyperkalaemic ventricular fibrillation. This is normally rapidly fatal, although occasionally, especially in children, drowning in freezing water may sufficiently suppress tissue oxygen demands as to be consistent with survival after immersion for as long as 30 min or more. Sea-water drowning results in diffusion of sodium, calcium and magnesium ions into the bloodstream, again leading to cardiac arrest.

In either type of drowning, prompt initiation of mouth-to-mouth respiration may result in the patient being resuscitated, although with freshwater drowning the chances of this are less. It has been advised, apparently paradoxically, that external cardiac massage should not be attempted if the victim is hypothermic, as recovery of temperature is accompanied by recovery of sinus rhythm while massage may provoke ventricular fibrillation [200]. If the victim is not obviously hypothermic, signs of cardiac arrest should be an indication for external massage. Resuscitated patients, as well as those who have inhaled water but who have not suffered arrest, should be admitted to hospital for correction of hypothermia and electrolyte abnormalities. If they become breathless and show falling oxygen tensions, secondary pulmonary oedema should be suspected and assisted respiration with PEEP instituted early [201,202]. The aetiology of this condition is not clear but may be related to removal of surfactant from the alveoli, with loss of waterproofing.

## Uraemia

Pulmonary oedema is a common accompaniment of chronic renal failure. Many factors may play a part in its aetiology; sodium and fluid retention leading to circulatory overload, protein loss with reduced plasma oncotic pressure and left ventricular failure may all contribute. There is almost certainly an element of increased permeability but the mechanism of this is unclear [203,204]. The clinical features of renal pulmonary oedema are similar to those of other forms of the disease, although care has to be exercised in distinguishing it from infections, pulmonary arteritis and reactions to drugs used in the treatment of the primary condition or for immunosuppression to enable transplantation [205]. The distribution of radiographic

changes is usually central rather than peripheral, and this may be helpful in making the distinction from the more typical peripheral pattern of oedema in shock lung.

## Lung re-expansion oedema

Occasionally the rapid relief of a pneumothorax may be followed by ipsilateral pulmonary oedema. The patient coughs and complains of shortness of breath, and blood gases may show hypoxaemia due to shunting of blood past unventilated alveoli [206]. Similar episodes may occur following the rapid drainage of a pleural effusion, and in these circumstances fatalities have been described [207,208]. Part of the explanation of these episodes may be the generation of excessively negative intrapleural pressures [209], although it is likely also that loss of surfactant in the collapsed lung makes the alveolar epithelium excessively liable to leak interstitial fluid [210].

Management of these episodes, all of which should be prevented by careful aspiration, depends on correcting hypoxaemia and allowing time for the oedema to resolve. In a very distressed or severely hypoxic patient, the condition could theoretically be alleviated by allowing the affected lung to collapse again, followed by cautious re-expansion.

## Pulmonary oedema in intravenous drug abusers

Intravenous drug abusers may develop pulmonary oedema following an overdose [211,212]. The patients are usually heroin addicts, although the syndrome may result from intravenous use of other drugs. The patient usually presents with typical signs of an overdose, cyanosed and with crackles in the lungs. Management is with oxygen, by respirator if necessary, and opiate antagonists. Recovery may occur, with clearing of the chest film, within 24–48 h if these measures are initiated sufficiently promptly. The condition is due to increased vascular permeability, possibly related to multiple small emboli of contaminants of the drugs. The diagnosis in such patients has become more complex with the increasing incidence of pulmonary complications of AIDS, as this is also not infrequently complicated terminally by diffuse pulmonary oedema.

## Pulmonary veno-occlusive disease

This is discussed in Chapter 26.

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# BRONCHIECTASIS

DOUGLAS SEATON

## Definition

The definition of bronchiectasis is based on morbid anatomical appearances, the word being derived from Greek roots, *bronchion* meaning windpipe and *ektasis* a stretching out. Thus bronchiectasis is present when one or more bronchi are abnormally and permanently dilated. The condition was clearly described by Laënnec in 1819 after the postmortem examination of the lungs of an infant who died following whooping cough [1], and a popular textbook of the late nineteenth century stated correctly that bronchiectasis was 'not a separate disease but a result of various affections of the lungs and bronchi' [2], this sentiment being echoed today in that the morbid anatomical changes represent a common end-stage of a variety of pathological conditions.

## Prevalence

Since bronchiectasis has depended upon CT, bronchography or morbid anatomical examination of the lungs for certain diagnosis, no reliable figures are available for its prevalence in the population as a whole. As long ago as 1953, 1.3 cases of bronchiectasis per 1000 were reported in Bedford [3]; a similar prevalence of 1.5 cases per 1000 was found from the chest clinic follow-up of abnormal 'routine' miniature chest radiographs obtained from a sample of over 3.5 million examinations carried out in England and Wales in 1956 during the tuberculosis eradication campaign [4]. Despite the lack of subsequent data, it is common experience that a marked fall in the prevalence of bronchiectasis has occurred since that time. This decline is a consequence of the more effective treatment of childhood respiratory infections, including pneumonia, so that sharp falls in the numbers of children admitted to hospital with bronchiectasis coincided with the introduction of antibiotics [5,6]. Other important factors have been the introduction of effective vaccination programmes for whooping cough and measles, the decline in the prevalence of pulmonary tuberculosis and better social condi-

tions. Although such improvements in health are sometimes taken for granted in Western society, this is not the case in many developing countries where bronchiectasis remains a common problem [7]. Thus a large South African thoracic surgical centre serving a population of about 6 million was still carrying out 60–70 resections per year on patients with bronchiectasis in the 1980s [7], whereas most respiratory physicians in the West see only a few 'new cases' of bronchiectasis each year. Paradoxically, improved antimicrobial agents and other supportive care have allowed some patients, notably those with cystic fibrosis (CF), to survive into adult life despite gross bronchiectasis. These patients with CF, who account for approximately 1 in 2000 births and who would previously have died in childhood, now represent a significant number of repeated hospital admissions under the care of adult respiratory physicians. The accurate diagnosis of bronchiectasis depends upon high-resolution CT (HRCT), which can detect less severe forms of bronchiectasis that may easily be missed unless the physician pursues this possibility doggedly, so that the current prevalence of bronchiectasis is unknown.

## Aetiology and pathogenesis

Whereas most bronchiectasis is acquired during childhood, the condition may rarely result from a gross congenital developmental anomaly or be predisposed by some other inherited defect, be it ultrastructural (as in ciliary dyskinesia), related to a generalized defect of ion transport (as in CF) or due to an immunodeficiency syndrome (e.g. hypogammaglobulinaemia) (Table 28.1).

### Mucociliary clearance abnormalities predisposing to bronchiectasis

#### Genetically determined syndromes of ciliary dyskinesia

The recognition that abnormalities of ciliary function

**Table 28.1** Bronchiectasis: aetiology and pathogenesis (see text).

Pathogenic mechanisms	Aetiology
Primary infective insult	Bronchitis/bronchiolitis Pertussis Measles Adenovirus Pneumonia Tuberculosis
Primary impairment of mucous clearance	
Genetic, biochemical	Cystic fibrosis
Genetic, ultrastructural	Primary ciliary dyskinesias
Immunodeficiency syndromes, congenital and acquired	Common varied immunodeficiency Selective immunoglobulin deficiency Functional immune deficiency Secondary hypogammaglobulinaemia Human immunodeficiency virus infection
Hyperimmune response	Allergic bronchopulmonary mycoses
Infection secondary to bronchial obstruction	
Intraluminal	Slow-growing tumour, aspirated foreign body
Extraluminal	Lymphadenopathy
Miscellaneous inflammation	
Autoimmune disease	Inflammatory bowel disease Coeliac disease Systemic lupus erythematosus Rheumatoid disease Cryptogenic fibrosing alveolitis Primary biliary cirrhosis Thyroiditis Pernicious anaemia
Inhalational/aspiration injury	Toxic fumes Gastric contents
Developmental defects	
Structural	Pulmonary agenesis Sequestered segment Tracheobronchomegaly Bronchomalacia
Biochemical	$\alpha_1$ -Antitrypsin deficiency

might result in the development of bronchiectasis followed the observation that male infertility was sometimes associated with immotile spermatozoa [8,9]. A proportion of these patients gave a history of recurrent sinusitis and lower respiratory tract infection from early life and some were noted to have Kartagener's syndrome (chronic sinusitis, bronchiectasis and situs inversus, first described by Siewert and later by the Swiss paediatrician whose

name the syndrome bears) [9–13]. Electron microscope studies of the sperm tails in these infertile patients showed distinctive abnormalities [8,11] and because respiratory cilia normally have a similar ultrastructural composition, these were also examined under the electron microscope to see whether the associated respiratory disorder could be explained by a similar defect [12,14]. Such was indeed the case, the important defects being the absence of one or both rows of dynein arms in some patients and the absence of spoke heads or central sheaths in others [15]. These structures are illustrated diagrammatically in Fig. 1.13. The dynein arms are ATPase radial projections, two of which normally arise from each of nine pairs of microtubules that run longitudinally and which are arranged circumferentially around the cilia (or sperm tail). Ciliary bending is normally achieved by the outer of each pair of microtubules sliding over its inner partner in a coordinated fashion, the energy for this being provided by the dynein arms. This microtubular shortening is converted into a bending motion because the outer pairs of microtubules are tethered to each other and to the central sheath. Individual cilia share the same ultrastructural plane of symmetry and therefore normally work in concerted fashion to propel the mucus blanket in a cephalic direction. Such coordinated sliding and bending cannot occur (i) in the absence of dynein arms or radial spokes [16,17], (ii) in the presence of spatial transposition of microtubules [18] and (iii) in the presence of random ciliary orientation in which the cilia are anchored in disorganized fashion at the cell surface [19]. These abnormalities prevent normal transport of mucus from the bronchial tree to the mouth and result in serious impairment of the lungs' defence systems. More than one gene is thought to be responsible for these defects, and Kartagener's syndrome [20] has been considered to be a subgroup in a heterogeneous collection of disorders to which the terms *immotile cilia syndrome* [15,21] or *dyskinetic cilia syndrome* [22] have been applied.

The finding of dextrocardia in about half those patients of European origin with ciliary dyskinesia has been explained in terms of the dependence of embryological organ position on the presence of a uniform pattern of ciliary beating, the absence of which might result in random rotation of primitive organ precursors to either the left or the right. However, this hypothesis has been questioned as it does not hold for Polynesians with ciliary dyskinesia, in whom organ position is normal [23]. The immotile cilia syndrome (syn. primary ciliary dyskinesia [24]) is rare, with a prevalence of about 1 in 30 000, which is about twice that of the subcategory of Kartagener's syndrome. It is probably transmitted by an autosomal recessive gene with incomplete penetrance. Parents of affected children seldom have chronic respiratory symptoms but the chances of a sibling being similarly afflicted are about 25%.

### *Clinical features*

The clinical features are a result of impaired mucociliary clearance from the upper and lower respiratory tracts, the paranasal sinuses and the middle ear. Male infertility is also usually present, although this need not be the case where mucociliary transport is defective because of random ciliary orientation rather than immotility [19], so that men with primary ciliary dyskinesia should have seminal analysis before being told that they are infertile. Dextrocardia occurs in about half of cases in the absence of other congenital anomalies. Respiratory symptoms date from infancy or early childhood and include chronic rhinorrhoea and sinusitis. There may be otitis media and mild deafness. Cough is prominent and is indeed essential to compensate for the absence of normal mucociliary transport by shifting otherwise stagnant mucus. Recurrent lower respiratory tract infection may result in bronchiectasis, which is therefore acquired, because of delay in the removal of infected material from the bronchi [21].

### *Diagnosis*

The diagnosis should be considered in any patient with a history of recurrent upper and lower respiratory tract infection since childhood and can be regarded as established if (i) the features of Kartagener's syndrome are present, (ii) an adult male gives a consistent respiratory history and is found to have immotile live sperm or (iii) a woman or child gives a consistent respiratory history and has a sibling with Kartagener's syndrome or has consistent ultrastructural defects on a nasal or bronchial epithelial brush biopsy [15]. Impaired mucociliary clearance may be detected in adults by the presence of an abnormal saccharin test, in which the time is recorded for saccharin to be tasted in the mouth after a 0.5-mm particle has been deposited on the inferior turbinate in the nose. This usually takes about 30 min but times of up to 1 h may be normal. It is also possible to measure ciliary beat frequency with appropriate specialized video microscopy. The availability of facilities for electron microscopy of sperm tails and respiratory cilia may produce diagnostic confirmation, although even these may demonstrate no abnormality in some variants of primary ciliary dyskinesia [25]. Specimens of cilia for both video and electron microscopy may be obtained without local anaesthesia by running a bronchoscopic cytology brush along the mucosal surface of the inferior turbinate [26].

### **Other syndromes of ciliary dyskinesia**

#### *Young's syndrome (idiopathic obstructive azoospermia)*

Young [27] described a group of 52 infertile men in whom

poorly motile sperm were present in the epididymal tubes but not in the ejaculate. A history of severe chest disease in childhood followed by recurrent bronchitis was obtained in half of the cases and bronchiectasis is about one-fifth. Sinusitis may also be associated. Azoospermia in this syndrome may be caused by an functional obstruction to the flow of secretions in the vasa deferentia and the association between chronic paranasal sinusitis, lower respiratory tract disease and obstructive azoospermia may be due to a common defect of the ciliated columnar epithelium at these different sites. Although Young's syndrome has been proposed as a variant of the immotile cilia syndrome, the respiratory cilia in such patients appear for the most part to be ultrastructurally normal [28] and evidence regarding the nature of ciliary dysfunction is conflicting, since the abnormalities that have been reported could be a consequence rather than the cause of recurrent respiratory tract infection. Thus patients with bronchiectasis may be colonized by bacteria that may themselves produce ciliary toxins [29,30], so that the pathogenesis of the respiratory abnormalities in Young's syndrome is still unexplained [31,32]. Although the rheological properties of mucus in Young's syndrome may be abnormal, it is unlikely to be a *forme fruste* of CF because sweat electrolyte concentrations are normal [33,34]. The condition has not been found to be familial and situs inversus has not been associated. A history of mercury intoxication in childhood ('pink disease', caused by mercurous chloride in teething powders and vermifuges) was obtained in some patients who later developed Young's syndrome, so that this apparent association and the subsequent observation of a temporal decline in the incidence of this syndrome following the removal of such preparations from general availability raised further questions about possible cause and effect [35].

### *Cystic fibrosis*

CF is a relatively common hereditary disorder in which activity of a chloride channel known as the cystic fibrosis transmembrane conductance regulator (CFTR) is reduced according to the individual genetic mutation present. The incidence of CF is approximately 1 per 2000 live births. Although early symptoms are related to pancreatic insufficiency, patients who survive into childhood, adolescence and adult life classically develop persistent lower respiratory tract infection and as a result acquire widespread bronchiectasis, more than 90% of patients with CF dying of lung disease [36]. The lungs of patients with CF are virtually normal *in utero*, but once breathing commences the desiccated and viscid secretions resulting from the electrolyte transport defect impair mucociliary clearance so that trapped organisms lead to a cycle of persistent and increasing inflammatory load, ultimately resulting in the widespread bronchiectatic changes that characterize this



disease [37]. The diagnosis is made by finding the classic triad of pulmonary disease, pancreatic insufficiency and a raised sweat sodium concentration of 70 mmol/L or more, only 0.1% of patients with otherwise typical CF having normal sweat sodium and chloride concentrations below 50 mmol/L [38,39]. More than 90% of men with CF are azoospermic as a result of congenital bilateral absence of the vas deferens, a finding that may raise Young's syndrome in the differential diagnosis, this being characterized by bronchiectasis, sinusitis and infertility but not by pancreatic insufficiency, a raised sweat sodium concentration or the appropriate genetic typing found in CF. The condition is described fully in Chapter 30 and is not considered further here. It has been postulated that the presence of CFTR gene mutations (occurring in the absence of overt CF) may be responsible for some cases of bronchiectasis in the community [40].

### **Other conditions predisposing to bronchiectasis**

#### **$\alpha_1$ -Antitrypsin deficiency**

Hereditary homozygous  $\alpha_1$ -antitrypsin (syn.  $\alpha_1$ -protease inhibitor) deficiency occurs in about 1 per 4000 of the population and is well known for its association with panacinar and predominantly basal emphysema (see Chapter 23) and also with cirrhosis of the liver. The development of bronchiectasis, rather than emphysema, in adult life is less well known but has been reported in a few patients [41–45]. Thus some of the proteases released from phagocytes during pyogenic infection may be more liable to cause bronchial wall damage if unopposed by antiproteases, of which  $\alpha_1$ -antitrypsin is one.

#### **Inhalational injury**

There have been occasional reports of bronchiectasis developing as a consequence of the inhalation or aspiration of toxic or irritant substances, either in liquid form or when contained in smoke or fumes [46–48].

### **Developmental pulmonary anomalies**

#### ***Pulmonary agenesis***

Rare cases of 'congenital bronchiectasis' have been described in which most of the bronchi in a lobe or lung are found to be dilated. These cases present in childhood with symptoms and signs consistent with bronchiectasis. Following resection, the affected part of the lung shows no evidence of alveoli ever having developed beyond the bronchial abnormality [49]. This type of bronchiectasis may therefore be regarded as an example of partial pulmonary agenesis with a failure of peripheral parts of the lung to develop. Ipsilateral bronchiectasis has been found

in some patients who have presented in adult life with unilateral pulmonary artery agenesis [50].

#### ***Pulmonary sequestered segment***

Bronchiectasis may also occur congenitally within an intralobar sequestration (see Chapter 50) that contains disorganized, dilated and deformed bronchi [51]. These may communicate with normal surrounding lung tissue if the sequestration becomes complicated by infection and ruptures. The anomalous blood supply of sequestered segments may be demonstrated by aortography.

#### ***Tracheobronchomegaly (Mounier-Kuhn syndrome)***

This is also a rare condition, considered to be congenital, in which the cartilaginous rings of the trachea and its divisions as far as the segmental bronchi are enlarged, producing marked dilatation of the trachea and central bronchi [52]. The elastic and muscular tissues between the rings of cartilage are atrophic and may tend to bulge between the rings in the manner of tracheal diverticulae. These changes have the effect of causing the intrathoracic trachea and main bronchi to dilate during inspiration and to collapse on expiration. It is associated with chronic lower respiratory tract infection and bronchiectasis and tends to be diagnosed in the fourth or fifth decades when patients with this clinical presentation may be found to have transverse and sagittal tracheal diameters three standard deviations or more above the norm on the chest radiograph [53]. The more distal bronchial tree is not primarily affected. Characteristic bronchographic and CT findings have been described [53–55]. Associations with Ehlers-Danlos syndrome, cutis laxa and skeletal dysplasia have been recognized.

#### ***Williams-Campbell syndrome (bronchomalacia)***

This rare congenital syndrome is characterized by defective or completely absent bronchial wall cartilage, producing a mechanical abnormality that may contribute to the formation of bronchiectasis [56]. Symptoms of cough begin from infancy. The defect may extend from the fourth to the eighth generations of bronchi and CT shows a remarkable ballooning expansion of the proximal bronchi during inspiration, with collapse during expiration, these appearances having originally been demonstrated bronchographically [57]. Familial cases may occur in siblings, possibly as a result of an autosomal recessive mechanism of inheritance, although the disorder may also present sporadically [58,59].

It may be possible for other developmental bronchial anomalies to lead to the formation of bronchiectasis possibly as a result of secondary infection.



### Immunodeficiency syndromes

Apart from the anatomical and mechanical defences afforded by the epiglottis, the larynx, the act of coughing and mucociliary transport, the lung is also protected by bacteriostatic substances and by humoral and cellular immune mechanisms that may become defective for various reasons. Such defects sometime lead to recurrent or chronic lower respiratory tract infection, which may in turn be complicated by bronchiectasis.

Immunodeficiency syndromes are found in less than one-tenth of adult cases of bronchiectasis. Some of these are treatable with intravenous immunoglobulin replacement therapy [60,61], which may help to prevent increasing lung damage if started early enough. Thus it is advantageous to request serum levels of IgG, IgA and IgM and also IgG subclasses in patients in whom bronchiectasis is suspected or evident, particularly when these patients present at a younger age or when recurrent infection dates back to early life. Such a diagnosis may be more likely where there has been no single triggering antecedent pneumonic episode. The humoral immunodeficiencies include (i) congenital X-linked (Bruton's) agammaglobulinaemia, producing infection in infancy once maternal IgG is exhausted, and (ii) the acquired form of common varied immunodeficiency (CVID; syn. common variable hypogammaglobulinaemia).

CVID is the most common of these defects, presenting at any age but with a peak incidence in childhood and adolescence, and is associated with chronic sinusitis and repeated episodes of infective bronchitis leading to bronchiectasis in adult life. The levels of immunoglobulins found are rather variable: IgG is often reduced to less than 2 g/L and IgA is often virtually undetectable; IgM may be reduced to less than 0.2 g/L but this need not be the case and normal levels may be found.

Other defects that may be associated with bronchiectasis include selective IgG subclass deficiencies that may be found in the presence of a normal total IgG level [62–66]. Not all IgG subclass deficiencies are clinically relevant and sometimes one subclass defect may be compensated for by the others. Bronchiectasis is not usually associated with isolated IgA or IgM deficiencies but is more likely if these occur in association with selective IgG subclass deficiencies (e.g. IgG<sub>2</sub> and IgA). Selective IgA deficiency [67] is quite common in people of European stock and leads to recurrent upper respiratory tract infection in only a small minority of those with the defect. Primary selective IgM deficiency is very rare and is more likely to be a consequence of lymphoma. Selective IgE deficiency appears to be of no consequence.

Functional immunoglobulin deficiencies should be considered in patients who have recurrent respiratory infections but in whom the neutrophil and lymphocyte counts are normal and who also have normal immunoglobulin

and complement levels. These patients fail to produce antibodies in response to a specific challenge and may sometimes be detected immunologically by their failure to produce a measureable serological response to pneumococcal vaccine and tetanus toxoid [68].

Immunity may also be impaired by both neutrophil and, less frequently, by T-cell dysfunction. Bronchiectasis has also been associated with a natural killer cell dysfunction in which lymphocytes do not express human leucocyte antigen (HLA) class I antigen on their surface, the so-called 'bare lymphocyte syndrome' [69].

Thus there are many different types of quantitative or functional immune deficiency [70–75] that reduce the capacity of the lungs to deal with pyogenic infection and some of these may lead to bronchiectasis. Impaired immunity with secondary hypogammaglobulinaemia may also result from coexisting disease, particularly malignancy such as lymphoma, chronic lymphatic leukaemia and myeloma, as well as from other non-neoplastic diseases with heavy protein (and therefore antibody) losses such as the nephrotic syndrome and protein-losing enteropathy [61].

For a detailed description of lung defences and immunology, the reader is referred to Chapter 4.

### Infection in the pathogenesis of bronchiectasis

Although the pathogenesis of bronchiectasis remains the subject of speculation and debate, it is probable, other than in rare congenital forms, that infection plays a fundamental role in both the initiation of the morbid anatomical defect and the perpetuation of the symptoms of bronchiectasis.

Many cases of bronchiectasis originate from a lower respiratory tract insult in early childhood, the patient often having been 'chesty' for as long as can be remembered. A remote history of childhood 'pneumonia', whooping cough, a bad attack of measles or tuberculosis may be cited by the patient, although in somewhat less than half of all cases such an event cannot be recalled. Thus a series of 116 cases from Edinburgh reported a history of pneumonia in 28%, pertussis in 10%, bronchitis/bronchiolitis in 5%, tuberculosis in 5%, measles in 3% and other causes in 5%, leaving the cause 'undetermined' in 44% [76]. One North American series obtained a history of pneumonia as the first known respiratory incident in two-thirds of cases [77], while a series of 187 children attributed the disease to infection in almost 70% of cases, the remainder being divided evenly between congenital abnormalities and aspiration [6]. A more recent North American study of 123 patients with proven bronchiectasis, half of whom had never smoked, found 'pneumonia' to be the most common antecedent event, this having been supposed to have occurred in 35% of cases; about 7% had been accounted for by whooping cough, 10% by 'granulomatous disease'

(including tuberculosis and sarcoidosis), 4% by genetic disorders (comprising CF,  $\alpha_1$ -antitrypsin deficiency and syndromes of ciliary dyskinesia) and 14% by miscellaneous disorders. No antecedent lung injury could be identified in 30% of cases [78].

### **Pertussis (whooping cough)**

Whooping cough (discussed in Chapter 12) has long been associated with bronchiectasis; indeed Laënnec believed it to be the commonest cause [1]. Nowadays in many Western countries the prevalence of pertussis has been reduced but the disease has by no means been eradicated and it continues to occur in unvaccinated individuals. It produces a necrotizing bronchitis, and associated endobronchial mucus and debris commonly cause small peripheral areas of atelectasis, radiographic evidence of these being found in over 40% of 150 consecutive childhood cases in one early series [79]. Such shadowing is usually short-lived and bronchiectasis probably only occurs in a small proportion of these patients, some of whom may first develop a secondary bacterial pneumonia.

### **Measles**

Measles may also be accompanied by severe inflammation of the bronchial wall and pneumonia is its most important complication. Measles was implicated in 14% of a series of patients with bronchiectasis from North Carolina in 1978 [77]. As with whooping cough, the prevalence of measles has fallen in the West following the introduction of vaccination (see Chapter 12), although this illness remains a common cause of morbidity and death among poorer people in developing countries. In Cape Town, South Africa, Kaschula and colleagues [80] reported 57 new cases of bronchiectasis in children, a strong causal link with measles being evident in 20 of them. These same workers reported the postmortem findings of 21 children who had died in the wake of measles. The majority had evidence of superimposed adenovirus or herpes simplex pneumonia that was associated with a severe bronchiolitis and bronchitis, leading the authors to speculate that the occurrence of these infections in children shortly after measles may be an important factor in the development of bronchiectasis [80,81]. A similar association between measles, adenovirus infection and bronchiectasis has been reported by others [82].

### **Adenovirus**

Adenoviruses alone account for about 5% of respiratory infections in children, some serotypes (e.g. 1, 3, 4, 7 and 21) being more virulent than others. A longitudinal study of 22 children who had adenovirus type 7 pneumonia showed

that over one-quarter of them had evidence of bronchiectasis at 10-year follow-up [83].

### **Mycobacteria**

Although 'postprimary' pulmonary tuberculosis almost always produced bronchographically demonstrable bronchiectasis [84,85], such morphological distortion seldom produces the clinical symptoms classically associated with bronchiectasis. The explanation for this is that the tuberculous process tends to selectively affect the upper lobes, from which secretions are able to drain with the aid of gravity, whereas other infections often involve dependent parts of the lungs from which unassisted drainage is poor so that sepsis persists. The initial tuberculous infection that produces a 'primary complex' may in some cases result in residual bronchiectasis when the infiltrate involves the middle or lower lobes. The relatively narrow middle lobe bronchus has long been known to be vulnerable to obstruction, including compression by enlarged hilar glands, sometimes producing the so-called 'middle lobe syndrome', with a variety of findings ranging from recurrent middle lobe pneumonia to atelectasis and bronchiectasis [86,87]. However, any associated bronchial wall infection and necrosis may play a summative role in the pathogenesis of postprimary tuberculous bronchiectasis [88].

Opportunistic mycobacterial infection may also be associated with bronchiectasis in immunocompetent patients. The organisms that have been implicated include not only *Mycobacterium avium-intracellulare* and *M. kansasii* but also occasionally so-called 'rapid growers' such as *M. fortuitum* and *M. chelonae* [89–92]. The usual radiographic findings are indistinguishable from tuberculosis, with a fibronodular infiltrate affecting the upper lobes, although occasionally a more specific CT appearance may be evident with scattered small nodules that may be associated with bronchiectasis [90,93,94]. In all probability, these 'atypical' mycobacteria are usually secondary colonists, although it has been suggested that the underlying bronchiectasis may progress more rapidly in patients from whom these organisms are persistently recovered [95].

### **Pneumonia**

When pneumonia precedes bronchiectasis, the acute event has often occurred in childhood and is poorly documented or half-forgotten as implied above [76–78]. The pneumonic episode may follow on the heels of an epidemic childhood infection such as whooping cough, measles, adenovirus or other infection. Bacterial pneumonic infections are much more likely to be controlled as a result of the widespread availability of antibiotics in countries with well-developed health services, tending to remain uncomplicated by so-called 'old-fashioned

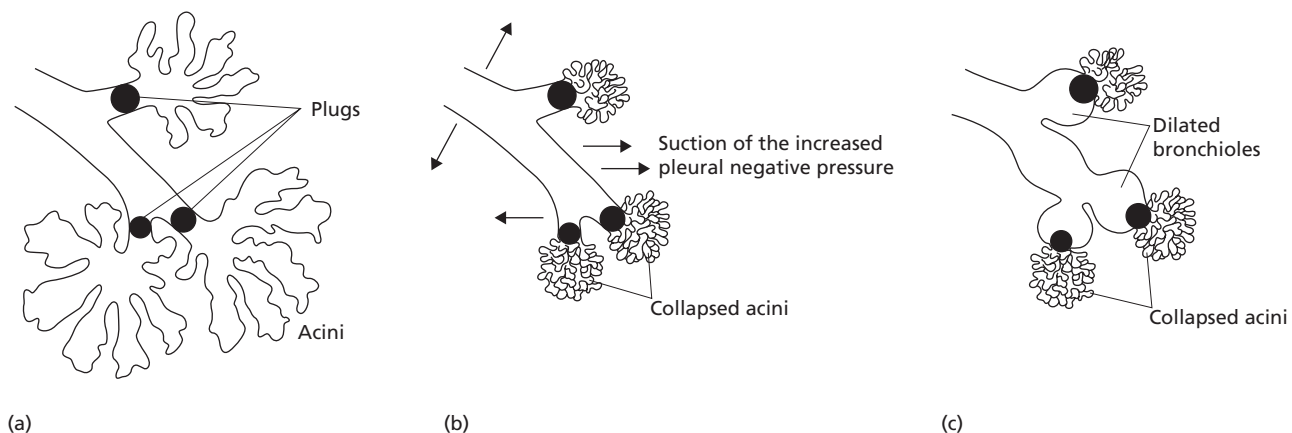
bronchiectasis'. This is not the case in most parts of the world where health resources are scarce and patchily spread, so that if the patient survives suppurative pneumonia is more likely to be followed by bronchiectasis. Although no detailed prevalence data exist, such complicated infection, which may occur in adult life as well as in childhood, has been recorded as a major problem in South Africa where developed Western medical and surgical facilities abut large and relatively poor communities [7].

Bronchiectasis may occasionally be acquired in adult life following pneumonia caused by organisms seldom associated with suppurative complications such as *Mycoplasma pneumoniae* [96–98].

### Human immunodeficiency virus

Although often first brought to clinical light by an episode of *Pneumocystis carinii* pneumonia, human immunodeficiency virus infection is increasingly recognized as a predisposing factor for repeated infection by other more common respiratory pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* particularly in patients with less severe immunological impairment [99]; such repeated infections may lead to bronchiectasis [100,101]. This does not represent a major clinical problem at present but it is possible that it could become one if prophylaxis and treatment of major infective episodes prolongs survival sufficiently to produce a cohort in whom the pathology has had time to develop [102].

**Fig. 28.1** Loss of volume in plugged acini results in traction on more proximal bronchi that then become dilated. (a) Terminal bronchioles subtending acini (primary lobules) are obstructed by secretions. (b) Air is absorbed from the acini which collapse, creating increased negative pressure on the bronchi. (c) The bronchi dilate into saccules. (Modified from Coope [105] with permission.)



### Obstruction in the pathogenesis of bronchiectasis

Obstruction to a part of the bronchial tree by itself is unlikely to cause bronchiectasis unless there is accompanying infection. Thus experiments in which the bronchi of rabbits and rats were ligated led to the conclusion that bronchiectasis in rabbits only occurred if the sterility of the preparation was spoiled, whereas rats, which possess a resident bronchial flora, developed infection followed by bronchiectasis [103,104]. Undoubtedly obstruction in any viscus in humans results in stasis, which then predisposes to infection. In the lungs of humans, bronchiectasis may result from (i) the obstruction of many small peripheral bronchi or (ii) the obstruction of a more central bronchus.

Obstruction of small peripheral bronchi is a feature of lower respiratory tract infection in children, notably in whooping cough [79], where mucus and inflammatory debris are shed into the lumina of peripheral bronchi, which because of their small diameters are more readily obstructed than is the case in adults. As a consequence of this, radiographic evidence of patchy areas of atelectasis is common in whooping cough [79]. Whether such atelectasis plays an important causal role in the development of bronchiectasis is unknown but it has certainly been proposed as a factor (Fig. 28.1). It is also possible that the epithelial disruption produced by whooping cough, or other primary infections such as measles, paves the way for more persistent lower respiratory tract infection by impairing the primary defences of the lungs.

Proximal and prolonged more central bronchial obstruction may result from (i) an intraluminal occlusion as may occur with a slow-growing tumour such as a carcinoid or sometimes with rare slow-growing benign tumours (e.g. lipoma, papilloma, fibroma, chondroma) [106–108] or with an aspirated solid foreign body, or (ii) extramural compression due to mediastinal or other masses or, in the case of children, whose bronchi are soft and more compressible, by enlarged hilar glands. The

middle lobe bronchus is especially susceptible to occlusion because of its relatively small lumen and its emergence from the intermediate bronchus at a right angle, at which point it is surrounded by lymph nodes that if enlarged tend to compress it. This produces the so-called middle lobe syndrome [86,87], in which the lung subtended by the obstructed middle lobe bronchus may become partially or completely atelectatic. This is also sometimes referred to as Brock's syndrome after the author of the original description, in which tuberculosis was put forward as the cause [109]. With the superimposition of infection, an inflammatory exudate is produced and the bronchial walls themselves become inflamed and weakened with the development of bronchiectasis.

Bronchiectasis resulting from the aspiration of a foreign body may occur in both adults and children [110–112]. The right side is affected more often than the left, usually the lower lobe or posterior segment of the upper lobe. Le Roux and colleagues [7] reported foreign body aspiration as the cause of bronchiectasis in 5.6% of 1003 resections carried out for this condition in a South African population. In series appertaining to Western populations, the proportion is in the order of 1% overall, but is higher in children. Frequently no history of the event itself is obtained and many months or even years may elapse before the diagnosis is made [113,114]. The site of retention of a foreign body is often sufficiently proximal for it to be viewed bronchoscopically. However, this is not always the case and the flowering heads (inflorescences) of timothy grass and other plants tend to move peripherally [112,115], in much the same way as they may migrate up the sleeve of a playing child.

### **Inflammation in the pathogenesis of bronchiectasis**

The foregoing sections have considered the association of certain forms of pulmonary infection and bronchial obstruction with the later development of bronchiectasis. This section considers in more general terms the ways in which chronic inflammation in the lower respiratory tract, once started, may cause progressive local damage, resulting in permanent dilatation of the affected bronchi.

The most common means by which such inflammation becomes established is infection. Any infecting organisms first have to overcome the lungs' primary defences in order to establish themselves. These defences include impaction on the mucous layer overlying the bronchial epithelium and clearance by a combination of normal respiratory ciliary function and coughing. Some organisms, such as *H. influenzae*, *Strep. pneumoniae* and *Ps. aeruginosa*, may themselves elaborate substances that have the capacity to impair normal ciliary movement and in doing so may reduce the capacity of the lungs to rid themselves of the infection [116–120].

Additional defence mechanisms include local cellular and immune responses, including the elaboration of antibodies. One crucial cellular response involves the migration of neutrophil leucocytes from the pulmonary capillary circulation across endothelium, interstitial tissue and respiratory epithelium in order to reach the bronchial lumen. These neutrophils mount an inflammatory response intended to assist in the phagocytosis and elimination of infecting organisms. However, when such elimination is not achieved and significant numbers of organisms become established as 'colonists' rather than behaving as ephemeral 'raiding parties', the host reacts with a persistent attempt to contain the infection, so that the inflammatory response becomes chronic, with the continuous elaboration of potentially harmful substances, including damaging free radicals and neutrophil elastase [121,122]. In keeping with this, the mucopurulent sputum of patients known to have bronchiectasis has been shown to contain elastase [123]. Elastase activity is also found in the sputum of patients with chronic bronchitis, but only during exacerbations and not when the sputum is mucoid [124]. Elastase has similarly been shown to clear from the mucopurulent sputum of patients with bronchiectasis should their sputum become mucoid following treatment with antibiotics [125]. Neutrophil elastase has the potential to attack elastin in the bronchial walls so that they may become weakened and subsequently dilated as a result of the elastic forces of the surrounding lung. Elastase also has the potential to disrupt ciliary action [126,127] and results in increased production of mucus in the lungs [128], as well as destroying important opsonins and seriously impairing the host's defences against pseudomonal colonization [129].

The cell-mediated immunological component of the process occurring in the bronchial walls is characterized by the presence of mainly T lymphocytes [130], with interleukins and other proinflammatory cytokines also being produced [131]. It has also been shown that the ratio of sputum to serum albumin is raised in these patients, implying increased protein transudation from the blood to the airways in the presence of inflammation [132], and that this ratio also falls following antibiotic treatment in patients with bronchiectasis [125].

It is therefore possible to hypothesize that the inflammatory process incited by certain infective organisms in the lungs tends to perpetuate infection by impairing clearance mechanisms and that this results in a vicious circle of increasing inflammatory damage to parts of the bronchial tree in the process; furthermore, this process is important in producing the gross pathological changes characteristic of bronchiectasis [133,134].

### **Immunological changes**

The presence of chronic lower respiratory tract infection

such as may occur in bronchiectasis is associated with measurable immunological abnormalities. Raised levels of IgG, IgA and IgM are common and have been reported in the literature [66,74]. Such raised levels have not been found in control groups comprising patients with asthma and chronic bronchitis [74] but in bronchiectasis have been found to correlate with the severity of disease. It has been postulated that they are a response to the persistent antigenic stimulation resulting from chronic infection in the bronchial tree and that the presence of bronchiectasis itself evokes a hyperimmune response.

The presence of rheumatoid factor was found in 52% of one series of 53 patients with bronchiectasis [74]. This finding is non-specific, since the presence of rheumatoid factor has been found with greater than expected frequency in many chronic pulmonary diseases as well as in other non-respiratory disease both acute and chronic, rheumatoid and non-rheumatoid. The production of rheumatoid factor can in these situations be regarded as a response to a wide variety of antigenic stimuli that may come from the products of infection or from those elaborated in the process of tissue destruction.

Antinuclear antibodies are also present in 10–28% of patients with bronchiectasis or 'chronically infected bronchitis' [74,134–136]. These antibodies have not been shown to have a causal role in the tissue damage associated with bronchiectasis and their presence may also be an epiphenomenon. Other antibodies against smooth muscle, thyroid and gastric parietal cells are found but are less common.

Immune complexes may be detectable in the circulation of patients with bronchiectasis [137] and have been taken to be indicative of a normal antibody response to the heavy antigenic level sustained by patients with the chronic pulmonary suppuration that may be found in bronchiectasis. However, such immune complexes have been causally associated with cutaneous vasculitis in a few patients with severe bronchiectasis, possibly occurring in response to circulating endotoxins [138]. Cutaneous vasculitis may also rarely occur in CF-associated bronchiectasis [139].

### Autoimmune disease

Autoimmune diseases are more frequently associated with bronchiectasis than would be expected to occur by chance. These include inflammatory bowel disease, particularly ulcerative colitis, coeliac disease, primary biliary cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, thyroiditis and pernicious anaemia [66,140–143]. Similar associations have been noted in cryptogenic fibrosing alveolitis [144]. The mechanisms by which autoimmune diseases develop in human are unknown. Allison and colleagues [145] postulated a lymphocyte-mediated defect resulting in a failure to recognize

'self', with the consequent production of antibodies against a range of normal tissue components, including mucosal surfaces. Speculation surrounds the possibility that immune complexes may have pathogenic effects on the lungs in bronchiectasis and in other associated autoimmune diseases [138,146].

An association between chronic productive cough (with or without bronchiectasis) and inflammatory bowel disease was initially reported in 1976 [142]. Butland and colleagues [141] laid further emphasis on the particular connection between ulcerative colitis and bronchiectasis when they reported seven cases in 1981. The chronic productive cough postdates the symptoms of colitis in nearly all cases, not uncommonly by months or years, and the occurrence of quite florid bronchiectasis after the bulk of inflammatory disease has been removed by total colectomy is well recognized although not satisfactorily explained. In such patients, large numbers of neutrophils have been found in fluid recovered by bronchoalveolar lavage, as well as in some samples of lung tissue, suggesting that these cells play a role in the inflammatory processes responsible for the lung lesions [143]. There are also reports of apparent symptomatic benefit when the respiratory symptoms are treated with systemic corticosteroids, an intervention that would be avoided instinctively in cases of chronic suppurative lung disease [141,143].

A probable association between bronchiectasis and rheumatoid disease has been reported [147,148]; indeed bronchiectasis was found to be 10 times more common in patients with rheumatoid rather than those with osteoarthritis [149]. It has also been suggested that bronchiectasis is found with the same frequency as pulmonary fibrosis in rheumatoid arthritis [147]. However, the latter condition is considered to be an extra-articular manifestation of rheumatoid disease, whereas it is speculated that bronchiectasis is more likely to result from a predisposition to lower respiratory tract infection as a consequence of either rheumatoid disease or its treatment [148]. Certain HLA variants have been shown to be more common in patients with rheumatoid arthritis and bronchiectasis together than in those with rheumatoid arthritis alone [150]. Some series have indicated that when bronchiectasis does occur it usually precedes rheumatoid arthritis [148], whereas others have implied that this is more often not the case [151,152]. Most patients have seropositive disease and those in whom the respiratory symptoms come first may have milder arthritis [151]. Seronegative arthritis that has been regarded as 'reactive' has been observed to remit when the lower respiratory tract infection associated with bronchiectasis is brought under control [153]. Xerophthalmia has been found to be more common in patients with rheumatoid arthritis and bronchiectasis than it is in rheumatoid arthritis alone [148].

Sjögren's syndrome may occur in primary form with keratoconjunctivitis sicca and xerostoma alone or in association with a connective tissue disease, commonly rheumatoid arthritis. High titres of anti-Ro and anti-La antibodies in the serum are characteristic. There may be associated atrophy of tracheobronchial submucous glands, leading to dryness with chronic cough and a tendency to develop recurrent lower respiratory infection and bronchiectasis [154].

Bronchiectasis has been reported in association with lung, heart–lung and bone marrow transplantation, possibly occurring as a more proximal airway manifestation of the obliterative bronchiolitis (syn. bronchiolitis obliterans) that is a usual finding in chronic rejection or graft versus host disease [155,156].

### Atopy and asthma

Comparisons of patients who have bronchiectasis with control subjects have shown no significant difference in the prevalence of atopy between the two groups in terms of the presence or absence of positive skin-prick tests to common allergens or with regard to relative serum IgE concentrations [66,157]. This is in contrast to patients with CF in whom atopy may be more common [158]. One study from Hong Kong found a higher prevalence of asthma (in the absence of evidence of allergic bronchopulmonary aspergillosis) in ethnic Chinese patients with diffuse or localized bronchiectasis [159], whereas another found the bronchiectatic group displayed greater bronchial hyperreactivity to histamine and methacholine than controls, although whether this had any pathogenic significance was, and still is, unclear [157].

### Allergic bronchopulmonary mycoses

Allergic bronchopulmonary aspergillosis (ABPA) has long been recognized as an occasional cause of bronchiectasis [160]. Atopic subjects, who also usually have asthma, are affected by this condition which arises as a result of allergy to *Aspergillus* spp., *A. fumigatus* being the fungus most frequently implicated. These patients typically have 'fleeting infiltrates' on their chest radiographs (or rounded opacities in the case of 'muroid impaction'; see below), a positive immediate skin-prick test to *A. fumigatus*, a peripheral blood eosinophilia and a raised serum level of IgE, this tending to reflect the level of activity of the allergic process. *Aspergillus* precipitins [144] are detectable in about 60% of typical cases. The fleeting shadows may clear spontaneously or with systemic corticosteroid treatment. The pathology shows an alveolar eosinophilic infiltrate. Additionally such patients may develop plugs of intra-bronchial mucus, containing eosinophils and sometimes fungal mycelia. These may result in bronchial obstruction

(or muroid impaction), producing various radiographic features that include rounded opacities (Fig. 28.2) and segmental, lobar or rarely whole lung atelectasis. These plugs of mucus (which are sometimes coughed up) are also associated with inflammatory changes in the bronchial wall that may result in permanent damage, demonstrable radiographically as proximal bronchiectasis in which relatively normal small bronchial and bronchiolar filling may be seen beyond grossly dilated proximal bronchi [160] (Fig. 28.3). The pathogenesis is probably a prolonged asthmatic late-phase reaction in response to persistent pulmonary *Aspergillus* antigenic stimulation. The upper lobes of the lungs are most likely to be affected by ABPA-associated bronchiectasis for reasons that are unclear, but in practical terms means that these patients are less likely to have trouble due to stagnant secretions than patients with other forms of bronchiectasis that typically affect the dependent parts of the lungs. Advanced cases of ABPA may develop considerable pulmonary fibrosis with loss of lung volume [161,162]. *A. fumigatus* commonly colonizes patients with CF and 10–15% of these patients go on to develop ABPA, which may result in further respiratory impairment [163]. A survey of 50 patients with 'idiopathic' bronchiectasis confirmed bronchographically found that 10% of cases had evidence of sensitization to *A. fumigatus* that was previously unsuspected and had been overlooked [164]. ABPA is described in detail in Chapter 21.

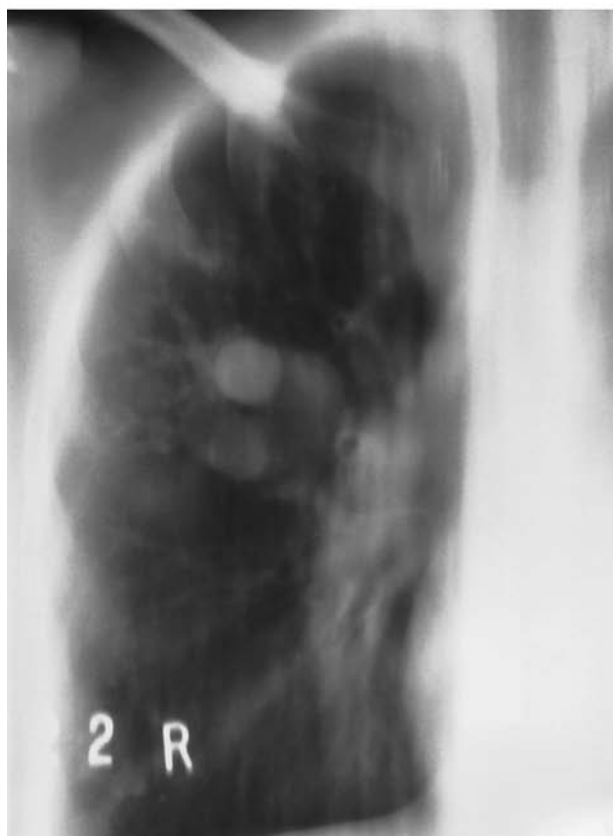
Fungi other than *Aspergillus* may cause allergic bronchopulmonary mycoses that produce clinical syndromes very similar to ABPA and these probably account for cases in routine clinical practice in which serological or skin-prick test evidence of *Aspergillus* infection cannot be demonstrated [165–168]. It is likely that some allergic mycoses other than ABPA may cause bronchiectasis but evidence is so far lacking.

### Other associated conditions

A variety of rare conditions have been associated with bronchiectasis. These include the yellow nail syndrome, comprising a triad of yellow, thickened, dystrophic finger-nails, chronic dependent lymphoedema and pleural effusions [169]. This condition, which may result from hypoplastic peripheral and pleural lymphatics, has also been associated with other respiratory abnormalities including sinusitis, recurrent pulmonary infections and bronchiectasis. Various immunological abnormalities have also been described in individual patients with the yellow nail syndrome, including lymphopenia, hypogammaglobulinaemia, reduced circulating levels of IgA and of B cells [170]. There are isolated reports of bronchiectasis occurring in association with Klinefelter's syndrome [171] and dyskeratosis congenita [172].

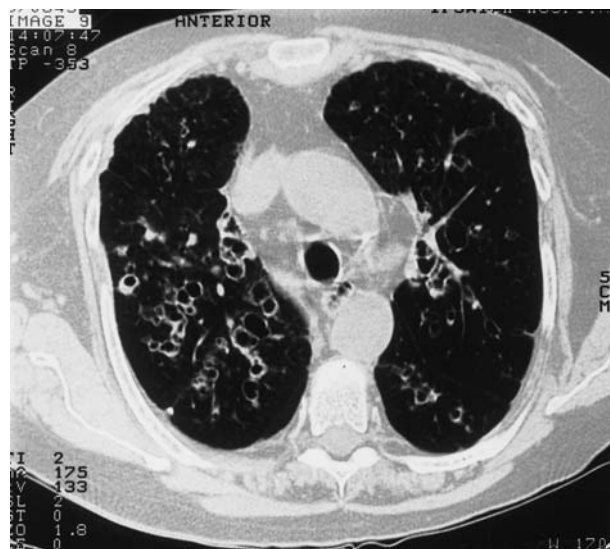


(a)



(b)

**Fig. 28.2** (a) Chest radiograph and (b) conventional tomogram showing rounded opacities caused by mucoid impaction in the right upper lobe of a 23-year-old woman with cystic fibrosis and allergic bronchopulmonary aspergillosis.



**Fig. 28.3** High resolution CT showing proximal bronchiectasis predominantly affecting the upper zones of the lungs of a 71-year-old woman with asthma complicated by allergic bronchopulmonary aspergillosis.

### Mechanisms by which the bronchi may dilate

Many explanations for the dilatation of the bronchi in bronchiectasis have been advanced, no single explanation being entirely satisfactory, so that it is probable that various mechanisms interact according to the primary pathology in order to produce a common end-result.

### Atelectasis theory

It was shown experimentally over 60 years ago that the aspiration of viscid material into peripheral parts of the bronchial tree may result in atelectasis and dilatation of the bronchi in the collapsed area [173]. Such dilatation is compensatory and occurs because atelectasis, in reducing lung volume, increases intrapulmonary negative pressure. This in turn dilates any bronchi proximal to the block, as these remain in communication with the atmosphere (see Fig. 28.1). Lander [174] subsequently concluded that three possible events might follow.

1 The collapsed part of lung might re-expand, with the disappearance of the compensatory bronchial dilatation. Such 'reversible bronchiectasis' is well recognized and is a reason not to diagnose bronchiectasis on the basis of the CT finding of bronchial dilatation when this is associated with apparent consolidation of surrounding lung after a recent pneumonic episode.

2 The lung collapse and consequently the associated bronchial dilatation may become permanent.

3 The collapsed portion of lung may re-expand but the bronchi remain dilated because of damage to their walls by an infective (or other inflammatory) process.



### Pressure of secretions theory

This states that following the plugging of a bronchus with mucus or other material, secretions distal to the obstruction accumulate and mechanically distend the bronchi beyond the block [175]. This mechanism has already been mentioned and would seem to be experimentally tenable only in the presence of bronchial wall inflammation such as might occur as part of an infective process [103].

### Traction theory

This states that bronchial dilatation occurs secondarily to fibrosis of lung parenchyma, the resulting scar tissue requiring high inflation pressures on inspiration to overcome abnormally high retractive forces. This mechanism would clearly not account for cases of bronchiectasis with little lung parenchymal fibrosis but does accord with the occasional pathological finding of bronchiectasis in cases of extensive pulmonary fibrosis ascribed to a variety of conditions, including radiotherapy, rheumatoid disease, scleroderma and cryptogenic fibrosing alveolitis [176].

It should be noted that with the possible exception of the traction theory, all other mechanisms require a weakening of the bronchial wall and, excepting rare congenital abnormalities such as bronchomalacia, this requirement is likely to be satisfied only as a result of the presence of inflammation. It is probable that inflammation usually results from infection, although other non-infectious inflammatory processes such as sarcoidosis [177] or allergic bronchopulmonary aspergillosis (see Chapter 21) may be responsible in a minority of cases. Once the morphological changes that constitute bronchiectasis have been instituted, then a vicious circle of secondary infection resulting in further lung damage may occur [134,178].

### Pathology

General pathological features in bronchiectatic lungs include the dilatation of medium-sized subsegmental bronchi from about the fourth to the ninth generations. The bronchiectatic areas may become lined by squamous or columnar epithelium frequently denuded of cilia; indeed there may be no recognizable epithelial lining at all on the surface of involved bronchi. Depending upon the severity of the process, inflammation of the walls of the bronchi results in a variable degree of atrophy, with destruction of muscle and elastic components, these being replaced by fibrous tissue so that sometimes little muscle or cartilage remains. The walls of the bronchi may be infiltrated by polymorphonuclear neutrophils, which are also found in the bronchial lumen. A dense intramural lymphoid infiltrate is common in certain cases (see below). According to the extent of disease, small side-branching bronchi and bronchioles may be cut off from their parent,

to be obliterated and lost as a result of the inflammatory process [179]. Reid [180] claimed that this destruction was more important from a functional standpoint than bronchial dilatation and suggested that the term 'bronchitis obliterans' might therefore be preferable to bronchiectasis, a terminological change that has not been adopted by clinicians or pathologists whose conceptions of bronchiectasis are firmly rooted.

Less severe bronchial deformities take the form of cylindrical (syn. fusiform or tubular) dilatation, whereas gross changes may be saccular (syn. cystic). Such saccular bronchiectasis in which dilatation is greatest in the more distal parts of affected bronchi may be clearly seen with the naked eye (Fig. 28.4), the saccules being in continuity with the bronchi [181]. Their walls are thin and composed of fibrous or granulation tissue sometimes lined by metaplastic squamous epithelium that is often ulcerated.

The affected airways may contain an exudate of mucopus, and in saccular bronchiectasis the saccules themselves may be filled with pus. The presence of such material indicates that infection is active. When there is no infection, there is minimal exudation and the condition may be termed 'dry bronchiectasis', whereas if hypersecretion of mucus continues as a result of chronic infection the condition is termed 'wet bronchiectasis', the symptoms of which may be indistinguishable from purulent chronic bronchitis [180] except that ordinarily the volume of mucopus is greater in bronchiectasis.

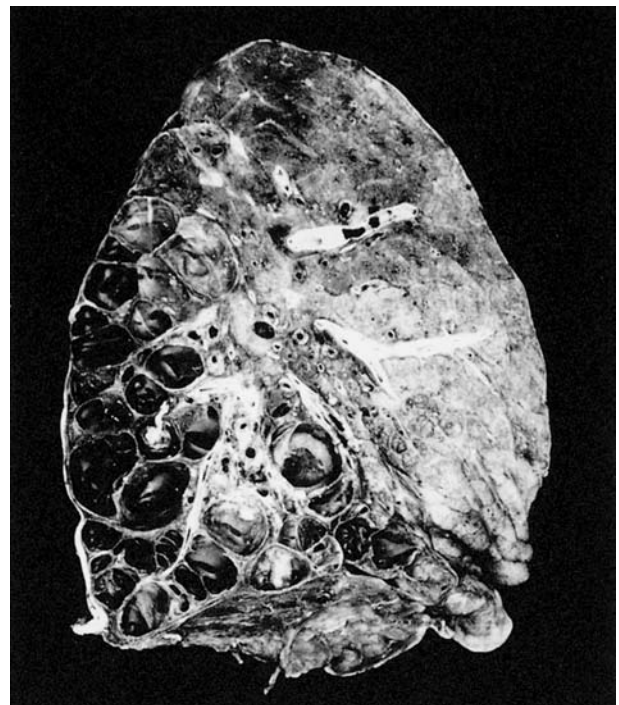


Fig. 28.4 Gross cystic bronchiectasis in the lower lobe of excised left lung.

Peribronchial fibrosis is common and the surrounding lung may also contain a variable amount of fibrosis, atelectasis and pneumonia.

The vascular supply to affected areas is altered, with the loss of much of the alveolar capillary bed as a consequence of destructive inflammation and scarring. This results in the opening up of precapillary anastomoses between large hypertrophied bronchial arterial branches, containing blood at systemic pressure, and the pulmonary arterial circulation [182,183]. The loss of this capillary bed and the presence of systemic-to-pulmonary shunting [184] may contribute to the development of pulmonary hypertension, with subsequent cor pulmonale that may complicate extensive hypoxaemic bronchiectasis.

### Site of bronchiectasis

A preponderance of bronchiectasis on the left side and in the lower lobes has been noted by many authors [7,49,185]. The upper lobes are affected least frequently and the middle lobe and lingula occupy an intermediate position with regard to frequency of involvement, as might be expected from their topographical position. When the left lower lobe is involved it is common for the lingula to be affected as well. One series of 215 bronchographically demonstrated cases found unilateral involvement in 65% of patients [185], a figure in close agreement with Spencer's review of three series comprising 322 cases in whom unilateral disease was found in 66% [49]. A breakdown of the 215 cases referred to above revealed disease confined to one lobe only in 31%, to more than one lobe unilaterally in 34%, and bilateral involvement in 35% [185].

### Classification

Pathological classifications of bronchiectasis have been based on the thesis of Francis Whitwell [49,181,186]. This work incorporated the microscopic examination of 180 surgical lobe or whole-lung specimens obtained in Liverpool between 1946 and 1948, before the general availability and use of antibiotics. Very few patients in this series were aged over 40 years. Of these cases, 18% were thought to be of congenital origin, characterized by the presence of large dilated bronchial sacs throughout the involved lobe or lung, with no microscopic evidence that more distal bronchiolar or acinar structures ever developed; 44% fell into no particular category and the remaining 87 patients (48%) were allotted to three morphologically distinct groups: follicular, saccular and atelectatic.

#### Follicular bronchiectasis

This type acquired its name from the presence of numerous lymphoid follicles situated in thickened, usually

cylindrically dilated bronchial walls. Enlarged hilar glands were noted to be a feature. The majority of specimens were obtained from patients aged 5–15 years [181]. Over half of 28 patients in whom records were available had been symptomatic from infancy.

#### Saccular bronchiectasis

This was characterized by the presence of macroscopically visible thin-walled, saccular (sometimes called cystic) bronchial dilatations. No patients in this group were aged under 15 years at operation and of 16 in whom clinical records were available, 70% became symptomatic between the ages of 13 and 25 years.

#### Atelectatic bronchiectasis

As the name implies, this form was associated with some pulmonary collapse. It was predominantly right-sided in contrast with follicular and saccular bronchiectasis, which involved the left lung more commonly. The right middle lobe was frequently involved and a number of specimens showed evidence of tuberculosis, suggesting that some of these cases resulted from proximal bronchial obstruction by enlarged hilar glands, to which the rather slender right middle lobe bronchus is particularly susceptible [86,87,109]. Most of these patients were submitted to surgery between the ages of 5 and 10 years, although a few patients up to the age of 30 years were included.

From the relatively few clinical records available in this series (59), it was concluded that all three groups were associated with pneumonia but a relationship with whooping cough or measles was only found in the follicular and atelectatic groups. The association between measles and follicular bronchiectasis is supported by more recent clinicopathological work from South Africa [80].

### Clinical features

Bronchiectasis may produce no symptoms and physical signs may be entirely absent [187,188], as has been shown in the past by the finding of typical bronchographic appearances following the investigation of a plain chest radiographic abnormality on a 'routine' film. At the other end of the clinical scale, it may produce a persistent cough productive of distressingly copious volumes of mucopurulent and sometimes fetid sputum, in a breathless and chronically disabled patient. Most cases belonging to the first category go fittingly undiagnosed for obvious reasons and those from the second are fortunately becoming increasingly uncommon [62,189,190], at least in countries that possess readily available antibiotics and facilities for immunization against measles and whooping cough. The majority of cases encountered nowadays in developed countries fall between these two extremes. Not uncommonly

monly the onset of symptoms may date back to childhood and an episode of severe whooping cough, measles or 'pneumonia' may be recalled by the patients or their relations.

### Symptoms

Cough is the most common symptom of bronchiectasis. It is usually persistent and productive of mucopurulent sputum but may be intermittent with 'dry' periods. As bronchiectasis involving the more dependent parts of the lungs progresses, sputum production often becomes more continuous, voluminous and purulent. Patients with such 'wet' bronchiectasis are liable to recurrent flare-ups of infection during this progression and sometimes these episodes may be complicated by pneumonia and pleurisy; indeed recurrent episodes of lower respiratory tract infection often raise the possibility of bronchiectasis. The sputum of patients with less severe disease may become mucoid or may dry up altogether during treatment with an antibiotic, whereas in those with severe disease the volume and purulence may only diminish. Bronchiectasis predominantly affecting the upper lobes of the lungs tends to be 'drier', and such may be the case when the structural damage is a consequence of postprimary tuberculosis, ABPA (see Fig. 28.3) or sarcoidosis. Children may produce sputum less frequently than adults, one series recording absent sputum in 32% of a cohort of 96 children despite positive bronchographic confirmation of bronchiectasis [191]. Frequently, cough and sputum production are triggered by postural change, such as lying down at night, rising in the morning or stooping down for some task.

Haemoptysis is also classically associated with bronchiectasis and sometimes it is this more alarming symptom that brings the patient to the physician rather than a chronic or recurrent cough, which may have become accepted as an almost 'normal' state of affairs. The reported incidence of haemoptysis has varied widely, from 4% of 116 paediatric patients [192] to 32% of a surgical series comprising 240 patients of whom the majority were in their twenties [193]. In this series, 12 patients (5%) were described as having 'massive' haemoptyses, four of these patients (1.6%) requiring blood transfusion. The bleeding may come from precapillary anastomoses between hypertrophied branches of bronchial arteries that contain blood at systemic pressure. Such haemoptyses usually occur spontaneously or as a result of superadded infection and has also been described as a complication of iatrogenic thrombolysis or anticoagulation [194,195]. Otherwise unsuspected bronchiectasis may be found on HRCT in 15–17% of patients presenting with haemoptysis [196,197].

Dyspnoea is regarded as a late symptom, other than when it occurs with pneumonia, pleurisy or ABPA with

asthma, and usually indicates widespread lung disease with extensive destruction and fibrosis.

Wheeze is by no means a universal symptom in adults despite the frequent presence of measurable airflow limitation; indeed patients who have demonstrable reversibility of airflow limitation do not always admit to wheeze on direct questioning [39]. Those whose bronchiectasis has resulted from ABPA are often wheezy as they commonly have asthma.

Other coexisting symptoms include general tiredness and malaise and those of upper respiratory infection, particularly sinusitis; at least two-thirds of a series of 116 children had the presence of mucopus in their antral cavities confirmed by aspiration [192]. These symptoms tend to persist into adulthood and it is not uncommon for bronchiectatic patients to have been seen previously in ear, nose and throat clinics; in Streete and Salzer's series [193], 11% of patients had been separately treated for sinusitis.

The presence of symptoms from childhood raises the possibilities of asthma and subsequent ABPA, CF, primary ciliary dyskinesia and congenital immunological defects. CF, primary ciliary dyskinesia and the acquired condition known as Young's syndrome (see above) are all associated with male infertility.

### Signs

Mild cases of bronchiectasis often have no abnormal physical signs. When the disease is sufficiently developed, the characteristic finding is that of persistent early and mid-inspiratory crackles (still often referred to as râles in the USA or crepitations in the UK), which are localized to one or more areas so that they are heard at the same site or sites on repeated examination. These crackles are frequently described as 'coarse' (as opposed to 'fine') and are not shifted by coughing, unlike other low-pitched interrupted noises produced by loose secretions in large airways (see Chapter 6). Although helpful when present, the absence of crackles does not exclude bronchiectasis since in a group of patients with chronic sputum production, auscultatory findings were found to be unreliable in distinguishing between those who had and those who did not have bronchiectasis on HRCT [198].

Clubbing of the fingers and/or toes is a feature of gross disease with prolonged bronchial infection [188]. The frequency with which it occurred in Field's original series of 1949 [199] was 44%, falling to only 7% in her follow-up data published 20 years later [5]. This change is likely, at least in part, to reflect the control of infection by antibiotic treatment, although the deaths of some severe cases cannot be discounted. Nowadays finger clubbing in bronchiectasis, other than that associated with CF, is uncommon in more developed countries.

Signs of collapse and fibrosis may be present in

advanced cases. There may also be cyanosis, with signs of pulmonary hypertension and right heart failure in such patients.

## Functional impairment

The functional impairment in bronchiectasis is related to the extent of lung damage as determined by the number of bronchopulmonary segments involved [184,200]. Other diseases that are much more prevalent in the community may coexist with bronchiectasis partly on the basis of chance, and abnormalities of lung function testing may therefore reflect more than one pathology [200,201].

Measurements of ventilatory capacity and static lung volumes in series of patients with bronchographically proven bronchiectasis tend to show that airways obstruction is the predominant ventilatory defect. Such impairment is often mild and not invariably present, 37% of a series of 116 patients from Edinburgh having an initial forced expiratory volume in 1 s ( $FEV_1$ ) greater than 70% of the predicted value [76]. Another smaller series has shown that 71% of 34 patients with bronchiectasis had airflow limitation in terms of an  $FEV_1$ /forced vital capacity (FVC) ratio of less than 65% [123]. Patients in this series who had 'purulent' sputum had significantly higher residual volume (RV)/total lung capacity (TLC) ratios than those whose sputum was 'mucopurulent' or 'muroid' [123]. The same difference was found between those whose sputum contained elastase and those whose sputum did not [123]. The implication of the findings in these patients was that the presence of infection/inflammation was associated with increased airways obstruction. A series of 23 patients with bronchiectasis from Dublin showed only a mild degree of airways obstruction in terms of  $FEV_1$  and peak flow rates, both of which were 67% of predicted [66]. Another series found evidence of obstruction in terms of reduced  $FEV_1$ /FVC ratios and increased RV/TLC ratios in over half of a group of 42 patients [200]. The degree of airflow limitation (as evidenced by  $FEV_1$ ) has been shown to correlate positively with both the duration of symptoms and the extent of disease on CT examination [202]. Such airflow limitation is likely to be a consequence of both sputum retention and the destruction of smaller side-branching bronchi (Reid's 'bronchitis obliterans'; see p. 805) as part of the bronchiectatic process.

Studies of lung mechanics have also been carried out, showing an elevated pulmonary resistance in a similar proportion and reduced dynamic lung compliance in 41% of 32 cases in whom these measurements were made [200]. No differences in lung function were noted between patients whose bronchiectasis was 'saccular' rather than 'cylindrical' but in whom the distribution of disease was similar [200].

Reversibility of airflow limitation may be present in bronchiectasis. The nature of the pathological changes

might at first suggest that treatment with bronchodilators would produce no benefit; however, the results from a number of studies indicate that their effect should certainly be tried, as a proportion of patients show objective improvement in lung function. Thus 39% of a series of 23 patients showed significant reversibility following a standard dose of fenoterol via a metered dose inhaler [39], and in another small series a mean increase in  $FEV_1$  of 16% was obtained after 5mg of nebulized salbutamol [203]. Improvements in the degree of airflow limitation have also been recorded following treatment with antibiotics [204], although these may be small and clinically insignificant [201]. Patients with bronchiectasis commonly show evidence of bronchial hyperreactivity when tested with substances such as methacholine [205].

In studies of gas exchange, the single-breath diffusing capacity for carbon monoxide ( $DLCO$ ) was found to be reduced to less than 70% of the predicted value in 38% of one series [200]. Pande and colleagues [184], using the steady-state technique, found subnormal values in 87% of their series from New Delhi and observed a correlation between the figures obtained and the number of pulmonary segments involved by bronchiectasis. Further studies of gas exchange were carried out in seven patients who had arterial hypoxaemia of varying severity. All had widened alveolar-arterial  $PO_2$  gradients and a mean true right-to-left shunt of 13.6%. Further evidence of shunting through bronchopulmonary anastomoses has been provided by the findings of (i) higher  $Sao_2$  in blood from the pulmonary artery draining the affected segments, (ii) higher pulmonary arterial wedge pressure in the affected segment and (iii) increased left ventricular output compared with right ventricular output [206]. Bronchospirometric studies of a severely affected lung have shown that although it received one-third of total 'ventilation', it contributed less than 10% of total oxygen uptake [207].

Plainly, radioisotope measurements of regional ventilation and perfusion will be abnormal in bronchiectasis [208]. Unfortunately the limited spatial resolution inherent in these techniques diminishes their value in the pre-operative assessment of bronchiectasis, other than in extensive unilateral disease in which pneumonectomy is envisaged. Radioisotopically labelled particle studies have been used for research purposes to demonstrate abnormalities of mucociliary clearance present in bronchiectasis of any type [209,210].

Lung function in CF is discussed in Chapter 30; suffice it to say that  $FEV_1$  is the best single predictor of mortality [37] and that an increase in RV/TLC ratio and a fall in  $DLCO$  have also been found to correlate with increasing severity of disease in adult patients with CF [211].

In conclusion, lung function tests are of little diagnostic value in bronchiectasis but are useful in measuring the extent of impairment and in demonstrating occasional response to bronchodilators or other treatments. The

simple and highly reproducible tests, such as FEV<sub>1</sub> and FVC, are also the most clinically useful and reliable.

## Other investigations

When a diagnosis of bronchiectasis is suspected on clinical grounds, consideration should be given to predisposing causes that if identified might modify clinical management. These include the possibility of foreign body aspiration, proximal bronchial stenosis as in the middle lobe syndrome or as a result of a slow-growing tumour, ABPA [212] (see Chapter 21), hypogammaglobulinaemia or other primary or acquired immune deficiency syndromes (see Chapter 4), and CF (see Chapter 30) which may occasionally present in adult life [213]. The rare syndrome of primary ciliary dyskinesia may be suspected clinically, although morphological confirmation requires electron microscopic examination of nasal mucosal biopsy material, a facility that is only available in certain centres. Radiographic or CT evidence of paranasal sinusitis may be present but this is often part of a generalized respiratory tract infection rather than the cause of bronchiectasis.

## Microbiology

As is well known, the passage of sputum from the lower respiratory tract to the specimen container results in its contamination by oropharyngeal commensal flora, which may include all the organisms commonly regarded as pathogenic in bronchiectasis. Despite this limitation, the frequent isolation of a relatively small number of different pathogens from purulent sputum, and the clinical response rates based on the sensitivities of these organisms, has led to the general conclusion that they play a clinically important role in bronchiectasis. *H. influenzae* (unencapsulated non-typable strains, not type b) is the bacterium most commonly isolated in such cases of chronic bronchial sepsis, *Strep. pneumoniae* being the second most common in Western series [192,201,214–216]. These are the same organisms as those that predominate in chronic bronchitis. Gram-negative organism such as *Ps. aeruginosa* and less commonly *Klebsiella* spp. may colonize bronchiectatic lung, particularly in patients in whom antibiotics have suppressed the more common invaders or colonizers. These organisms were more common than *Strep. pneumoniae* in one small series from Hong Kong in which lower respiratory tract specimens were obtained by protected bronchial brushing [217]. Patients with bronchiectasis whose lungs are colonized by *Ps. aeruginosa* have been shown to have more extensive and severe bronchiectasis on HRCT than those who do not harbour this organism [218]. *Staph. aureus* may also become a colonist and its presence should always be suspected if a serious clinical deterioration has occurred. Serum precipitins have been regarded as a measure of the patho-

genicity of the more common isolates [219], although not used in routine clinical practice; they have been reported in cases of chronic bronchial sepsis (excluding CF) with frequencies of 83% for *H. influenzae*, 35% for *Strep. pneumoniae*, 29% for *Staph. aureus* and 15% for *Ps. aeruginosa* [214]. The most appropriate culture techniques for isolating common pathogens have been described by Roberts [214]. The relationship between all these organisms and their bronchiectatic hosts is usually one of colonization, contrasting with the situation in pneumonia in which the organism behaves in an acute and invasive manner.

Once present in bronchiectatic lungs both *H. influenzae* and *Strep. pneumoniae* may produce factors that inhibit respiratory ciliary activity [134]. *Ps. aeruginosa* produces various substances, including 1-hydroxyphenazine, with similar effects [119] and also produces another pigment, pyocyanin, from which its earlier name was derived; some evidence exists to suggest that this is toxic to ciliated epithelium [118,220], a property also shared by *H. influenzae* [134]. Both *H. influenzae* and *Strep. pneumoniae* are highly chemotactic, i.e. they stimulate the migration of neutrophil leucocytes from capillaries through the bronchial wall to its lumen. Once present, these neutrophils are likely to result in the release of proteinases, with consequent local pulmonary damage.

Other organisms whose significance is not always clear may also be cultured from patients with bronchiectasis. *Moraxella* (formerly *Branhamella*) *catarrhalis* is one example [221] (see Chapter 13) and it is interesting to note that in Lindskog and Hubbell's series of 215 patients, published in 1955, this organism was the most common isolate [185]. Anaerobic organisms may also play a role. These organisms are probably responsible for the distressing symptom of foul-smelling purulent sputum production that was common in the era before antibiotics. Any effort to grow anaerobes from sputum is wasted because of their invariable habit of massive colonization of the mouth, although transtracheal aspiration has shown that they, along with other unsuspected organisms, occasionally reside in the lower respiratory tract in bronchiectasis [222]. They may be important not only as pathogens in their own right but also as  $\beta$ -lactamase producers, contributing to the failure of  $\beta$ -lactam antibiotics to control other more common pathogens. Other organisms that need not be truly pathogenic may also colonize bronchiectatic lung and also produce  $\beta$ -lactamase, which may protect otherwise susceptible pathogens from penicillins or other  $\beta$ -lactams [223].

Sometimes pathogens may not be isolated from sputum even though it appears to be mucopurulent. This may occur if the patient has recently taken an antibiotic. No pathogens were isolated from the sputum in 39% of one series of 33 bronchiectatic patients, although such patients may nevertheless respond clinically to antibiotic treatment [224]. Unusually, mucopurulence may be caused by

the presence of eosinophils as the main cellular constituent of sputum, as may sometimes occur in eosinophilic pulmonary syndromes.

The pathogenic bacteria in bronchiectasis associated with CF differ from those found in other forms of bronchiectasis in the relative frequency with which different organisms are isolated. Thus infections with *H. influenzae*, *Staph. aureus* and *Ps. aeruginosa* are all common, whereas *Strep. pneumoniae* is a relatively rare pathogen. For a full description of CF the reader is referred to Chapter 30.

Needless to say, whenever there is the remotest possibility of tuberculous infection, the sputum should be stained and cultured for acid-fast bacilli [225].

The role of viruses as a cause of exacerbations of infection in patients with bronchiectasis is uncertain, although it is entirely possible that these organisms may have an important effect by causing further impairment of the already compromised lung defences, thereby allowing greater bacterial proliferation [226]. In a study of US Navy personnel, higher rates of raised adenovirus antibody titres were recorded in 137 patients with bronchiectasis compared with patients with bronchopneumonia, bronchitis and other conditions [227]. The causal association between measles and adenovirus infections has been mentioned above in connection with the pathogenesis of bronchiectasis, as has the causal role of bacteria such as *Bordetella pertussis*.

## Radiological features

### Plain chest radiography

The plain chest radiograph is an unreliable means of diagnosing bronchiectasis as it has been found to have a sensitivity of <50% when bronchography was still widely regarded as the diagnostic 'gold standard' [228]; nevertheless certain plain radiographic features may be taken in support of a clinical diagnosis or may lead to further investigation using HRCT, which has displaced bronchography as the confirmatory investigation of choice. Plain chest radiographic features have been described by Simon and others [229,230] and may include any of the following.

#### *Evidence of dilated bronchi*

**Ring shadows.** Ring shadows produced by dilated bronchi seen 'end-on' (Fig. 28.5). These may be small, numerous and widespread, being one of the causes of the radiographic appearance sometimes referred to as honeycomb lung. Honeycomb lung is not a specific radiographic feature of bronchiectasis and may be seen in other diffuse lung diseases, such as advanced fibrosing alveolitis of any type. Larger (0.5–2 cm diameter) ring shadows may also

occur in bronchiectasis and sometimes contain fluid levels, formed by retained mucopus. They may be localized or widespread, giving the radiographic appearance of cystic lung.

**Parallel lines.** Parallel lines are produced by dilated bronchi viewed 'side-on'. Fine parallel, air-containing, hair-line opacities may be seen in normal subjects close to the hilum and represent a longitudinal view of lobar or segmental bronchi. In bronchiectasis such opacities may be more obvious, their walls being thickened rather than hair-line, and may be more numerous or crowded together, indicating lobar shrinkage (Fig. 28.6). They are sometimes called 'tramlines' because they stand out in parallel fashion against the central lucent column of air that they contain.

**Solid tubular opacities.** If such bronchi contain mucopus they may be seen as solid tubular rather than tramline opacities, looking like a scaled-down column of toothpaste. Their width is obviously variable, depending upon the size of the dilated bronchus, but diameters of 5–8 mm and lengths of 2–4 cm may be attained [229]. They may branch, and when seen *en face* or tangentially may produce 'gloved finger shadows' (Fig. 28.7), each finger of the glove tending to have a rounded end, representing a large dilated bronchus containing mucopus.

#### *Appearances consistent with volume loss*

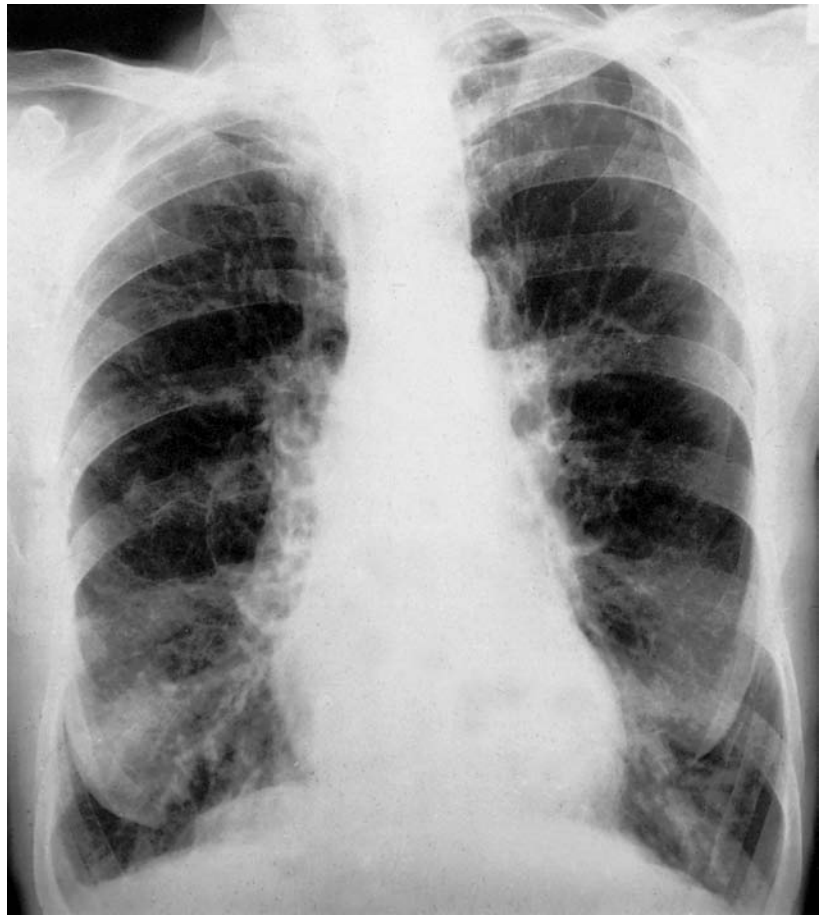
Appearances consistent with volume loss in one or more lobes or segments may be indirect evidence of bronchiectasis and may be caused by long-standing shrinkage of part of the lung as a result of previous atelectasis and/or fibrosis. Occasionally these changes may be localized enough to suggest a proximal bronchial obstruction, such as may occur in the middle lobe syndrome (see above), in which case HRCT and bronchoscopy help to elucidate. Sometimes the distribution and appearances may raise the possibility of previous tuberculous infection, either in the case of such middle lobe involvement or more usually as a result of upper lobe fibrosis and volume loss. Similar upper lobe changes may result from sarcoidosis and ABPA. 'Fleeting' pulmonary infiltrates on the chest radiograph may have been previously noted in patients with ABPA.

#### *Appearances of pulmonary hypertension*

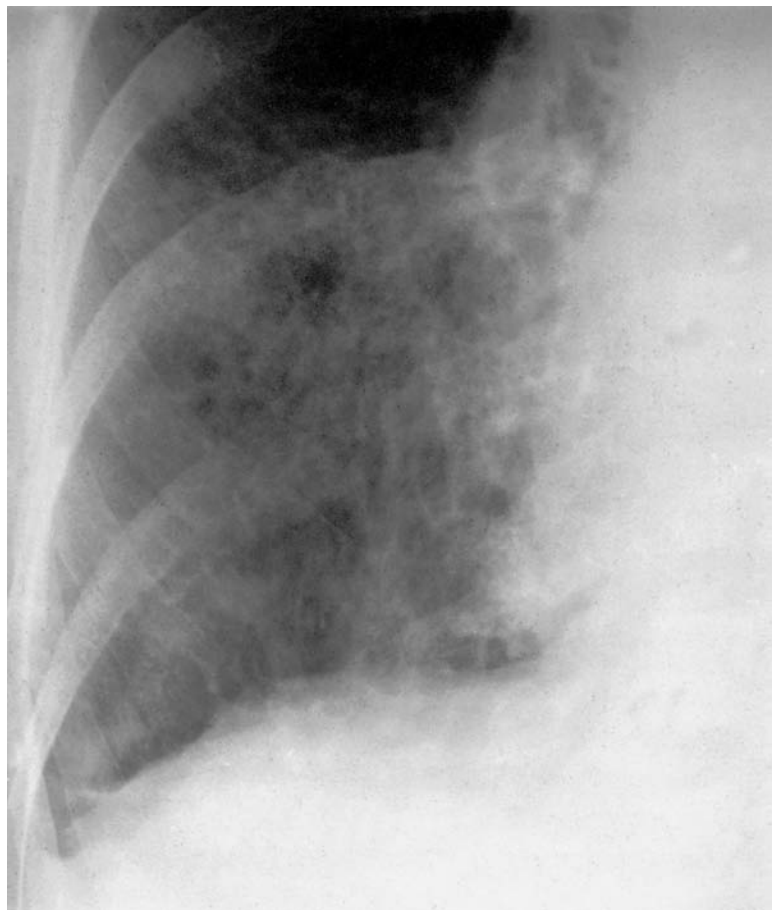
In extensive disease, there may be evidence of pulmonary hypertension, with prominent proximal pulmonary artery trunks and possible cardiac enlargement.

#### *Kartagener's syndrome*

About half of all cases of the immotile cilia syndrome

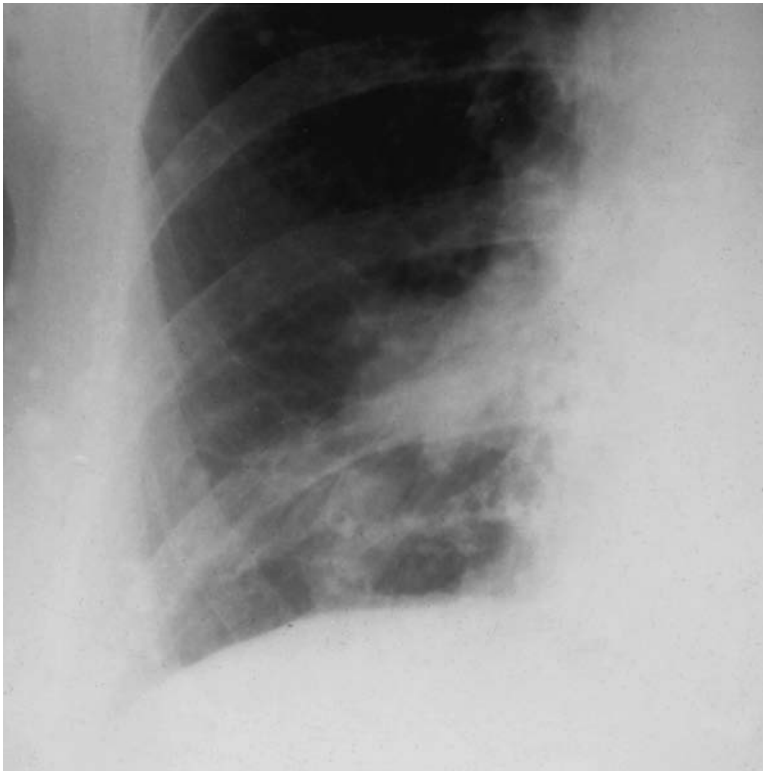


**Fig. 28.5** Ring shadows grouped around the hila bilaterally. Two of the larger ones contain small collections of fluid.



**Fig. 28.6** Ring and tramline shadows in the right lower zone of patient with bronchiectasis.





**Fig. 28.7** Gloved finger shadows in right lower zone.

(syndromes of primary ciliary dyskinesia) may exhibit the full Kartagener's syndrome (pp. 795–6), with situs inversus and therefore dextrocardia on the chest radiograph.

#### *Cystic fibrosis*

Systems of scoring the severity of chest radiographic changes in CF (Figs 28.2, 28.8) have been reported, although CT provides more specific information [231,232] (Fig. 28.11).

#### ***Usefulness of plain films in the diagnosis of bronchiectasis***

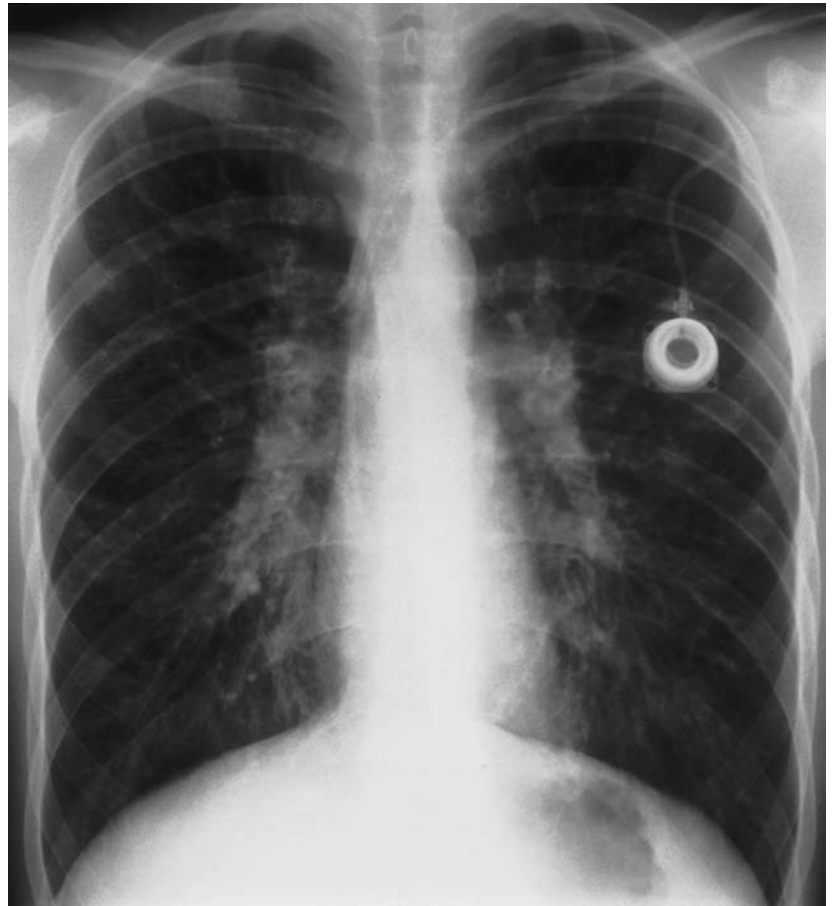
It has long been appreciated that plain chest radiographs may be normal in patients with bronchiectasis in whom the area of involvement is limited [233]. This is particularly relevant nowadays due to the changing severity of the disorder, so that in one large series plain films in 7% of 112 such patients were reportedly normal [234]. Even when the film is judged to be abnormal, the interpretation of the significance of opacities is highly subjective. A study in which two experienced pulmonary radiologists interpreted plain chest films independently and in ignorance of the bronchographic findings demonstrated agreement on plain radiographic evidence of bronchiectasis in only 9 of 19 patients in whom bronchograms subsequently confirmed the diagnosis. This gave the plain chest radiograph a sensitivity of only 47%, a figure that was not improved

by the additional assessment of a lateral as well as a posteroanterior view [228]. Needless to say, plain radiographs are very inaccurate in localizing the site of bronchiectasis and false-positive results may also be obtained [228].

#### **Bronchography**

Bronchography was for many years the investigation of choice when it became necessary to confirm a diagnosis of bronchiectasis with certainty and was considered mandatory if surgical treatment was contemplated. When the diagnosis seemed highly probable on the basis of the history, physical signs and plain radiographic appearances, bronchography was sometimes omitted when the responsible physician judged that no harm would come to the patient through lack of an accurate topographical demonstration of bronchial pathology. However, it is known that mucopurulent sputum may be produced chronically in patients in whom bronchographic appearances are inconsistent with bronchiectasis [228] and, conversely, that areas of relatively 'dry' bronchiectasis may be discovered bronchographically in patients without such chronic sputum production but who may come to medical attention because of another symptom such as unexplained haemoptysis [235]. Thus in either situation bronchography could fulfil a useful function, if only to put the medical management of the patient on a firmer and more confident footing.

The technique of bronchography involves the instilla-



**Fig. 28.8** Typical diffuse chest radiographic changes of bronchiectasis in a 23-year-old man with cystic fibrosis. Note totally implanted drug delivery system for repeated administration of antipseudomonal antibiotics.

tion of a liquid contrast medium into the tracheobronchial tree. It may be carried out either under general anaesthesia or more usually using a local anaesthetic, in which case the contrast medium may be conveniently directed through a fine catheter (e.g. 4.8 French gauge) introduced through the operating channel of the fiberoptic bronchoscope, which also allows secretions to be aspirated first and enables better penetration of contrast to specific areas of interest [236,237]. Aqueous or oily propylidone (Dionosil) was commonly used for this purpose but has been removed from the market for commercial reasons following the increasing use of HRCT. Propylidone, a highly viscous liquid, was not injected directly through the bronchoscope channel as damage to the instrument might have resulted; furthermore, once the injection had been made vision was 'whited out' and lost. Iotrolan has been used as an alternative contrast medium, with an iodine concentration of 300 mg/mL [238]. This is a clear solution that does not obscure vision. It has a much lower viscosity than propylidone and is therefore easier to inject but requires a faster radiographic recording system and is not without adverse effects, as it may cause headache, nausea and flushing.

Nowadays bronchography is regarded as obsolete in

most centres, HRCT having been found to be a more satisfactory alternative that is diagnostically accurate. Bronchography is an unpleasant procedure for the patient, carrying some morbidity. Allergic reactions to the contrast medium, although unusual, may occur and in inexperienced hands serious local inflammatory reactions have occurred when faulty technique has resulted in soft tissue injection of propylidone when the cricothyroid route was used; in addition, the contrast behaves as a foreign body and gas exchange may be impaired [239]. Despite this, bronchography provided useful information for many years and mention of the typical findings is made below.

### *Bronchographic findings*

Affected parts of the lungs showed areas of bronchial dilatation (Fig. 28.9), described as cylindrical, fusiform, sacular (syn. cystic) or varicose. Such descriptive terms need not imply any particular cause; indeed all have been found in the same patient. Bronchiectatic changes are found more commonly in the left lung and are bilateral in about one-third of cases. Other features include the failure of bronchi to taper as they become more peripheral and a diminished number of bronchial side branches. This last



**Fig. 28.9** Bronchogram showing fusiform and cystic bronchiectatic change in left lower lobe and lingula, with severe bronchitic changes also in proximal airways.

feature is most noticeable beyond the fifth order of bronchi, as these have incomplete cartilagenous support [229], and gave rise to the term 'bronchitis obliterans', which has been used as a synonym for bronchiectasis by some pathologists in the past [180]. Luminal filling defects due to bronchial secretions may be present. Affected areas may show bronchial crowding as a result of pulmonary fibrosis or atelectasis. Proximal fusiform or cylindrical bronchial dilatation, with the preservation of relatively normal distal bronchial branches, is a feature of the bronchiectasis that may complicate ABPA [160].

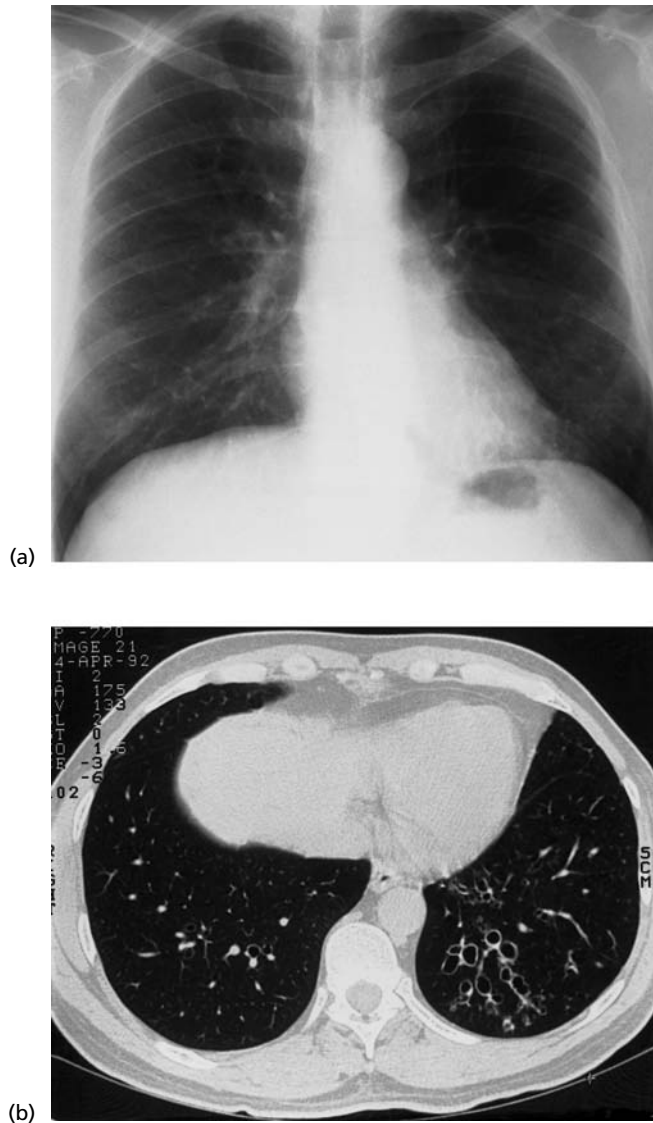
There have sometimes been difficulties with bronchography in deciding whether changes represent minor degrees of bronchiectasis, particularly as bronchographic abnormalities are described in chronic bronchitis [229]. Such changes may include minor irregularities in the calibre of medium-sized bronchi in particular. The bronchial mucosa may have a beaded appearance and small diverticula (or mucous pits) may arise from the bronchial walls. These have been shown to represent dilated mucous gland ducts [240]. Poor peripheral filling due to bronchial secretions may occur in both chronic bronchitis and bronchiectasis. Whether such changes in a patient with chronic cough productive of mucopus are regarded as being consistent with a minor degree of bronchiectasis or 'purulent bronchitis' is somewhat semantic. It has been well known for many years that temporary bronchial dilatation similar to that seen in bronchiectasis may occur in an area of lung affected by

pneumonia despite clinical resolution and that such reversible bronchiectasis, or pseudobronchiectasis, may persist for several months [241].

The interpretation of bronchograms tends to be subjective, with interobserver variation even between experienced radiologists, so that one study showed disagreement about the presence or absence of bronchiectasis in 7% of a sample of 27 patients whose symptoms were consistent with this diagnosis [228]. When one or other of the two radiologists felt that bronchiectasis was present, the level of disagreement increased from 9% on a single lung basis to 22% for lobar involvement. There were major disagreements about the presence or absence of specific features of bronchiectasis but more concurrent views in terms of overall subjective impression [228].

### Computed tomography

HRCT has become the investigation of choice in bronchiectasis since the last edition of this book was published (Figs 28.3, 28.10, 28.11). As CT has the attraction of being non-invasive and safe, several early studies were carried out to determine whether it might be possible to use this technique as a reliable alternative to bronchography in the diagnosis of bronchiectasis. These showed that *conventional* CT was less sensitive for diagnosing bronchiectasis than bronchography, the sensitivities for 10-mm slices at 20-mm intervals being in the order of 65% [242–244]. When compared with bronchography as the



**Fig. 28.10** Increased retrocardiac lung markings were suspected in the left lower lobe on the chest radiograph (a) of this 53-year-old man with a chronic productive cough. High resolution CT (b) confirmed the presence of an area of bronchiectasis in the corresponding retrocardiac area with great clarity.

'gold standard', Cooke and colleagues [244] found that conventional CT diagnosed bronchiectasis correctly in 71% of 45 bronchiectatic lobes (i.e. sensitivity 71%), indicating that this form of CT cannot be used to rule out bronchiectasis reliably. False-positive results at lobar level occurred in 14% of 81 lobes judged to be bronchographically free of bronchiectasis (i.e. specificity 86%). The development of thin-section HRCT changed this so that sensitivities increased to 82–97% in expert hands [233]. The recommended HRCT technique comprises scanning from apex to base with 1–2 mm cuts at 10-mm intervals, reducing to 5-mm intervals for areas of particular interest. Movement artefact at the bases may simulate bronchiectasis [245] and can be reduced by using a scan time of 1 s or

less and by using the prone position; images are reconstructed using a high-resolution algorithm [233].

HRCT criteria for diagnosing bronchiectasis have been reviewed elsewhere, the two main features being bronchial dilatation and bronchial wall thickening [233]. A bronchus is taken to be dilated if its internal diameter is greater than that of the pulmonary artery branch that accompanies it, measurements being conventionally made in the short axis of both the bronchus and the vessel. Such changes may produce a 'signet ring' appearance. However, minor degrees of apparent dilatation should be treated with caution as a few such bronchi may be found in normal subjects. A lack of normal bronchial tapering towards the lung periphery should be sought in such subjects. Bronchial wall thickening can be said to be present if the thickness of the wall is at least equal to the diameter of the adjacent pulmonary artery branch [246], although a generally accepted definition of this feature has yet to be found. The occurrence of bronchial wall thickening prior to the development of bronchial dilatation has been described in patients with hypogammaglobulinaemia [247]. Air trapping on expiration has been demonstrated as areas of increased transradiancy in patients with severe bronchiectasis, this having been found to correlate negatively with the  $FEV_1$  [248]. It has also been proposed that scanning during both inspiration and expiration may be used to distinguish between an area of cystic bronchiectasis and emphysematous blebs or bullae, the bronchiectatic cysts changing in size with the phase of respiration whereas the bullae do not [249]. Reactive mediastinal lymph node enlargement greater than 1 cm in diameter is not uncommon in bronchiectasis [250]. It is claimed that good HRCT technique can demonstrate the different morphological types of bronchiectasis: cystic bronchiectasis typically shows grouped ring shadows, representing clusters of dilated bronchi that may contain mucopus, sometimes with air–fluid levels; cylindrical bronchiectasis shows dilatation that remains relatively uniform as the bronchus extends peripherally; and varicose bronchiectasis, in which the affected bronchus assumes a beaded appearance. HRCT may sometimes indicate the likely cause of bronchiectasis in terms of morphology and distribution but its discriminatory value has been found to be lacking in individual patients [251]. HRCT has been found to have greater sensitivity than spiral CT when applied to patients in whom bronchiectasis is suspected [252].

## Treatment

The treatment of bronchiectasis may be medical or surgical. Medical treatment aims to relieve and control the symptoms, whereas surgical treatment is intended to eliminate the disease itself. A cure would obviously be preferable if a satisfactory result could be ensured and were it not to carry the inconvenience, morbidity and

small risks of mortality inherent in any major surgical procedure. Such surgical operations were devised before the advent of antibiotics, at a time when bronchiectasis was often socially distressing, physically debilitating and also frequently shortened life [253], so that the choice between a chance of cure and continuing misery was reasonably straightforward. Nowadays the situation differs, since medical treatment with antibiotics has much to offer and surgery therefore plays only a small role.

### Medical treatment

The main arms of medical treatment are (i) the control of lower respiratory tract infection/inflammation with appropriate antibiotic treatment and (ii) the removal of bronchial secretions by postural drainage. Bronchodilators may be useful when there is an obstructive impairment of ventilatory capacity.

### Antimicrobial chemotherapy

Three questions beset the clinician with regard to the use of antibiotics in patients with bronchiectasis: when should they be used, which drug should be chosen and how should they be given?

#### Decision to treat

The decision to treat is usually based on the patient's symptoms. Those whose symptoms are minimal and whose sputum is mucoid require no antimicrobial treatment. Such mild cases are likely to seek medical advice when their sputum becomes mucopurulent, often after an upper respiratory tract infection, and can be treated with a broad-spectrum antibiotic in standard dosage for 1 week or until their sputum becomes mucoid once again, in much the same way as a patient with chronic bronchitis is treated for an exacerbation (see Chapter 23). Antibiotics may render such mild cases infection-free until the next exacerbation follows a viral upper respiratory tract infection. The role of antibiotics in moderate or severe cases whose sputum is chronically mucopurulent or purulent is uncertain. It is the professional inclination of most clinicians when confronted with green or yellow sputum to take steps to clear it. The indirect evidence, cited above, that production of such sputum indicates an inflammatory process that may be causing progressive lung damage via the production of proteases and ciliary dyskinetic factors would support this action [123,126,254,255]. It is perfectly reasonable to attempt to use an antibiotic in such a situation in order to render the sputum mucoid, and indeed some work suggests that patients show improvement both subjectively and in terms of lung function when their sputum clears in this way [204,224,246]. Unfortunately, as discussed below, conventional doses of antibi-

otics either fail to render the sputum mucoid or, if they do, achieve this for only a relatively short time, depending upon the severity of the case [125,224]. The foregoing remarks apply to patients who are in a relatively 'stable' state and there is no doubt that antibiotics should be used vigorously in patients who show evidence of clinical deterioration in terms of increased sputum production or purulence, or following the onset of systemic symptoms.

### Choice of antibiotic

The choice of antibiotic is based on a knowledge of the likely pathogens present in the lower respiratory tract (see pp. 809–810) and their usual susceptibilities. Unfortunately, routine methods of sputum culture do not always provide helpful information and close liaison between the attending clinician and the microbiologist is advisable and indeed essential in difficult cases. Pending any such discussion, antimicrobial therapy is frequently prescribed on an empirical basis. The choice of antibiotic in an exacerbation of infection in a mild case of bronchiectasis, whose sputum is usually mucoid or only faintly mucopurulent, is made by applying the same principles to those discussed under the treatment of exacerbations of chronic bronchitis since the pathogens are frequently the same, notably *H. influenzae* and *Strep. pneumoniae* (see Chapter 23). For a patient who is considered to be a moderate or severe case, with larger volumes of more heavily mucopurulent sputum, then the ability of the antibiotic to penetrate sputum becomes more important [256]. Most acute respiratory infections such as pneumonia (see Chapter 13) and exacerbations of chronic bronchitis respond well to antibiotic treatment, whereas chronic suppurative lung diseases such as moderate or severe bronchiectasis (including CF) and chronic purulent bronchitis unfortunately fail to respond as well. The reasons for this poor response are not entirely clear but are likely to include the following.

- 1 Poor penetration of antimicrobial agents through the thickened, relatively avascular bronchial walls into the lumen, where organisms reside in thick secretions both free and within phagocytes. Such problems of penetration are less likely to arise in acute infections such as pneumonia, in which tissues are hyperaemic so that lung and blood levels of antibiotic are probably better matched [257].

- 2 The infecting organisms may be only moderately sensitive or even resistant to the antibiotics used. In the case of  $\beta$ -lactam antibiotics, such resistance may result from the production of  $\beta$ -lactamases, either by the principal pathogen itself or by other colonists such as anaerobic bacteria. Frank anaerobic infection, characterized by foul-smelling sputum, is now rare in the West but the presence of a smaller lower respiratory tract anaerobic microbial load could be relevant in cases that seemingly fail to respond to antimicrobial treatment.

In view of the foregoing points, when using an antibiotic in a patient whose bronchiectasis is severe enough to produce chronic mucopurulent or purulent sputum, it is necessary to consider both the penetrance of the chosen antibiotic and the most likely pathogens. As *H. influenzae* is the most common pathogen isolated in bronchiectasis and as *Strep. pneumoniae* may also play a role in some exacerbations, the use of amoxicillin (amoxycillin) is a reasonable first choice. This drug has been shown to have better sputum penetrance, dose for dose, than ampicillin, and although the drugs are otherwise very similar this quality makes the former preparation preferable in the treatment of bronchiectasis [134]. Patients who fail to respond clinically to this antibiotic at dosage schedules discussed below may respond to other broad-spectrum antimicrobial agents, when used either empirically to cover the usual pathogens or on microbiological advice. Local patterns of microbial resistance are relevant and the addition of clavulanate (e.g. as co-amoxiclav) may overcome  $\beta$ -lactamase-producing strains of *H. influenzae* and *Moraxella catarrhalis*. One of the newer macrolides (e.g. clarithromycin, azithromycin) may be substituted in the case of penicillin allergy.

There may be prior knowledge of the usual lower respiratory tract isolates in individual bronchiectatic patients dating from previous cultures and this may well influence the clinician in the initial choice of antimicrobial. Thus previous repeated isolates of *Ps. aeruginosa* may lead to the prescription of specific antipseudomonal agents. Similarly, the knowledge that *Staph. aureus* has often been isolated leads to an appropriate response. Sometimes there may be considerable difficulty in achieving sufficient antimicrobial penetration into secretions without causing toxicity at the doses required, in which case patients may require hospital admission for more intensive treatment than can be adequately managed on an outpatient basis. Allergy to penicillins places similar restrictions on management.

#### **Dose, route and duration**

The optimum dose of antibiotic, duration of treatment and route of administration have not been clearly established. In the case of oral amoxicillin, it has been shown that the minimum bactericidal concentration in the sputum of patients with bronchiectasis is only satisfactorily achieved with doses in the order of 3 g twice daily [134]. Ampicillin at the same dose produces sputum levels only one-fifth as high. However, this does not mean that all patients with bronchiectasis should receive such high dosages.

Another study showed that patients with mild bronchiectasis (mucopurulent sputum only in exacerbations) responded satisfactorily to a 2-week course of amoxicillin at standard oral dosage of 250 mg three times daily [224]. Those whose sputum was usually mucopurulent and occasionally purulent also responded to the same

schedule but the median response time was shorter, being only 9 days before the purulence returned. Very few patients with more severe bronchiectasis (sputum persistently purulent) responded to this standard regimen, although about 60% did respond to 3 g amoxicillin 12-hourly [224]. These improvements may be accompanied by a sense of increased well-being and a reduction in symptoms; furthermore, such improvement may occur despite the presence of pretreatment microbiological isolates suggesting the presence of resistant organisms [224]. Most clinicians reserve such high-dose treatment for patients who have shown some clinical deterioration rather than using it in patients whose sputum is mucopurulent or purulent but who are considered to be in a 'stable' state.

Although it has been shown that high-dose amoxicillin treatment reduces the number of microorganisms infecting the lower respiratory tract while treatment is in progress [63] and that such treatment appears to produce some benefit when administered for short periods, it has not yet been shown whether prolongation of this treatment prevents the progression of bronchiectasis in the long term. The rationale for long-term treatment in bronchiectasis has been that diminution of the inflammatory process in the lungs may prevent further destruction and fibrosis and also that it might reduce the frequency of clinical exacerbations. The published long-term trials of antibiotics in bronchiectasis are somewhat sparse. In 1957, a Medical Research Council trial using 2 g of tetracycline twice weekly for 12 months reported a reduction in days off work, days in bed and episodes of fever in the treatment group [258]. Since the results of this study some clinicians have used tetracycline or other more modern antibiotics prophylactically, either through the winter months when upper respiratory tract infections are more prevalent or throughout the year, according to their judgement of the severity of the case [259]. It has to be said that the evidence of benefit accruing from such standard dose regimens is slender. In a more recent trial, patients with bronchiectasis received high-dose oral treatment (amoxicillin 3 g twice daily) on a placebo-controlled basis for a period of 8 months. There was no significant difference in the frequency of exacerbations but severity was judged to be diminished and less sputum was produced between exacerbations. Patients receiving active treatment also spent less time in bed and off work than those treated with long-term placebo, in similar fashion to the old Medical Research Council trial [260].

Long-term treatment with antibiotics at doses that may achieve suboptimal sputum levels also carries the potential risk of selecting resistant strains of the primary pathogen or of promoting the overgrowth of secondary pathogens, such as *Ps. aeruginosa* or *Klebsiella* spp. [261]. As with all long-term medication, the potential for adverse effects also has to be weighed against the likelihood of

benefit. High-dose amoxicillin given long term seems to be remarkably well tolerated by some but not by others, the principal adverse effects being rashes and diarrhoea [257,262]. It is less expensive than was previously the case if non-proprietary capsules rather than sachets are used but it is still not clear whether the cost is offset by the benefits. Any  $\beta$ -lactamase-producing organisms may sometimes be dealt with by combining 2.75 g amoxicillin with one co-amoxiclav 375-mg tablet. Patients whose exacerbations fail to respond to oral medication or whose condition is considered more serious from the outset are often treated with parenteral antibiotics *ab initio*.

'Pulses' of regular intravenous antibiotics, for example for 2 weeks at 3-month intervals irrespective of symptom state, have been used by some centres in the subgroup of patients with bronchiectasis caused by CF [263], although controlled data on the unequivocal benefit of such an approach are presently lacking. Such regularly repeated intravenous antimicrobial therapy eventually produces difficulties with venous access, in which case a totally implantable drug delivery system may be an advantage [264–266] (see Fig. 28.8).

Antibiotics are sometimes used in nebulized form (Chapter 9, p. 216) to treat lower respiratory tract infection in patients with bronchiectasis [224,267]. This form of treatment is most commonly reserved for *Ps. aeruginosa* and, while sometimes used in conjunction with parenteral antibiotics in acute exacerbations, is likely to be more effective when given in the longer term between exacerbations by reducing the pseudomonal colonial population and thereby also reducing airway inflammation. The polymyxin antibiotic colistin (1–2 megaunits twice daily after postural drainage) is commonly used in this regard in adults with CF [268]. Tobramycin may be used as an alternative [269].

It follows that antibiotics may be used either intermittently to treat symptomatic exacerbations of infection or preventively in more severe cases between exacerbations using long-term oral therapy, intermittent intravenous 'pulsed' therapy or long-term nebulized therapy singly or in combination. The great majority of patients are dealt with by treatment of symptomatic exacerbations with courses of oral antibiotic, the magnitude of the dose and the duration of the course being varied according to the perceived severity of the disease. A significant minority have an inadequate symptomatic response with continued functional deterioration, in which case one or other of the alternative methods may have to be tried.

### Postural drainage

Physiotherapy, including postural drainage of chest secretions, has been regarded for many years as a mainstay in the treatment of bronchiectasis. Fluoroscopic studies in patients with bronchiectasis have demonstrated that

instead of resulting in expectoration of sputum, cough may cause complete collapse of the more proximal part of an affected bronchus, possibly due to the destruction of supporting cartilage, so that more distally situated secretions tend to become trapped in the lung periphery. Indeed fiberoptic bronchoscopists know to their annoyance that coughing causes even healthy segmental bronchi to collapse temporarily. This effect of coughing is of no consequence in ordinary circumstances as the mucociliary escalator wafts secretions up to the more rigid proximal airways that can maintain their patency despite a cough. However, in bronchiectasis the usual sputum clearance mechanisms are disrupted by (i) swamping of the normal blanket of mucus via excessive secretion, (ii) the replacement of ciliated epithelium with squamous cells so that the mucociliary escalator cannot operate for the area subtended by this denuded mucosa and (iii) the elaboration of various factors that produce ciliary dyskinesia, as previously outlined. The sum effect of this is that cough alone is of limited usefulness in patients with bronchiectasis who produce excessive tracheobronchial secretions [270]. This is particularly true when, as is usual, the more dependent parts of the lungs are the areas most affected, since bronchial secretions do not readily drain from these zones and their accumulation produces a 'sump' or 'septic tank', which acts not only as a constant source of damaging inflammatory substances but also as the force behind acute exacerbations of infection.

When sufficient bronchial secretions are produced, this sump requires drainage that is best assisted by the force of gravity using so-called postural drainage, often known to patients as 'tipping'. Postural drainage has been shown in the short term to increase rates of mucociliary clearance [271,272] and to increase the expectoration of sputum, particularly in patients whose secretions are copious. It has also been found to improve airway function in the short term, although such experience is not universal [273,274].

The technique of postural drainage is designed to assist the removal of bronchial secretions from the more peripherally affected parts of lung towards the more rigid bronchi near the hilum, which once reached can be emptied by coughing. A knowledge of the affected lobes is necessary to achieve optimal drainage. The disposition of affected sites may be suggested by physical examination or by plain radiographs but is only accurately demonstrated by bronchography or nowadays almost invariably by HRCT.

The basal bronchi may be emptied in someone of moderate strength and agility by the technique of leaning forwards over the edge of a low bed using the arms as a support against the floor. Older patients may have to manage by using cushions, a folding frame, plastic-covered foam wedge, 'bean bag' or by arranging for the foot of the bed to be elevated. Drainage of the middle lobe or lingular bronchi is achieved if the patient lies supine with the foot of the bed elevated and the affected side



lifted off the bed by pillows. Once correctly positioned, the patient is instructed to take deep breaths in order to aid drainage from the peripheries. After 10–15 min, the patient should cough in order to clear the larger air passages. Sometimes the patient finds that spontaneous coughing occurs once an upright posture is regained and that most of the sputum is cleared in this way.

These procedures should be practised under the supervision of a chest physiotherapist, who should have been told which areas of the lung are thought to be bronchiectatic and require drainage. Chest percussion may be used as an adjunct to tipping. However, the evidence that this so-called 'ketchup bottle method' is effective in bronchiectasis is insubstantial [272,275,276]. It is helpful if the patient's spouse or other relative attends one or two physiotherapy sessions, in the hope that this will reduce embarrassment on the part of the patient and improve compliance, which is often poor despite encouragement [277,278].

If possible, postural drainage should be carried out several times daily during exacerbations that are being treated in hospital. Each session should be continued until the chest is apparently 'dry'. Patients who produce about 30 mL (an eggcupful) of sputum per day or more should be encouraged to tip themselves daily on rising and on retiring as a matter of course. Resistance to this advice is often strong, and in a stable patient postural drainage once daily, increasing to twice daily in an exacerbation and certainly if an antibiotic is being taken, may have to be accepted. It is unlikely that patients with only a little sputum production benefit from postural drainage, which should probably be reserved for those who produce 30 mL daily or more [279,280]. Humidification of inspired air prior to physiotherapy may aid tracheobronchial clearance [281].

It is now usual to combine traditional postural drainage with the forced expiration technique, or 'huffing', in which forced expirations without closure of the glottis are made, thereby avoiding the strongest compressive phase of coughing. This is followed by a period of diaphragmatic breathing in order to avoid the worsening of wheeze that sometimes occurs following a forced expiratory manoeuvre [282,283]. The purpose of this modification is to reduce the bronchial collapse induced by coughing, which might actually tend to trap secretions peripherally. 'Huffing' should therefore propel secretions from the periphery to the more rigid central airways, after which coughing expels them.

The place, if any, of other techniques, such as high-frequency chest wall compression [284] and high-frequency mouth oscillation [285], have yet to be determined. Although no study has been carried out to demonstrate objectively that physiotherapy has an effect on morbidity or the long-term outcome in bronchiectasis, there is usually short-term benefit to the patient [273] and

postural drainage remains central to the treatment of this group of patients.

### Other medical treatment

The potential benefit of bronchodilators has already been referred to and when tests of ventilatory function show evidence of airflow limitation, as is often the case, it is common practice to prescribe an inhaled  $\beta$  sympathomimetic to be taken by metered dose inhaler, especially when there is evidence of a significant improvement of  $FEV_1$  [66,203]. Airways obstruction is predictably irreversible in some patients and indeed a paradoxical effect has been reported in children with CF [286]. Increased sputum yield and increased clearance of secretions, as measured by radioaerosol marker, has been demonstrated in a group of patients with 'stable bronchiectasis' when they received a nebulized bronchodilator before chest physiotherapy [287]. There were also small but significant improvements in lung function indices that were not seen following nebulized saline [287].

A trial of corticosteroids, such as prednisolone 30–40 mg daily for 10 days, may be attempted when there is a failure to obtain an adequate response to bronchodilators in patients with significant airflow limitation, provided that the patient is in a stable phase, so that an objective assessment of response may be made. Isolated reports of benefit are recorded in the literature [288], for example in some cases of bronchiectasis occurring in association with inflammatory bowel disease [141,143], but if objective improvement is not obtained then there is no point persisting with this potentially harmful line of treatment and, generally, long-term adverse effects preclude their use. However, oral corticosteroids are indicated in the treatment of the eosinophilic lung infiltrates associated with ABPA (see Chapter 21) in order to suppress inflammation that may lead to further bronchial damage; indeed long-term suppressive therapy with a maintenance dose of corticosteroid may well be indicated in this condition.

It has been postulated that high-dose inhaled corticosteroids may reduce the inflammatory response in bronchiectasis; 750  $\mu$ g beclometasone (beclomethasone) dipropionate every 12 h was shown to reduce sputum production in a group of 20 patients with bronchiectasis, with diminished coughing and small improvements in indices of ventilatory function [289].

It is not generally accepted that mucolytics have a role in the management of bronchiectasis, other than the case of recombinant human DNase (rhDNase or dornase alfa) in certain categories of patient with CF (see Chapter 30), since much of the viscoelasticity of sputum in this condition has been shown to be due to DNA released from neutrophils and bacteria. Short-term rhDNase has not been shown to be of benefit in adults with bronchiectasis not caused by CF [290]. *N*-Acetylcysteine is a mucolytic that

reduces sputum viscosity by cleaving glycoproteins. Its prolonged administration via the nebulized route causes airway irritation and inflammation and it may also cause bronchoconstriction. Although claimed to be useful in some patients with bronchiectasis, orally available preparations are generally regarded as of unproven benefit. The nebulized form has been supplanted by rhDNAse in CF.

Rare cases of bronchiectasis that occur in association with immunodeficiency syndromes (see Chapter 4) are subject to recurrent lower respiratory tract infection and may be treated with normal human immunoglobulin obtained from the pooled plasma of healthy donors. Such treatment may make a substantial impact on the clinical well-being of such patients with panhypogammaglobulinaemia or selective immunoglobulin deficiencies and impedes the progression of lung damage. It may be given intravenously at a dose of at least 200 mg/kg at 2-weekly intervals or 400 mg/kg at 4-weekly intervals, according to clinical assessment. Mild anaphylactoid reactions may occur initially and can be prevented by giving intravenous hydrocortisone before the first three infusions and running them at a slower rate of 1 mg/min.

Gastro-oesophageal reflux sometimes exacerbates lower respiratory tract symptoms and should be treated medically if present.

The long-term outcome of domiciliary nasal intermittent positive pressure ventilation in a small group of patients with hypercapnic ventilatory failure due to end-stage bronchiectasis has been found to be poor [291].

### Surgical treatment

Surgical treatment plays only a small role in the present-day management of bronchiectasis in Western countries, having had its greatest popularity in the 1950s and early 1960s at a time when the disease was still highly prevalent and when thoracic surgical procedures had become relatively safe. At the same time, medical treatment was unable to control symptoms adequately in many patients. As the results of antimicrobial treatment improved during this period, the place of surgery began to be questioned [292–295] and the pendulum has since swung well in the direction of management by medical means. Unfortunately, this has led to the widespread belief that surgery has no role in the treatment of bronchiectasis, which is erroneous. Elective surgical treatment should not be considered ordinarily unless:

- 1 the diagnosis has been confirmed radiographically (technically adequate HRCT has replaced bilateral bronchography in virtually all centres);
- 2 the disease is sufficiently localized to one lung or to part of one lung to enable curative resection;
- 3 the residual lung is judged to be sufficiently healthy in terms of measured lung function;

4 the patient is significantly disabled by persistent sputum production, recurrent infective exacerbations or haemoptyses despite all reasonable medical measures having been taken over a period of at least 12 months;

5 there is no persisting systemic causal factor likely to result in the development of new disease in previously unaffected lung.

It is the common experience in countries with developed and evenly spread health services that cases fulfilling these requirements are rare. Thus, on the one hand, most patients with sufficient disability as a result of bronchiectasis have disease that is too widespread to be amenable to surgery and, on the other, those patients with localized disease may have symptoms that are too minor to justify surgery with its attendant risks even though these may be small.

Published surgical results are frequently difficult to evaluate as patterns of referral and operative policies differ from one centre to another and cases have usually been collected over many years, during which period treatment policies inevitably change; furthermore, prospective trials comparing operative and non-operative treatment for patients with disease of similar extent are non-existent.

The largest surgical series is that of Le Roux and colleagues [7], which is based on a South African experience of 2776 bronchographically confirmed cases; 449 (16%) of these were children aged under 10 years, of whom 247 (55%) underwent surgery; 2327 patients were aged over 10 years and of these one-third (756) underwent resection; 85% of those operated on were said to have been 'satisfied with the symptomatic relief' provided by pulmonary resection. The overall resection rate after initial assessment was 36%, being 55% for those aged under 10 years and 33% for those over 10. The operative mortality was 1%. Postoperative empyema occurred in 1.5%. Overall, 64% were considered unsuitable for surgery, the usual reasons being extent of disease or 'poor respiratory reserve'. Another series of 125 patients operated on from 1952 to 1962 was reported to show complete absence of symptoms in 55% of unilateral cases. A further 42% were said to be physically fully active but with occasional cough or clear sputum. Most patients were aged 10–40 years and there was one operative death [296]. In the modern antibiotic era, a more recently reported series of 134 patients aged 4–89 years (mean 48 years) treated surgically for bronchiectasis at the Mayo Clinic achieved complete cure in 59% for an operative mortality rate of 2.2% [297]. The usual indication for surgery in this group was 'failure of medical treatment' but some of them had been free of chronic symptoms and were operated on for haemoptysis, lung abscess or 'unresolved pneumonia'. Unsurprisingly the results were better when complete resection was achieved [297].

From the surgical viewpoint, patients whose symptoms

can be controlled medically but which recur when treatment is stopped are preferred for reasons of lower risk, as they can be well prepared preoperatively [7]. Pneumonectomy has been satisfactorily carried out provided that the remaining lung is normal, although it appears to be a higher-risk procedure when the lung damage is a consequence of remote tuberculous infection [298]. When less than the whole lung is removed, sufficient normal lung should be left to enable its expansion to fill the available hemithoracic space. This may be best achieved when the bronchiectatic lung removed is shrunk, fibrotic and functionless from childhood so that the remaining lung has undergone compensatory growth to fill the hemithorax. The question of bilateral surgical resection in bronchiectasis is controversial. Some series report that the degree of improvement after the first operation on the worst affected lung is often such that further surgery was not proceeded with even though originally envisaged [7,299]. Others have reported complete relief from symptoms in 34% of patients with bilateral resections and that a further 53% were left with minimal symptoms [296]. The optimal age for surgery is undetermined. It has been shown that minor bronchographic changes in very early childhood may progress to undoubted bronchiectasis in one-quarter of cases and that resection should be postponed until patients are aged 6–12 years by which time the full extent of the disease has declared itself [191].

A retrospective study compared 24 patients who underwent surgical treatment with 16 patients of similar age and disease extent who were also considered to have been surgical candidates but who were treated medically because of either non-referral or patient preference; 46% of those treated surgically became asymptomatic compared with 12% of the medically treated group. The authors concluded that medical treatment is unwarranted in disabling disease if the patient is fit for surgery [300]. This view is supported by others who followed 87 children considered to be candidates for surgery but who were treated medically [191]; over 90% of these patients continued to experience symptoms.

From the foregoing it can be seen that surgical treatment in well-selected cases of bronchiectasis produces excellent results and that it offers a chance of cure. Localized bronchiectasis subtended by a bronchial stenosis that produces symptoms such as recurrent cough, fever and pleuritic pain appears to be the type most amenable to successful resection. Few would disagree that distressing localized disease that is uncontrolled by medical means should, in an otherwise fit patient, be submitted for surgical consideration. However, with the decline of whooping cough, measles and tuberculosis in the more developed countries, the opportunities for such curative treatment have become increasingly few and far between.

Young adults with severe bilateral end-stage bronchiectasis may be amenable to double lung or heart–lung trans-

plantation. This is most likely to be an option in carefully selected patients with CF (see Chapters 30 & 59) in whom actuarial survival at 1 year and 3 years after transplant of 78% and 65% has been reported [301,302]. Other patients with bronchiectasis are much less commonly considered for transplantation [303,304].

Occasionally surgical resection has to be carried out for moderate or severe haemoptysis that may be recurrent, arising in an otherwise fit patient with a relatively localized area of bronchiectasis. In such previously undiagnosed cases, bronchoscopy may be helpful by establishing the anatomical site of the bleeding.

## Prognosis

Numerous personal series of patients with bronchiectasis have been published over the years and the outcome of the disease differs confusingly from one set of results to the next (Fig. 28.11). This is unsurprising since patterns of referral to individual centres and local policies regarding selection for a given method of treatment are highly variable. These difficulties are compounded by the facts that (i) bronchiectasis is a morbid anatomical end-result with many different pathogenic factors, (ii) the natural history of the disease may span decades, during which attitudes towards treatment have gradually changed following the availability of effective antimicrobial treatment for suppurative lower respiratory tract disease and (iii) the prevalence of the disease has declined greatly in the West, so that countries that possess the facilities to conduct controlled trials (notable by their absence in the literature) no longer have sufficient numbers of patients on which to carry them out.

Notwithstanding these difficulties, a number of general observations can be made and conclusions drawn from earlier published work.



Fig. 28.11 Diffuse changes of bronchiectasis in a 22-year-old man with cystic fibrosis.

1 Poor prognosis is usually a function of the extent of disease and it is in extensive cases that a relentless deterioration to a fatal outcome, sometimes in association with cor pulmonale, may be seen [5]. The mortality rate in a series of 116 patients comprising both surgical and medical cases was 19% over an average follow-up period of 14 years, with a mean age at death of 53 years [76]. However, extensive disease was not incompatible with long life even well before the advent of antibiotics, Laënnec recording the case of an 82-year-old *maitresse de piano* whom he saw shortly before her death. She had steadily followed her occupation despite the presence of a persistent cough since the age of 16 and at postmortem examination was found to have gross bronchiectasis involving the whole of the right lung and the left upper lobe [1]. However, before the introduction of antibiotics others have cited mortality rates of 30–50% over a 10-year period, the selection of severe cases no doubt contributing to this gloomy outcome [253,305].

2 There was a sharp fall in the incidence of cases of bronchiectasis attending children's hospitals between 1950 and 1960, at the time broad-spectrum antibiotics were introduced [5]. Present-day treatment with antibiotics must have affected the short-term outcome and may well also have affected the long-term prognosis of bronchiectasis [5].

3 In a 20-year follow-up study of patients from childhood, when bronchiectasis was diagnosed, to adulthood (mean age 28 years), Field [5] found that both surgically and medically treated groups tended to improve symptomatically in the second decade, remaining static in the third and fourth. It has been known for over 50 years that spontaneous improvement may occur in some cases of bronchiectasis, a number of whom become 'dry' or symptom-free [3,306–308]. A series of 116 patients with proven bronchiectasis showed that decline in FEV<sub>1</sub> was no greater than expected in 80% of patients, and that in a further 15% it was of the order found in cigarette smokers with mild airways obstruction [76].

4 Whereas symptoms may improve with time in some patients, in others the disease may extend radiographically, evidence of new disease being found in 19% of 79 patients in one bronchographically evaluated series [192]. In a bronchographic series of 195 Alaskan children, Wilson and Decker [191] distinguished between (i) progression of disease from early ill-defined changes to full-blown bronchiectasis, this being common in early childhood and occurring in 26% of their series, and (ii) extension of disease to previously healthy and uninvolved bronchi, which was rare, occurring in only 2% of cases.

5 The results of some surgical series have already been mentioned and, as might be expected, improvement is evaluated in subjective terms so that it varies with individual selection criteria, period of follow-up, etc. Three series

over the last two decades have recorded figures ranging from 50% of patients achieving 'freedom from symptoms', 59% having a 'complete cure' to 75% being 'well or much improved' [191,297,309].

6 Some causal or associated disease may affect the prognosis. Thus the outcome is inevitably much worse in CF (see Chapter 30) and asthma has also been found to have an unfavourable effect on the mortality rate [5]. Bronchiectasis occurring as a result of tuberculosis is paradoxically associated with a better outcome [5], possibly because of the predominantly upper lobe involvement, secretions draining better from these zones.

Life expectancy for *most* patients is good, although there is a tendency towards gradual progression of the extent and severity of disease with increasing symptomatology.

## Complications

### Infective exacerbations

Infective exacerbations occurring in patients with bronchiectasis are marked by both increased volume and purulence of sputum as described above. They may follow upper respiratory tract infections in much the same way as exacerbations of chronic bronchitis. Occasional progression to pneumonia occurs and this may be indicated by patchy infiltrates on the chest radiograph, situated in the region of affected bronchi. Suppurative pneumonia and lung abscess are both uncommon but well-recognized complications, the latter occurring in either an area of pneumonia or unaffected lung, presumably as a result of endobronchial dissemination of infection. Pleuritic pain may be associated with any of the foregoing infections or may occur in apparently isolated fashion as dry pleurisy, sometimes recurring at a given site. Other pleural complications are unusual and include pleural effusion, empyema and pyopneumothorax.

Extensive lung fibrosis may progress to respiratory failure and cor pulmonale, this having been found at post-mortem examination in over one-third of 22 fatal cases of a series of 116 patients [76].

### Haemoptysis

Haemoptysis occurs commonly in bronchiectasis, usually in association with lower respiratory tract infection but occasionally as an isolated event [235] and as the declaring symptom. Such episodes are usually small, although major (>200 mL per 24 h) or rarely massive (>1000 mL per 24 h) haemoptyses may occur [299], this being an indication for prompt admission to either a thoracic surgical unit or to a facility with access to an interventional radiography unit with expertise in bronchial artery embolization techniques. Such patients are at risk of asphyxiation and should be placed in a head-down lateral decubitus posi-

tion with the bleeding lung dependent (if this side is known) in order to protect the other lung. Rigid bronchoscopy should be carried out by a thoracic surgeon as soon as possible if bleeding continues, in order that blood may be removed and to attempt localization and tamponade of the likely bleeding site. Emergency thoracotomy and resective surgery may need to be undertaken when bleeding is brisk and continuous. Centres with appropriate radiological expertise may be able to carry out bronchial arteriography to localize a bleeding point, which may then be embolized [310]. Repeated moderate haemoptyses may also be an indication for elective surgical excision of the source of bleeding, unless a bronchial feeding vessel can be localized and embolized [311]. A retrospective study of major or massive haemoptysis due to various causes, conducted before the development of embolization techniques, found that only 4 of 59 such patients underwent surgery and that no patient with bronchiectasis who was managed conservatively had a fatal outcome [195].

### Sinusitis

Chronic paranasal sinusitis occurs in a high percentage of patients with bronchiectasis and is very common in severe cases. It has never been entirely clear whether the sinusitis occurs as a precursor or as a sequel to bronchiectasis, although the latter is more probable. Lindskog and Hubbell [185] found sinusitis in 12% of 215 patients with bronchiectasis; 27% of those whose symptoms had been present for less than 10 years had sinusitis compared with 45% of those whose symptoms exceeded this period. This finding suggested that sinusitis was a consequence of bronchiectasis rather than a cause; nevertheless once chronic infection is established in the upper respiratory tract, it may act as a feeder so that it tends, like a trickling down-pipe, to perpetuate infection in the septic tank of bronchiectatic pulmonary infection. The management of sinusitis is discussed in Chapter 12. Radical measures to clear sinusitis are probably not worth attempting unless the bronchiectasis has been controlled either medically or surgically. Cases in whom bronchiectasis has been treated by surgical excision and in whom sinusitis persists should

be considered for endoscopic surgical treatment (antrostomy) of their sinus infection if it fails to respond to adequate medical measures. These measures include a dual approach, in which an attempt is made to suppress paranasal mucosal inflammation with an aqueous solution of topical steroid solution, applying it in a head-down and forward position in order to allow better distribution. This is intended to allow secretions to drain through hitherto blocked ostia and may be combined with a prolonged course of an appropriate broad-spectrum antibiotic if the secretions are thought to be infected [312,313].

### Other complications

Brain abscess used to be a feared complication of bronchiectasis in the era before antibiotics, occurring in 12% of 193 fatal cases of bronchiectasis in three old series [188,314,315]. It may complicate limited bronchiectasis but is nowadays rare [316]. The absence of abscess formation elsewhere suggests that infection may reach the brain via the vertebral plexus of veins or possibly from paranasal sinus infection.

Amyloidosis [317,318] is now a very rare complication of bronchiectasis. Fibrils of amyloid A protein may be deposited in any tissue in the body. If this increases sufficiently in quantity, it may disrupt normal cellular structures, producing functional disturbances. It most commonly presents with proteinuria as a result of renal glomerular disruption. Hepatosplenomegaly and cardiac involvement may also occur. The diagnosis can be confirmed by histological examination of tissue, rectal mucosal biopsy often being used for convenience.

Disseminated aspergillosis has been described as a rare complication of bronchiectasis [319].

Systemic hypersensitivity vasculitis has been reported in association with bronchiectasis infected by *Ps. aeruginosa* [320].

There have been occasional cases of lung cancer reportedly developing in an area of scarred bronchiectatic lung [321].

Operative complications include haemorrhage, atelectasis, pneumonia, empyema, bronchopleural fistula and pneumothorax [185,192,193].

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# BRONCHIOLAR DISEASE

ANTHONY SEATON

The bronchioles have been regarded aptly as a silent part of the lung, unassociated with well-recognized diseases, invisible on radiography and the function of which is difficult to measure physiologically. Older readers may recall the interest engendered in the 1960s when it was suggested by Hogg and his Montreal colleagues [1] that the bronchioles were the site of the lesion that leads to chronic airflow obstruction in smokers, and the subsequent search for a simple test of small airways function that could be used for screening purposes. Paediatricians also have long been aware of the infective bronchiolitis syndrome in infants, most usually associated with respiratory syncytial virus. More recently, however, it has become apparent that there are a number of relatively unusual but important bronchiolitic syndromes in adults apart from that associated with smoking.

The bronchioles are airways without cartilage, lined by bronchial epithelium and leading into air sacs. They comprise three to four orders of conducting or membranous bronchioles, the terminal ones in turn bifurcating into the first of two to three orders of respiratory bronchioles. These last give rise directly to some alveoli before ending in air sacs. There are approximately 25 000 terminal bronchioles. Therefore it is not unreasonable to suppose that they may be affected not only directly but also indirectly, either by disease arising primarily in alveoli or by extension of disease occurring in the cartilagenous airways. The former situation is recognized for example in extrinsic allergic alveolitis, which were it not so difficult to pronounce might more accurately be called allergic bronchioloalveolitis; the latter situation is found in cigarette-induced lung disease.

Three factors have contributed to an increased recognition of the importance of bronchiolar disease. The first was the work on the physiology of small airways as part of a search for a means of early detection of those who would become disabled by airflow obstruction [2]. The second was the recognition of a wide spectrum of pulmonary syndromes that caused breathlessness but which did not fit easily into traditional classifications of lung disease [3,4],

and the third was the increasing availability of relatively safe and more acceptable methods of lung biopsy.

## Physiological considerations

Because there are so many bronchioles, each with a diameter of about 1 mm, it would clearly require a considerable number to be obstructed before this would have a result comparable to the effect that obstruction of the larger-diameter major conducting airways has on crude overall measurements of airflow obstruction, such as forced expiratory volume in 1 s (FEV<sub>1</sub>). Thus substantial obliteration may occur before symptoms and evidence of airflow limitation become apparent. However, other functional impairment may be detected earlier. For example, air may be trapped distal to partly occluded airways leading to a rise in residual volume and closing volume. Similarly, the presence of some narrowed small airways may produce different time constants in different parts of the lung and this may cause reductions in dynamic compliance when measured at increasing respiratory rates. These tests have provided useful information but have, perhaps undeservedly in the case of closing volume, fallen into disuse. Flow rates measured at low lung volumes may also indicate small airway obstruction, although this test proves too variable in practice to be of diagnostic value. Diffusing capacity for carbon monoxide may also be reduced, either if alveoli are involved in the pathological process or if access of the gas to the alveoli is reduced in the 10 s available during the single-breath test.

It should be apparent from this discussion that there is no one test or even combination of tests that provides diagnostic information in patients with bronchiolar disease. The patterns of abnormality described in the literature are quite variable, and need to be considered with other evidence in coming to a diagnosis.

## Syndromes of bronchiolitis

There is no generally agreed clinical classification of

bronchiolar diseases, and many of the described syndromes are relatively unfamiliar to chest physicians. Review of the literature suggests that the 'splitters' have had a field-day, many syndromes being described on the basis of a search through pathological and clinical archives in order to describe a few cases with apparently similar features under a new name. Sometimes the same condition appears at different dates described by different names. It is important for the clinician to remember that there are in fact relatively few pathological manifestations of bronchiolar disease and that these represent inflammatory reactions to a wide range of possible causes. Clinical classifications have tended to depend on cause, known or unknown, while pathological classifications have relied on distinctive histological features. A relatively simple clinical classification suggested by the author is given in Table 29.1.

The obliterative type of bronchiolitis may be separated pathologically into two subtypes: one in which there are intrabronchiolar plugs of organizing connective tissue (proliferative bronchiolitis obliterans) and one in which the bronchiolar walls are inflamed and fibrosed with marked narrowing or complete obliteration of the lumen (constrictive bronchiolitis). The former is often accompanied by extension of the proliferative changes into alveolar ducts and alveoli, a lesion referred to as bronchiolitis obliterans with organizing pneumonia (BOOP) or, confusingly, cryptogenic organizing pneumonia.

**Non-oblitative bronchiolitis**

**Infective bronchiolitis**

Viral infections may cause direct inflammation of the airway mucosa at any point, sometimes leading to desquamation and increased airway reactivity. In children the most common syndrome is bronchiolitis due to respiratory syncytial virus occurring before the age of 1 year

[5]. Almost all infants are infected by this virus and a proportion develop cough, wheeze, a hyperinflated chest and inspiratory crackles. The predominance of bronchiolitic symptoms in this age group is probably explained by the relatively larger contribution of the not fully developed bronchiolar airways to overall airflow resistance in such infants. Some 2–3% are sufficiently ill to require admission to hospital. While some children continue to suffer recurrent wheezy attacks afterwards, it seems likely that these represent those already predisposed to asthma and that the infection itself does not lead to this disease [6–8].

In adults it is commonplace to see patients with persistent cough after viral infections. These patients often have increased airway reactivity and respond poorly to bronchodilators and corticosteroids. It may be suspected that bronchiolitis is present in some, but histological evidence is not available. The usual course is towards slow recovery.

**Toxic bronchiolitis**

Persistent cough without airflow obstruction is a frequent sequel to inhalation of a very wide range of irritant gases or fumes. In more severe cases airflow obstruction is present and this is often sufficiently variable for the diagnosis of asthma to be made. In these cases airway hyper-reactivity is present and the syndrome is usually called reactive airways dysfunction syndrome. Some patients respond in a different manner, with fixed airflow obstruction, and in these subjects bronchiolitis obliterans is probably present (see below). It is likely that inflammation of bronchioles is a feature of all patients with persisting symptoms after irritant gas inhalation but that relatively few develop the full-blown obliterative features.

**Smokers' bronchiolitis**

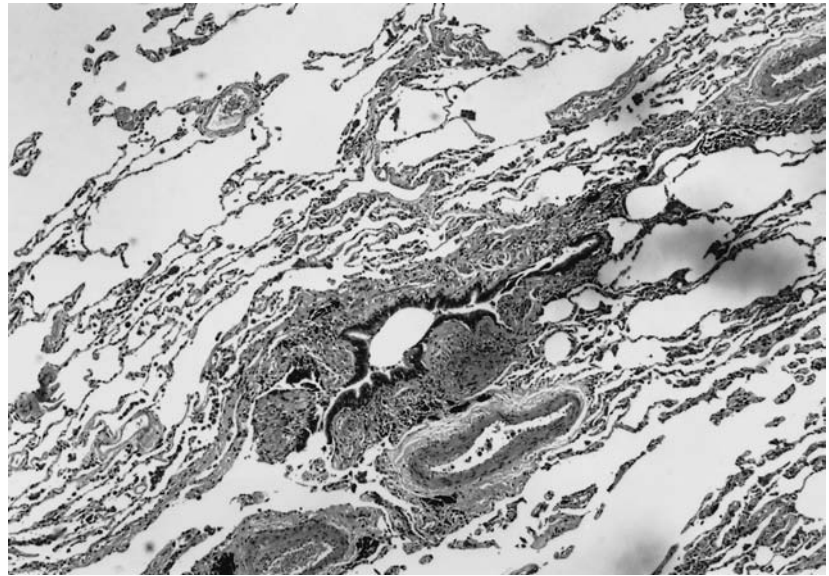
It has long been recognized that cigarette smokers develop inflammation in the bronchioles (Fig. 29.1) as well as in the major airways and alveoli [9,10]; morphometric studies have shown that smokers with airflow obstruction have increased thickness of bronchiolar walls with decreased luminal diameter [11]. At one time it was thought that this lesion might be the primary one leading to the development of airflow obstruction in a proportion of smokers and that early detection by lung function testing might allow targeted treatment. This hope has not been fulfilled, partly because the lung function tests have proved unable to predict reliably the future fall in airway conductance [12,13] and partly because small airway disease is but one aspect of the inflammatory damage wrought by cigarette smoke.

Correlation between CT findings and pathology in heavy smokers undergoing lung resection for peripheral

**Table 29.1** Aetiological classification of bronchiolar diseases.

Non-oblitative bronchiolitis
Infective
Toxic
Cigarette-induced (including respiratory bronchiolitis–interstitial lung disease)
Mineral dust bronchiolitis
Diffuse panbronchiolitis
Oblitative bronchiolitis
Idiopathic
Toxic inhalation or ingestion
Infective
Associated with connective tissue and bowel diseases
Drug-related
Transplantation-related
Carcinoid tumour-associated





**Fig. 29.1** Section from lung resected for bronchial carcinoma in a smoker showing typical peribronchiolar fibrosis (haematoxylin & eosin  $\times 100$ ).

tumours has shown that alveolitis and accumulation of pigmented macrophages in alveoli relate to areas of ground-glass attenuation and that bronchiolitis or bronchiolectasis relates to micronodules [14]. What may be an extreme variant of this pathological condition has been reported as 'respiratory bronchiolitis causing interstitial lung disease', in which heavy smokers develop cough, shortness of breath and diffuse infiltrates on their chest radiographs [15]. Lung function has been reported as showing a primarily restrictive pattern, with only minimal airflow obstruction. Pathologically, the few subjects described have shown pigmented macrophages throughout the acinus, some non-specific alveolar wall thickening and a mild chronic inflammatory cell infiltrate in bronchiolar walls and alveoli with alveolar cell hyperplasia. The condition appears to have had a relatively benign prognosis even when the patient continued smoking.

#### Mineral dust bronchiolitis

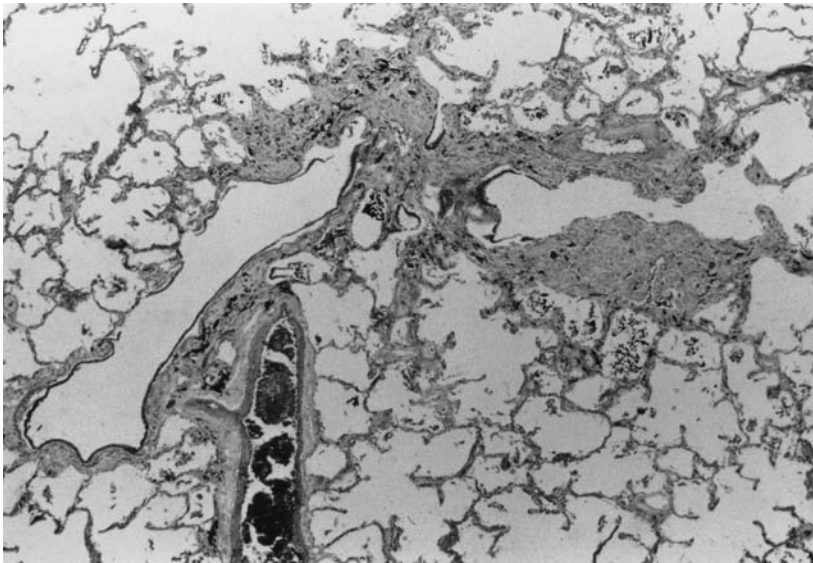
As with cigarette smoke, so also chronic inhalation of a wide variety of toxic substances is likely to cause inflammation, *inter alia*, of small airways. Pathologically, the membranous and respiratory bronchioles are the primary site of reaction to inhaled mineral dusts such as coal, quartz and asbestos [16–18] (Fig. 29.2). Physiological evidence of small airways disease has been demonstrated in coal-miners, silica-exposed workers and asbestos workers [19–21], and there has been much argument as to the significance of these lesions in terms of future development of disabling airflow obstruction. An important difficulty in assessing this has been the fact that most such workers smoke as well, while a more academic argument surrounds the attribution of the obstruction to emphysema or small airways narrowing. To the practising chest physi-

cian these matters are of little importance, although they are of relevance for the prevention of occupational disease and become extremely contentious when dust-exposed workers sue their employers for industrial injury compensation. From a preventative point of view, the evidence suggests quite strongly that mineral dust exposure contributes (with cigarette smoking) to the development of this type of physiological impairment, and account should be taken of this in setting dust standards.

#### Diffuse panbronchiolitis

Diffuse panbronchiolitis is a well-defined clinicopathological syndrome occurring not uncommonly among people of Japanese, Chinese and Korean descent, with a possible association with HLA-Bw54 [22,23]. It has been described infrequently in the West [24–26]. The condition occurs predominantly in males over the age of 30, who present with cough, wheeze and sputum production. Chronic sinus infection is a usual accompaniment. The chest radiograph shows diffuse small nodular shadows and high-resolution CT (HRCT) shows small rounded centrilobular lesions with linear shadows extending from them, thickened dilated peripheral airways and evidence of peripheral air trapping [27]. The pathological features are of a diffuse chronic inflammatory reaction in respiratory bronchioles, with lymphocytes, histiocytes and plasma cells extending to peribronchiolar tissues but not to alveoli. There is often ectasia of the terminal membranous bronchiole [22].

The natural history of the disease resembles that of cystic fibrosis, in that recurrent infection with *Haemophilus influenzae* becomes persistent and is succeeded by superinfection with *Pseudomonas aeruginosa*. While rapidly fatal cases occur, the usual course is chronic with gradually



**Fig. 29.2** Lung of rat showing early peribronchiolar fibrotic reaction in response to experimental inhalation of asbestos.

worsening cough, sputum production and increasing breathlessness, leading to death in cardiorespiratory failure. Lung function shows an obstructive pattern with overinflation, leading to reduction in vital capacity and diffusing capacity in the later stages. Untreated, the survival rates at 10 years have been reported as 12% in patients infected with *Pseudomonas* and 73% in those not so infected [28]. The cause of the disease is not known but is presumably related to a genetic impairment of lung defences to the infecting organisms which, once established, cause the pathological lesions [29].

The airflow obstruction in these patients is poorly if at all reversible, and bronchial reactivity is little increased [30]. Nevertheless, 8 weeks of treatment with oxitropium bromide has been shown to decrease airflow obstruction and reduce sputum production in some patients [31]. More importantly, Japanese workers have demonstrated that the prognosis can be substantially improved and symptoms relieved by long-term treatment with low-dose erythromycin (600mg daily), which improves the 10-year survival to better than 90% [28,32]. Other new macrolide antibiotics have also been shown to be of help. It appears that these benefits may accrue, at least in part, from other than direct antibacterial properties of the drugs as a result of interference with both the ability of neutrophils to respond to chemotaxis and the capacity of *Pseudomonas* to produce the biofilm that makes it ineradicable [33–35].

### **Obliterative bronchiolitis**

#### **Aetiological factors**

Obliterative bronchiolitis occasionally occurs without known cause, when it most usually takes the form of the

proliferative type known as BOOP. However, the syndrome does occur rather more frequently, although still rarely, as a response to known causes, the most important of which are shown in Table 29.1. The idiopathic type sometimes follows an influenza-like illness and one suspects that it may sometimes be due to an undetected viral infection [36]. Occasional cases in adults have been described following mycoplasmal or viral infections [5,37–39] and it has been recognized as a complication of human immunodeficiency virus infection [40,41]. A dramatic outbreak in Taiwan in 1996 was caused by consumption of a salad vegetable, *Sauropus androgynus*, either eaten or drunk as a juice. It caused severe impairment in most of the 115 subjects studied and death in seven [42,43]. In infants and children, whose lungs are not fully developed, the condition is usually transient, although permanent damage to bronchioles may occur [44,45]. The development of obliterative bronchiolitis after infection in these circumstances may lead to the maldevelopment of acinar structures with a small avascular and transradiant lung and expiratory air trapping, a condition known as Macleod's or the Swyer–James syndrome [46–48]. This condition is often also associated with bronchiectasis.

Obliterative bronchiolitis may occur after inhalation of a wide range of toxic gases or fumes [49–55]. The classic episode is nitrogen dioxide exposure, although the author has seen it also after acute exposure to chlorine, dimethyl disulphide, hydrochloric acid and several other accidental gassings, as well as (on two occasions) after inhalation of a fine powder of a chlorine-liberating disinfectant. It may therefore be regarded as a possible consequence of exposure to any gas, fume or fine soluble dust with the potential to injure airways either on account of its strongly acidic or alkaline pH or because of its ability to release



toxic free radicals. This latter mechanism may explain the one episode reported following inhalation of fly ash [54], which contains high concentrations of transition metals such as vanadium that are capable of releasing hydroxyl radical by a redox mechanism. It appears to be a relatively rare consequence of such exposures [55], most people recovering with simply transient symptoms or after a period of several months of bronchial hyperreactivity. The episode that leads to it usually appears to be a high-dose exposure associated with symptoms, but this is not always the case and symptoms may develop after what seems to have been a much less severe episode, sometimes unassociated with symptoms.

Bronchiolitis obliterans has been described in all connective tissue disorders, although it is a very infrequent complication in any of them. Rheumatoid disease is the one in which it is most likely to be seen, especially in women [3,56], although it has also been described in Sjögren's syndrome, scleroderma, polymyositis, lupus erythematosus, cryoglobulinaemia and various vasculitic conditions [57–61]. In some cases suspicion has been cast on drugs used to treat the condition, especially penicillamine and gold [58,62]. However, there is no doubt that bronchiolitis can occur in the absence of such treatment. Other drugs that have been associated rarely with development of the syndrome include several cytotoxics, amiodarone, acebutolol, sulfasalazine (sulphasalazine) and overdose of L-tryptophan [63–66]. A spectrum of pulmonary diseases may also be associated with inflammatory bowel disorders, both ulcerative colitis and Crohn's disease, including suppurative bronchitis, bronchiectasis and obliterative bronchiolitis [67] (see Chapter 53).

Bronchiolitis obliterans is now well described in recipients of marrow or lung transplants. In recipients of bone marrow, usually allogeneic but sometimes autologous transplants may lead to graft-versus-host disease in which some 10% develop bronchiolitis [68,69]. In heart–lung transplantation, some 10–70% of recipients develop obliterative bronchiolitis, and a similar risk applies also in single or double lung transplantation [70–72]. The risk relates more to the development of a prolonged rejection reaction, possibly made worse by associated infection, than to the type of transplant [73–75].

In patients with peripheral lung carcinoid tumours, obliterative bronchiolitis has been found in a surprisingly high proportion, 8 of 25 in one study, suggesting that the fibrotic reaction in the small airways was a direct consequence of the tumour [76]. A similar association has been described in one patient with the very rare condition of multiple carcinoid tumourlets [77].

As a footnote to the aetiology, clinicians need to beware of too readily accepting a pathology report of bronchiolitis obliterans as meaning that there is generalized lung disease, since local inflammation and obliteration of small

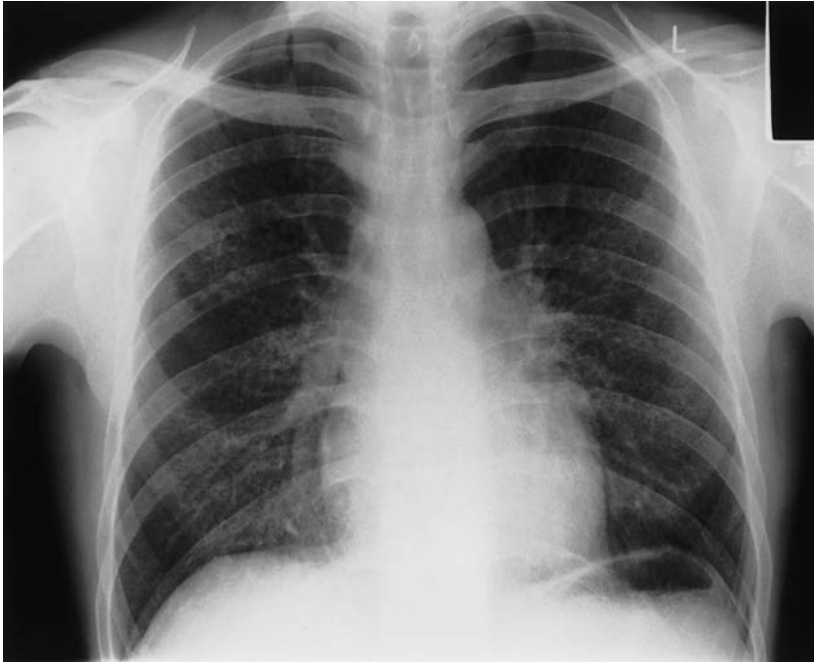
airways as a consequence of, for example, infection or aspiration is not uncommonly seen in biopsy specimens. As always, biopsy evidence has to be interpreted in the light of the entire clinical picture. Bronchiolitis obliterans is essentially a description of a pathological appearance that has many causes.

### Presenting features

The patient usually presents with dry cough and increasing breathlessness over several weeks or months, and the diagnosis is most easily made in those cases where a predisposing condition such as collagen disease, inflammatory bowel disease or transplantation is present [78]. In idiopathic cases, the condition is most likely after the age of 40. There may be a history of a recent viral type of illness. There may be evidence of a generalized illness in patients with BOOP, with fever, malaise and loss of weight [79–81]. An exposure to inhalation of a toxic substance usually occurs some days or weeks previously; indeed it is usual for any acute symptoms to have settled and for there to have been a period of apparent recovery prior to the development of cough and breathlessness, in contrast to the reactive airways dysfunction syndrome where symptoms usually follow the episode immediately. This period relates to the time taken for obliteration of the small airways to become severe enough to cause noticeable obstruction to overall airflow, as a consequence of their very large total cross-sectional diameter.

The reason bronchiolitis goes unrecognized so often is that there is no distinctive pattern of physical signs [82]. Despite clear evidence of exertional dyspnoea, there may be no signs on auscultation. On the other hand, there may be diffuse gravity-dependent inspiratory crackles, wheezes or both. In idiopathic BOOP, crackles are the most consistent sign, being present in up to 75% of patients. Digital clubbing is not a feature.

The radiographic appearances are also quite variable. It is not uncommon for the chest film to be essentially normal and this should not be regarded as evidence against the diagnosis. Diffuse nodular or ground-glass opacities are common in idiopathic BOOP (Figs 29.3 & 29.4) and a fine interstitial nodularity may be seen in toxic gas exposure. There may be evidence of overinflation. CT may be helpful in showing subtle abnormalities even when the plain film appears normal [83]. For example, in obliterative bronchiolitis without the pneumonitis a mosaic pattern of reduced attenuation on HRCT may indicate air trapping, and expiratory CT has been used to demonstrate this in localized areas [84–86]. In the BOOP syndrome it would be expected that more obvious abnormalities might be seen on CT, reflecting the interstitial component of the disease (Fig. 29.5). Even so, CT studies of histologically diagnosed BOOP have shown a bewildering range of different appearances, including



**Fig. 29.3** Chest radiograph of patient with idiopathic biopsy-proven bronchiolitis obliterans with organizing pneumonia showing diffuse nodular shadows. (Courtesy of Dr Lesley Gomersal.)



**Fig. 29.4** High resolution CT of patient in Fig. 29.3 showing diffuse small centriacinar nodularity. (Courtesy of Dr Lesley Gomersal.)



**Fig. 29.5** High resolution CT of patient with biopsy-proven bronchiolitis obliterans with organizing pneumonia showing patchy irregular consolidation. (Courtesy of Dr Lesley Gomersal.)

consolidation, focal nodular lesions and ground-glass attenuation [87]. As with the physical signs, radiography and CT do not provide a distinctive pattern on which the diagnosis can confidently be made but usually contribute sufficiently to the whole picture to lead to the correct diagnosis.

Lung function tests are usually abnormal in people with symptomatic obstructive bronchiolitis, although again the

findings vary. Impaired exercise tolerance and arterial desaturation are important indicators of severity. In the idiopathic type a restrictive pattern with impaired gas transfer is most common, whereas in those types that follow transplantation or toxic gas inhalation and in collagen diseases severe irreversible airflow obstruction is more frequent. However, either of these, or a mixed pattern, can occur in any of the aetiological types of bronchiolitis.

It can therefore be seen that no one distinctive clinical picture leads to the diagnosis of obliterative bronchiolitis, yet paradoxically the clinical diagnosis is not difficult if one considers the possibility. In the case of someone with predisposing disease, the onset of a persistent dry cough and increasing breathlessness in the absence of other obvious cause such as infection or heart failure should always arouse the suspicion of bronchiolitis. In otherwise previously well people, similar symptoms are usually first thought to be due to asthma or, if the chest film is abnormal, sarcoidosis or a pulmonary arteritis. The clinical features of these diseases differ quite markedly, although in cases of doubt it is usually necessary to test one's suspicion with a lung biopsy.

### Pathology

Two distinct histopathological appearances may contribute to obliterative bronchiolitis [88]. In one, there is constriction of many membranous bronchioles by fibrous tissue in the adventitia and submucosa, a chronic inflammatory cell infiltrate and bronchiolar ectasia distal to the constriction with mucous plugging (Fig. 29.6). The changes are often patchy, and more proximal bronchial inflammation and fibrosis may be associated. This type is called constrictive bronchiolitis obliterans and is the one most characteristically seen in collagen diseases, inflammatory bowel disease and after transplantation, although it may occur as a consequence of all the other aetiological factors. Physiologically it is associated with an irreversible obstructive syndrome. The second type, usually known as proliferative bronchiolitis obliterans, is characterized by organizing connective tissue forming polyps that partially or completely obstruct the lumen of the bronchioles. These polyps contain fibroblasts, foamy macrophages and lymphocytes in loose connective tissue (Fig. 29.7). This type

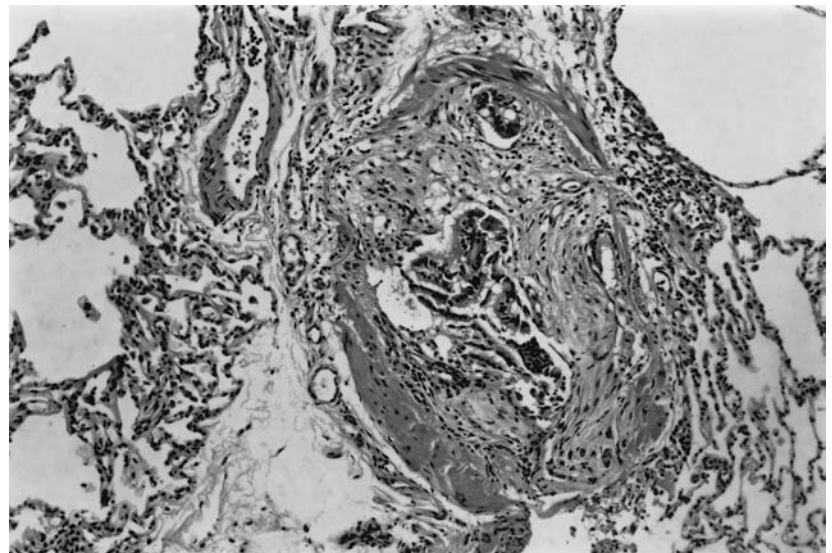
tends to be more peripheral, sometimes involving respiratory bronchioles and alveoli; in the latter case the extension of the plugs of granulation tissue into the acinus, with some chronic inflammatory cell infiltrate in alveolar walls, allows the pathological diagnosis of BOOP or cryptogenic organizing pneumonitis [4,79]. The former term is preferable, since the condition is primarily a bronchiolar disease and may not be cryptogenic. Alveolar wall fibrosis and honeycombing are not significant features of this condition, in contrast to cryptogenic fibrosing alveolitis. Idiopathic bronchiolitis obliterans is most commonly of the proliferative type, although identical pathological features may be found after viral infections, toxic fume exposure, systemic diseases and transplantation. The physiological abnormality tends towards a more restrictive pattern of lung function.

From the foregoing, it is apparent that the pathological features do not usually help in determining the aetiology of the bronchiolitis, which is established on clinical grounds. However, lung biopsy is helpful in identifying the cause of the functional disorder, in excluding other causes of peripheral lung disease and in pointing towards prognosis, since the proliferative type is far more likely to respond to treatment than the constrictive type.

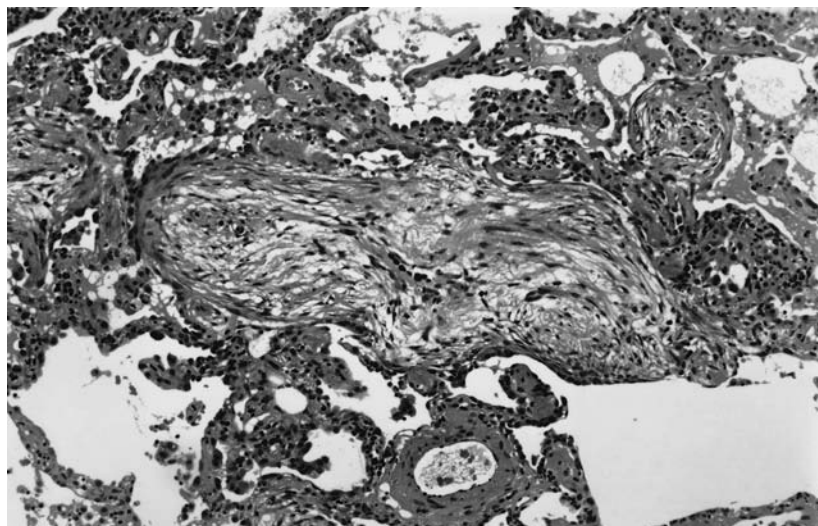
### Clinical course and management

#### *Idiopathic bronchiolitis obliterans with organizing pneumonia*

Bronchiolitis obliterans with patchy or diffuse infiltrative lesions (BOOP) appears to be the most common adult presentation of bronchiolitis obliterans, being found in 57 of 67 cases of bronchiolitis analysed in Boston, USA [4]. The patients often presented with a history of cough or an



**Fig. 29.6** Section of lung of patient with constrictive bronchiolitis obliterans after heart–lung transplantation showing chronic inflammatory cells and fibrous tissue occluding the bronchiolar lumen (haematoxylin & eosin  $\times 240$ ).



**Fig. 29.7** Section of lung in patient with proliferative type of bronchiolitis obliterans showing obliteration of a respiratory bronchiole by proliferating fibrous tissue (haematoxylin & eosin  $\times 100$ ).

influenza-like illness 4–10 weeks previously. Age at presentation was 40–60 years with an equal sex incidence. Crepitations were audible on auscultation in the majority. The chest radiograph showed a pattern of patchy, often irregular, densities with a ground-glass background appearance in 81%. Unlike patients with bronchiolitis associated with connective tissue diseases, these patients showed evidence of restrictive lung disease in 72%, with a decreased diffusing capacity in 86%. An obstructive pattern was only seen in smokers. The pathology showed plugs of granulation tissue involving bronchiolar and alveolar ducts, with extension of the organization from distal alveolar ducts into alveoli and variable degrees of interstitial infiltration by mononuclear cells, i.e. the pattern of an organizing pneumonia.

The course of the disease is usually (though not always) progressive and may occasionally be fulminant [89,90]. Nevertheless it frequently responds to therapy with corticosteroids in an initial dose of 60–80 mg daily. This dose is continued for 1–3 months, with a graduated reduction thereafter over 6–12 months to a low maintenance dose or to zero. In the Boston series 65% recovered and other authors have reported a good prognosis [91,92].

### ***Toxic gas bronchiolitis***

The characteristic feature of bronchiolitis following exposure to toxic gas or fume is a latent period between exposure and development of symptoms of a few days to several weeks. Thereafter there is progressive increase in shortness of breath over several months followed by stabilization of irreversible airflow obstruction. The condition may be, indeed usually is, preceded by acute symptoms of irritative bronchial disease and is often accompanied by persistent but slowly improving reactive airways dysfunction syndrome. Thus the clinical picture may seem complicated until one realizes that acute airway irritation may

cause several effects at all levels of the airways simultaneously. Since these patients present sporadically with an acute illness it is not surprising that controlled trials of therapy have not been reported. However, based on anecdotal clinical evidence it remains sensible to treat patients with apparently progressing symptoms early with high-dose steroids and to follow their response with lung function tests [49,93–95].

### ***Other aetiological types***

Several aetiological types have rather characteristic clinical courses, although any course may occasionally occur in any type. In those of viral aetiology, the course corresponds to the histopathological type and it seems likely that in some cases the proliferative type may heal by fibrosis and become the constrictive. High-dose steroid therapy is therefore indicated in apparently progressive cases [96]. However, some less severely affected patients show spontaneous resolution without treatment. In the collagen diseases, the constrictive type is more frequent, the course more indolent with a poor prognosis and progression less likely to be arrested by steroids [3]. In contrast, in inflammatory bowel disease steroid responsiveness is more likely. An interesting feature of this condition is the occasional occurrence of lung disease after total colectomy for ulcerative colitis. Transplant-associated bronchiolitis occurs as a consequence of repeated episodes of rejection, and may be prevented by treating patients who have suffered three such episodes by daily nebulized budesonide at a dose of 500  $\mu$ g [97].

In progressive bronchiolitis obliterans, whatever the aetiology, a fatal outcome is possible and in these circumstances there is a case for considering lung transplantation in suitable patients. Paradoxically, this technique has been used most frequently in the management of post-transplant bronchiolitis [98,99].

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# CYSTIC FIBROSIS

ANDREW P. GREENING

Cystic fibrosis (CF) is the most common fatal inherited disease in Caucasian populations of European origin. A carrier rate of about 1 in 25 and an autosomal recessive inheritance gives rise to approximately 1 in 2500 children being affected in the UK. The consequent physiological abnormality results in faulty ion transport and water movement across epithelial cells.

Despite the disease being the result of a defect in a single gene that codes for an ion channel, there are many differences in clinical expression. Abnormality of transport of chloride and sodium ions across some epithelia is an essential feature. The respiratory tract and the pancreas are the organs that bear the predominant burden of disease, with some 80% of patients having both recurrent pulmonary infections and pancreatic insufficiency. About 15% of patients have apparently normal pancreatic function but have lung disease and some 5% have gastrointestinal problems but no overt respiratory manifestation. Clinical presentation is usually at birth, with meconium ileus, or early childhood, with recurrent respiratory infections and/or failure to thrive. However, some patients with milder variants of the disorder may present later in life, when the diagnosis may be much less obvious.

## Historical review

The disease may have been recognized in folklore [1]. In old European cleansing ceremonies it was customary to lick the forehead of newborn infants. The child was feared 'bewitched' and soon to die if it tasted salty. In 1938, Dorothy Andersen in New York is credited with the first formal description of CF as a separate pancreatic pathological and clinical entity, differentiating it from coeliac disease [2]. Blackfan and May [3] reported similar findings from Boston in the same year and Blackfan and Wolbach [4] had published analogous cases in 1933 without specifically naming a 'new' disorder. In 1936, Fanconi and colleagues [5] had also identified a consistent relationship between congenital pancreatic cystic fibromatosis and bronchiectasis, which proved later to be compatible with

CF. Farber [6] introduced the term 'mucoviscidosis' in 1943 following studies which suggested that all exocrine glands had evidence of pathological changes. A high incidence of heat prostration was observed among CF patients during a New York heatwave in 1948, attracting di Sant'Agnese and colleagues [7] to study patients' sweat. They showed the sodium and chloride levels to be elevated and this formed the basis of the subsequent sweat test as the diagnostic procedure for CF; indeed it has remained the cornerstone of diagnosis to the present day. Initially this was carried out by warming the patient to produce sweating but in 1959 a test was introduced whereby sweat was induced by the iontophoresis of pilocarpine [8], which is reproducible and avoids the possible risks of heat prostration.

The autosomal recessive nature of inheritance was first suggested by Andersen and Hodges in 1946 [9] and established in the 1960s [10]. The gene was localized to the long arm of chromosome 7 in 1985 [11,12] and isolated in 1989 [13–15]. Such is the pace of current applied molecular biology that the first trial of gene therapy for CF in humans was published only 4 years later [16]. Studies of the gene product, the cystic fibrosis transmembrane conductance regulator (CFTR), have advanced the understanding of the pathogenetic processes and revealed potential new therapies. Molecular analyses of CF genotypes have taken the history of the disease full circle and helped trace its evolutionary path. Haplotype analysis of chromosomes carrying the CF mutation from different geographical regions has suggested that the most common mutation probably first occurred over 52000 years ago during the palaeolithic era [17] in a population that migrated into Europe. It has been estimated that no lethal recessive disorder could reach the high frequency that CF has in Europe just by genetic drift. Heterozygous advantage (sickle cell disease [18], cholera [19], gastroenteritis and tuberculosis [20]) or increased fertility among CF carriers [21] have therefore been postulated. Protection against gastrointestinal disorders is an empirically attractive hypothesis and supported by recent work. A thermostable



enterotoxin from *Escherichia coli* induces chloride secretion only in cells with normal CFTR, which could give a CF heterozygous person advantage for *E. coli* diarrhoea [22]. In addition, CF heterozygous mice may show resistance to cholera toxin [23].

## Genetics

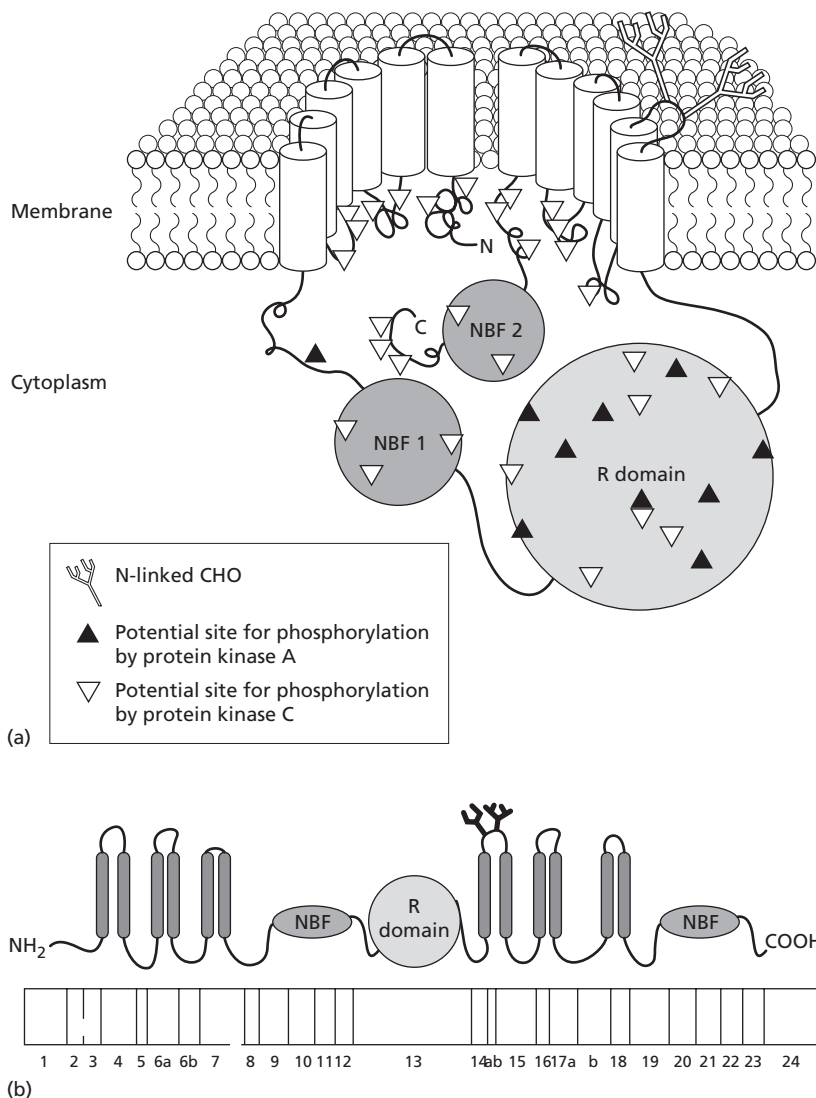
### CF gene and CFTR

The CF gene is large, comprising 27 exons [24] and encompassing approximately 250kb of genomic DNA. This encodes a mature mRNA of 6.5kb [13] that codes for a protein, CFTR, with a molecular mass of approximately 168kDa [14]. There are two hydrophobic membrane-spanning domains, two regions that bind ATP and a regulatory domain containing multiple sites for phosphorylation by protein kinases A and C [14] (Fig. 30.1). This overall structure is similar to a large family of proteins

that transports molecules into or out of cells in an ATP-dependent fashion [25]. One of these is the human multiple-drug resistance protein, which confers resistance to cancer chemotherapy by exporting drugs from cells. However, despite the similarities, CFTR does not appear to function as an ATP-dependent transporter but as a cyclic AMP-activated chloride channel [26–30]. Cross-species analyses show marked structural conservation between the human CFTR and its bovine, mouse, rat and dogshark homologues [31–34] (90% human to cow; 76% human to mouse), with 95–100% homology in some regions. These cross-species studies suggest that the function of CFTR may be similar in evolutionarily very diverse organisms.

### CFTR promoter

The sequence of the CFTR promoter region has been determined. The structure has led to the proposition that the



**Fig. 30.1** (a) Diagrammatic representation of the structure of the cystic fibrosis transmembrane conductance regulator (CFTR) showing two transmembrane regions, two domains that bind with ATP (nucleotide-binding domains) and a regulatory domain that has multiple sites for phosphorylation by protein kinases A and C. (Adapted from Riordan *et al.* [14].) (b) Schematic representation of CFTR and the corresponding exons of the gene.

CFTR gene may belong to a group of genes that have been characterized as 'housekeeping' genes that in addition have tissue-specific functions [35]. For example, like housekeeping genes the CFTR gene contains no TATA or CAAT box element. However, there are sequences that suggest it could be under transcriptional regulation. Potential AP-1 and AP-2 binding sites have been identified, as well as candidate sequences for cyclic AMP and glucocorticoid response elements [36].

### CFTR function

CFTR appears to have additional functions to those of a chloride channel in the apical membrane of epithelial cells. Endocytosis and exocytosis are defective in a CF pancreatic cell line, although this is corrected by the expression of wild-type CFTR [37]. It has also been proposed that in CF there is a defect in the acidification of the trans-Golgi network, of prelysosomes and of endosomes because of diminished chloride conductance in the membrane of these intracellular organelles [38].

In addition, there is a considerable amount of evidence that expression, and probably activity, of CFTR is capable of modulating the function of other ion channels in epithelial cells [39]. A separate chloride channel, the outward rectifying chloride channel (ORCC), has been shown to have a regulatory relationship with CFTR [40,41]. It is uncertain whether this involves direct protein-protein interactions [42], interaction through cytoskeletal elements [43] or activation of ORCC via a purinergic receptor [44] involving CFTR-mediated release of ATP from cells [45,46]. Early work had shown a consistently elevated and abnormally regulated sodium absorption in CF airway epithelia [47]. It is now recognized that these observations reflect an absence in CF cells of negative regulation of sodium channels by CFTR [48,49]. The nature of the interaction between CFTR and this epithelial sodium channel is unclear. However, the epithelial sodium channel has a two to three fold higher probability of being open in the CF cell and hence the increased sodium absorption.

### CFTR expression

CFTR RNA is expressed in epithelial tissues classically affected in CF, such as the lung, pancreas, liver and sweat glands [14] but also large intestine, testis [50,51] and kidney (Table 30.1). RNA studies indicate a low level of CFTR transcripts in respiratory epithelium and much higher levels in the pancreas and intestine [50,52] and in the airway submucosal glands [53].

### CF gene mutations and effects on CFTR

More than 600 mutations of the gene have now been rec-

**Table 30.1** Tissue and cellular localization of CFTR.

Organ localization	Cells	Cellular
Airways	Ciliated epithelium Submucous glands	Apical membrane Intracytoplasmic
Pancreas	Ductal epithelium	Apical membrane
Liver	Bile duct epithelium	Apical membrane
Sweat glands	Reabsorptive duct epithelium	Apical and basolateral membranes
Intestine	Basal cells of crypts	Apical membrane
Kidneys	Collecting tubules	Apical membrane

ognized, although the frequency of the different abnormalities is very unevenly distributed and varies between geographical regions [54–56]. The most common mutation, a deletion of three nucleotides in exon 10 resulting in the omission of a single amino acid, phenylalanine, at residue 508 (termed  $\Delta F508$ ), accounts for 68% of CF alleles worldwide, reported to the CF Genetic Analysis Consortium [54], and just over 70% in the UK and other parts of northern Europe. Only 13 mutations reported to the Consortium have a frequency of greater than 1% (Table 30.2) but these account for approximately 85% of all CF alleles. The majority of the rest occur infrequently, although again with significant geographical variation [57] and many in single families.

### Mutations that alter CFTR mRNA

About half the mutations reported to the Consortium are predicted to affect RNA processing. These can be divided into two groups: those that introduce a premature signal for the termination of translation and those that alter the mRNA but leave the reading frame intact. The former group includes changes in a single nucleotide that substitute an amino acid with a termination signal (nonsense mutation), deletion or insertion of one, two or more nucleotides that are not multiples of three (frameshift mutation), or abnormal exon splicing (splice-site mutation).

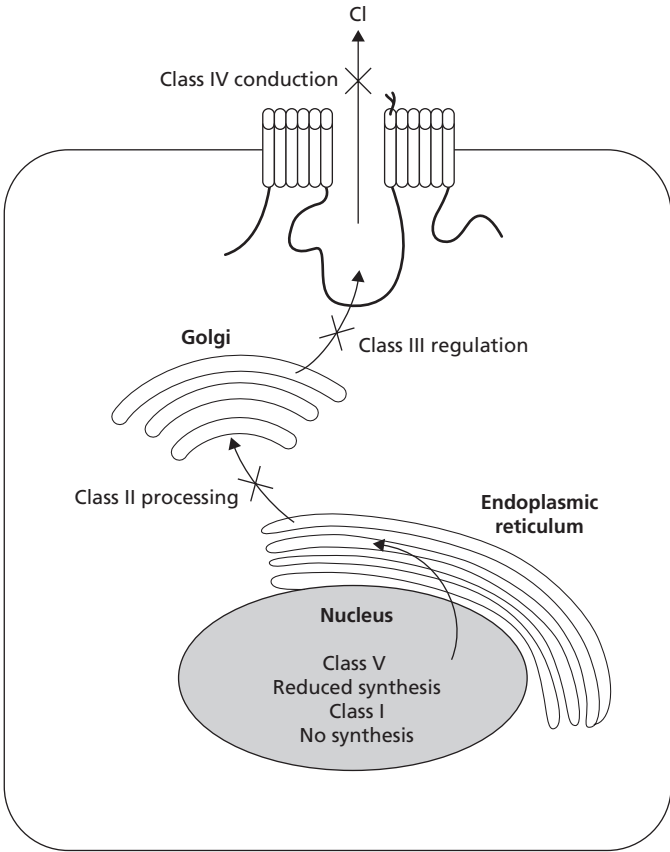
### Nonsense mutations

The most common outcome of these mutations is a severe reduction of mRNA levels from the gene containing the alteration. The RNA is produced in normal amounts but is not transported out of the nucleus into the rough endoplasmic reticulum for translation [58]. Examples of this type of mutation include G542X, R553X and W1282X [59–61]. Severe reduction in mRNA transcripts should cause reduction or absence of CFTR protein and this appears to be the case [62] (Fig. 30.2).

**Table 30.2** CFTR gene mutations reported to the Cystic Fibrosis Genetic Analysis Consortium [54] with a relative frequency of >1%.

	Relative frequency	Mutation	Consequence
ΔF508	67.2	Deletion of 3 bp between nt 1652 and 1655 in exon 10	Deletion of Phe at codon 508
G542X	3.4	G→T at nt 1756 in exon 11	Gly→Stop at codon 542
G551D	2.4	G→A at nt 1784 in exon 11	Gly→Asp at codon 552
W1282X	2.1	G→A at nt 3987 in exon 20	Trp→Stop at codon 1282
3905insT	2.1	Insertion of T after nt 3905 in exon 20	Frameshift
N1303K	1.8	C→G at nt 4041 in exon 21	Asn→Lys at codon 1303
3849+10 kbC→C	1.4	C→T in a 6.2 kb <i>Eco</i> RI fragment 10 kb from 5' junction on intron 19	Aberrant splicing
R553X	1.3	C→T at nt 1789 in exon 11	Arg→Stop at codon 553
621+G→T	1.3	G→T at nt 1 from 5' junction of intron 4	Splice mutation
1717-1G→A	1.1	G→A at nt 1 from 3' junction of intron 10	Splice mutation
1078delT	1.1	Deletion of T at nt 1078 in exon 7	Frameshift
2789+5G→A	1.1	G→A at 5 nt from 5' end of intron 14b	Splice mutation
3849+4A→G	1.0	A→G at 4 nt from 5' end of intron 19	Splice mutation

nt, nucleotide.



**Fig. 30.2** Effects of the five classes of mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) and the sites influencing CFTR synthesis, processing and function.

**Splice-site mutations**

The effects of splice-site mutations are more difficult to predict. Two examples, 621+1G→T and 711+1G→T, account for 1.3% and 0.9% of mutant CF alleles respectively [56]. The former mutation alters the splice site immediately following exon 4 and produces two aberrantly spliced RNAs, both of which retain an open reading frame [63,64]. The latter mutation changes the splice site following exon 5, causing skipping of the entire exon, but since the number of nucleotides here is a multiple of three the reading frame is left intact [40]. It can be predicted that these aberrant transcripts will be translated into protein products that may be unstable, non-

functionally active, or both. The former mutation produces two aberrantly spliced RNAs, both of which retain an open reading frame [63,64]. The latter mutation changes the splice site following exon 5, causing skipping of the entire exon, but since the number of nucleotides here is a multiple of three the reading frame is left intact [40]. It can be predicted that these aberrant transcripts will be translated into protein products that may be unstable, non-

functional or partially functional. Determining which of these possibilities occurs usually requires protein expression and analysis.

A putative disease-associated mutation was discovered that should lead to a CFTR mRNA transcript missing exon 9 [65]. This would be expected to produce non-functional protein because exon 9 encodes a critical region of the first ATP-binding domain. However, exon 9 is missing from a significant fraction of CFTR mRNA transcripts in most normal individuals [66]. The length of a polypyrimidine tract upstream of the 3' splice acceptor site within intron 8 appears critical [67] for the splicing efficiency of exon 9 (Fig. 30.3). An optimal splice acceptor site lies downstream of 11 consecutive cytosines or thymidines [68]. In intron 8 of the CFTR gene this tract exists in three polymorphisms, consisting of five, seven or nine thymidines [69]. Consequently, the longest tract length, 9T, results in the most efficient splice acceptor, producing over 95% of CFTR transcripts with exon 9 intact. The 7T tract results in 50–90% intact transcript, but the 5T tract is inefficient and produces as little as 5% per allele [68,69]. This allows for some individuals to display variant clinical CF if they have a mutant CF allele and their 'normal' allele carries

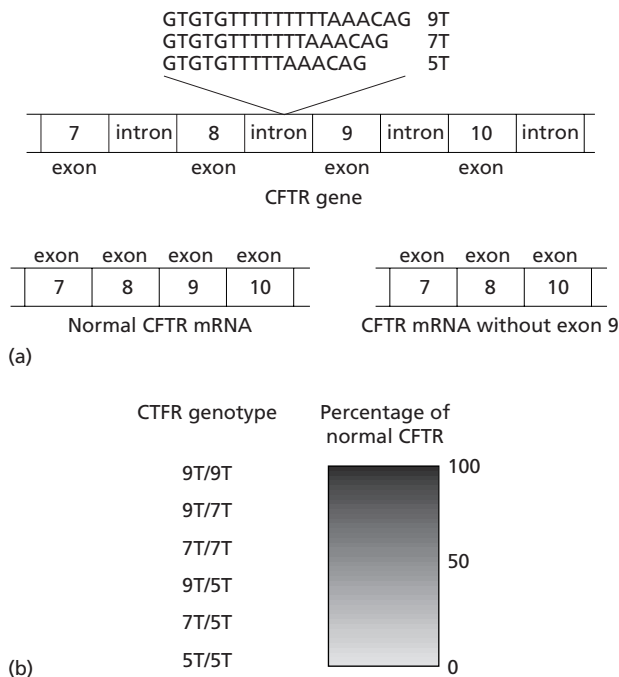
the inefficient 5T variant or if they are homozygous for the 5T allele. Under such circumstances very little functional CFTR protein may be produced, possibly under 10% [60,61,67].

### Mutations and abnormal CFTR processing and trafficking or chloride channel function

Early investigations showed that CFTR bearing the common  $\Delta F508$  mutation was incompletely glycosylated, suggesting that it was incompletely processed and not transferred to the cell membrane [70] (see Fig. 30.2). Also it appears to be temperature sensitive [71], and at lower temperatures can traffic to the cell membrane [72,73] where it has reasonable function as a cyclic AMP-dependent chloride channel [74]. Other mutations traffic to the cell membrane under normal circumstances, for example the relatively common (3% worldwide) allele G551D [75], where they display impaired function. Welsh and Smith [76] have reviewed these. At least two categories appear to exist (see Fig. 30.2). Mutations may impair the activation of CFTR; these occur in the ATP-binding domains and may respond to high levels of stimulation [77]. Other mutations alter the conduction properties of the CFTR chloride channel. Three such mutations (R117H, R334W, R347P) have been reported to be associated with milder disease and the CFTR channel appears partially functional [78–80].

### CF gene mutations and patient phenotype

CFTR mutations can be grouped into five classes, as indicated above, on the basis of CFTR protein alterations (see Fig. 30.2): class I, no synthesis; class II, block in processing; class III, block in regulation; class IV, altered conductance; class V, reduced synthesis. CF shows markedly variable clinical features. Although some of these may be explained by differences in CFTR mutation, the majority show no clear relationship. On examining the common  $\Delta F508$  mutation, while there appears almost complete association with pancreatic status and sweat chloride concentrations, the pulmonary disease varies from extremely mild to very severe [81,82]. Pancreatic function does appear more closely related to the specific mutation carried, and mutations associated with exocrine pancreatic sufficiency (PS) are dominant to those associated with pancreatic insufficiency (PI) [83]. An early report linked mild disease and PS [78] and, by and large, this observation holds. A more extensive assessment of over 500 patients attending a single clinic identified five mutations (R117H, A455E, R334W, R347P and P574H) found exclusively in pancreatic sufficient patients [83]. However, the PS phenotype and genotype relationship is not absolute. In the large genotype-phenotype Consortium analysis [82], 10 of 396  $\Delta F508$  homozygotes were pancreatic



**Fig. 30.3** (a) A section of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. During processing, introns (sequences not involved with protein synthesis) are eliminated and the remaining sequences, exons, are spliced to form mature mRNA. DNA variations in intron 8 affect splicing efficiency and lead to different proportions of mRNA missing exon 9. (b) The relative percentage of normal CFTR depends on the number of thymines in the polyT sequence in intron 8, and the pairing of 9T, 7T and 5T alleles.

sufficient and 3 of 23 R117H/ $\Delta$ F508 compound heterozygotes were pancreatic insufficient.

In CF, more than 95% of men are azoospermic because of congenital bilateral absence of vas deferens.  $\Delta$ F508 mutation in men with this lesion is about 0.5 as opposed to the 0.03 in the general population [84]. A number of these men carry a second CF mutation and many who appear to have only one detectable CF mutation are also carriers of the 5T exon 9 splice variant on the other chromosome [85]. The association of specific organ involvement with specific CFTR mutations allows speculation that there exists a hierarchy of organ sensitivity to deficits in functional CFTR.

## Ion transport

The evolving knowledge of CFTR function in ion transport provides a physiological basis for the more long-standing recognition of chloride, sodium and water abnormalities involving the sweat glands, airways, intestine and the pancreatic and biliary ducts. The disordered ion transport and water movement in these tissues is the basic abnormality leading to the pathophysiological consequences.

## Sweat glands

While the abnormal sweat is only of clinical consequence in a hot environment, it has provided the basis of the 'gold standard' diagnostic test for CF for over 30 years. Sweat is formed from an electrolyte solution secreted into the secretory coil and is isotonic with plasma. It is modified as it passes through the duct by absorption of chloride and sodium. In CF the volume and rate of sweat production are normal [86], as is the composition of the primary secretion, but the reabsorption of ions is reduced because the ductal cells are impermeable to chloride and sodium ions are secondarily retained by the negative charge of the chloride ions. The sweat reaching the skin has a high sodium (~80 mmol/L) and chloride (~100 mmol/L) content and the duct lumen has a high negative charge [86].

However, other abnormalities of CF sweat glands are not so readily explained. Vasoactive intestinal peptide innervation is markedly reduced in comparison to normal tissues [87] and the role of prolactin in sweat formation may be altered in CF glands [88].

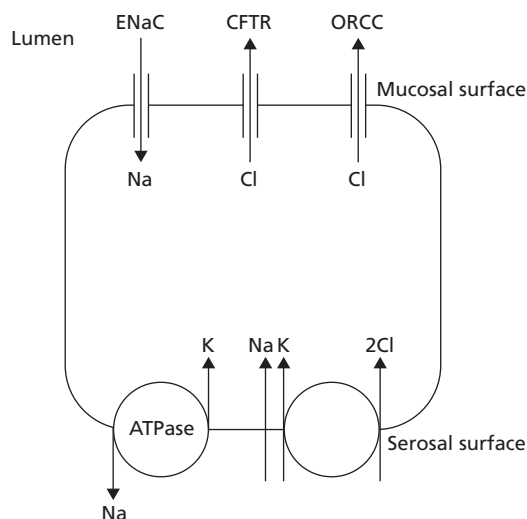
## Airways epithelium

Cilia on airway cells beat within an aqueous environment, the 'sol'. This fluid is thought to be generated predominantly in the periphery of the lung and moved cranially by ciliary beating [89]. The alveolar surface volume is vastly greater than the airway surface volume, and if the hypoth-

esis is correct the airway epithelial cells must be predominant reabsorbers of the fluid. As in the sweat duct cells, sodium is absorbed through sodium channels in the apical membrane and transported out through the basolateral membrane by the sodium-potassium ATPase [90]. Water follows by osmosis. This sodium and water absorption is probably important for limiting the volume of the periciliary fluid layer.

Obversely, ion transport mechanisms also exist to rehydrate the airway surface. The relatively low intracellular concentration of sodium allows sodium to enter the cell from the basolateral surface via a sodium-potassium-chloride cotransporter (Fig. 30.4). Chloride is thus able to enter the cell and exits, down a gradient, via chloride channels in the apical surface. Water follows the movement of chloride, allowing hydration of the cell surface. Under basal conditions, sodium and water absorption predominate but at times of potential airway dehydration, such as exercise, chloride secretion can be activated to maintain the periciliary fluid volume.

As discussed above, CFTR is a cyclic AMP-dependent chloride channel and modulates the epithelial sodium channel and the ORCC. The consequence of an abnormal CFTR in the airway epithelium is therefore excessive inward sodium and water movement and impaired outward chloride and water movement. This gives rise to a relative dehydration of the pericellular environment, which is believed to contribute to bacterial adherence and colonization. It also leads to an increased (more negative)



**Fig. 30.4** Hydration of the mucosal cell surface depends upon interrelationships between the cystic fibrosis transmembrane conductance regulator (CFTR), the outward rectifying chloride channel (ORCC) and the epithelial sodium channel (ENaC) on the mucosal surface of the epithelial cell and the sodium-potassium ATPase cotransporter and the sodium-potassium-chloride cotransporter on the serosal surface of the cell (see text).

transepithelial potential difference. This change is also seen in the upper respiratory tract, where it is easier to make a measure of potential difference. This valuable observation was first made in 1981 [91], with subsequent research and proposal that nasal potential difference could be used as a diagnostic test [92–97]. As with the sweat test, however, patients with milder clinical disease, presumably with some preservation of CFTR function or alternative channel function, may yield equivocal rather than abnormal results [98].

### Submucosal glands

CFTR is present in the submucosal glands, probably in greater amounts than in the airway epithelium [99]. Cyclic AMP-stimulated chloride secretion is defective [100,101] but there are conflicting data on calcium-stimulated chloride transport [101,102] and no data on sodium transport. The likelihood is that there is reduced mucin output and altered composition of mucus. It is unclear how important such abnormalities may be in the pathophysiological processes.

### Gastrointestinal tract

There are conflicting data on basal chloride conductance [103–105] and amiloride effects on sodium transport [104–107]. However, cyclic AMP-induced chloride secretion has been reported abnormal in the jejunum [108,109], small intestine and colon [110], and rectum [105,106,111]. The combined effect of the abnormalities of ion transport appears to contribute to the development of meconium ileus and the distal intestinal obstruction syndrome. Gastric juices appear to have decreased volume, and increased viscosity and sodium levels [112]. Whether this is related to the increased frequency of gastro-oesophageal reflux is not clear.

### Pancreas

Less is known about pancreatic abnormalities. *In vivo*, in response to infusion with secretin and cholecystokinin, the CF pancreas produces lower than normal chloride, sodium, potassium and bicarbonate [113–115]. The fluid secretion is lower but in proportion to the chloride and bicarbonate levels, suggesting that this is a secondary event [114]. CFTR appears localized principally to the proximal pancreatic ducts, with little at acinar level [116]. This supports the proposition that the pancreatic defect is principally of electrolyte and water secretion rather than pancreatic enzyme production.

### Other tissues

B and T lymphocytes express CFTR and have abnormal

chloride transport [117]. However, this does not appear to yield a functional defect. CFTR is also expressed in the kidney but similarly renal function appears normal.

## Epidemiology

### Incidence

CF is found in all racial groups, although the frequency varies markedly. Reported frequencies in different populations are an underestimate. Neonatal screening does not occur widely and any molecular screening of necessity only examines a limited number of genotypes. As an increasing number of genotypes are recognized, patients with much milder variant disease are identified but will have been 'missed' from population screens.

Large population studies have been reported from Sweden [118], the former Czechoslovakia [119], The Netherlands [120], the USA [121], Ireland [122] and the UK [123], and other smaller reports provide additional information. The data are summarized in Table 30.3. These large population studies have been based on case finding rather than screening. The Swedish study of births from 1950 to 1957 found an incidence of 1 in 7700 [118], the Czechoslovakian study 1 in 5200 [119] and the Dutch study 1 in 3600 [120]. The more recent data from the American CF Registry estimates an incidence of 1 in 3500 live births for whites [121], although much lower incidences for other racial groupings (1 in 10500 for American Indians, 1 in 14000 for Blacks and 1 in 25500 for Asians). The Irish and recent UK surveys give commoner frequencies, 1 in 1461 [122] and 1 in 2415 [123] births respectively.

### Survival

In the 1930s most affected children died in the first few years of life. The prognosis has improved spectacularly since then, with a continuing worldwide increase in

**Table 30.3** Estimated frequency of cystic fibrosis, at birth, in different populations.

National group	Birth incidence	Reference
UK	1/2500	Dodge <i>et al.</i> [123]
USA (white)	1/3500	Fitzsimmons [121]
USA (Black)	1/14000	Fitzsimmons [121]
USA (Asian)	1/25500	Fitzsimmons [121]
Sweden	1/7700	Selander [118]
Former Czechoslovakia	1/5200	Brunechy [119]
The Netherlands	1/3600	Ten Kate [120]
Ireland	1/1500	Cashman <i>et al.</i> [122]
Finland	1/25000	Kere <i>et al.</i> [124]
Israel (Ashkenazi Jews)	1/3300	Kerem <i>et al.</i> [125]
Japan	1/323000	Imaizumi [126]
Faroe Islands	1/1800	Schwartz <i>et al.</i> [127]



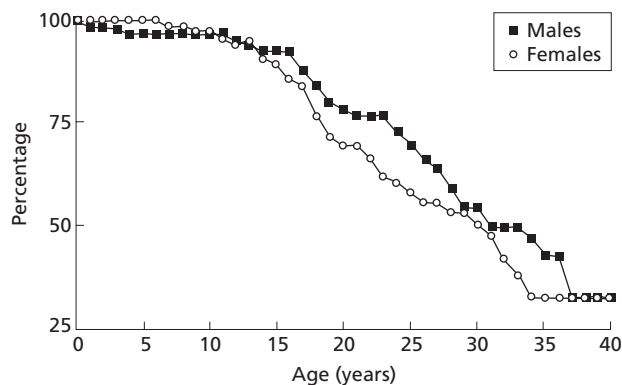
survival rates. In the USA, the median survival in 1969 was only 14 years but rose to 21 years in 1978 and 28 years in 1990 [121]. In the UK, the median survival was 31 years in 1994 [123] (Fig. 30.5), although estimates taking into account rates of improvement have suggested that patients born in the 1990s will survive beyond 40 years [128]. The survival of 3-year cohorts for males and females is shown in Fig. 30.6. It is clear that the reduction of mortality in the first year of life, caused principally by meconium ileus, has made a major contribution to the improved survival rates. Other factors, almost certainly antibiotic therapy and probably better nutrition, have effected the improvements beyond the first year, revealed by the progressive change in slopes of the cohort curves.

There are wide ranges in clinical severity of CF, which are reflected in the mortality rates. Genetic and environmental factors probably contribute. Although some genotypes appear to have a better prognosis, the relationship between genotype and phenotype is obtuse, with only a weak but favourable effect of pancreatic sufficiency.

Clinical decision-making may require a reasonable estimate of likely short-term to medium-term survival. Some studies have shown that a range of clinical variables may have such a predictive value [129–134], including infection with *Burkholderia* (*Pseudomonas*) *cepacia*, low weight [129–131], poor lung function [132], short stature and chronic liver disease [134], all of which may be associated with poorer prognosis.

### Clinical presentation and morbidity

The majority of patients present in the first year of life (70% in the 1990 USA registry), although some patients are diagnosed later in life. The same registry indicated that 10% had not been diagnosed by 12 years. Some of the patients with much milder, variant disease escape diagnosis until their thirties or forties, although at times this is because the diagnosis had not previously been consid-



**Fig. 30.5** Survival of UK residents with cystic fibrosis for both sexes for 1994. Median survival is 31 years. (Adapted from Dodge *et al.* [123].)

ered. Most patients present with the symptoms one would anticipate: the USA registry reported that meconium ileus was present at birth in 16%, and that 45% had acute or persistent respiratory problems, 36% failure to thrive and malnutrition, and 21% steatorrhoea and malabsorption at presentation.

Morbidity is a more difficult parameter to assess readily on a population basis. However, the height and weight of CF patients are simple indicators of the effectiveness of treatment. Recent data of over 3000 patients from 31 CF centres in the UK show improvement over earlier published observations [135]. Thus, during the first decade of life the height and weight of patients are now maintained at about 0.5 standard deviations below those of the general population, although they then show a progressive decline (Fig. 30.7).

## Childhood presentations

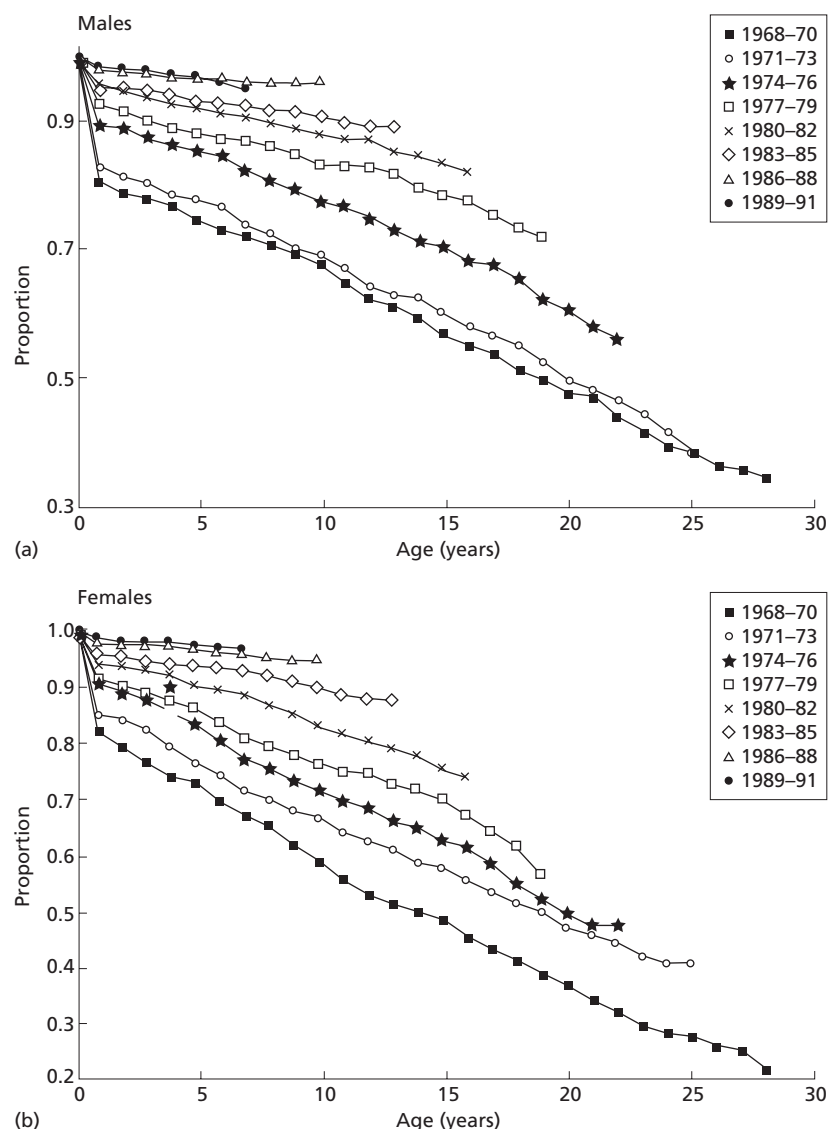
### Meconium ileus

Meconium ileus presents as intestinal obstruction in the neonatal period in up to 16% of children [121], although it may be diagnosed *in utero* at routine ultrasound scanning during the first trimester. The neonatal clinical features are abdominal distension, failure to pass meconium and bile-stained vomiting. Opacification of the right lower abdomen and distended loops of small bowel in the left hypochondrium are seen on radiographs. Calcification may also be seen as small specks or more extensive curvilinear areas. In one study, calcification was seen radiologically in 26% of cases of meconium ileus but identified histologically in 37% of the resected specimens, with the majority being intramural rather than serosal or luminal [138].

The obstruction is due to impaction of inspissated fetal meconium, usually occurring at the ileocaecal junction and extending proximally but sometimes found also in the ascending colon. It is associated with volvulus, ileal atresia or perforation in over 50% of cases. Rarely, a Gastrografin enema may relieve the obstruction [139] but surgery is required in the vast majority of cases. This often includes resection of a non-viable segment of ileum, usually with primary anastomosis. Improvements in the management of this complication of CF have made a major contribution to the improved survival rates.

The pathogenesis of meconium ileus is not fully elucidated. The bowel electrolyte and water transport abnormalities appear to provide the basic mechanisms. The G551D genotype, which is associated with greater apical membrane expression of CFTR than  $\Delta F508$ , has a lower frequency of meconium ileus [140,141]. Pancreatic function has a less clear influence, with the severity of pancreatic insufficiency being no greater in affected individuals than in many other CF neonates. Indeed, meconium





**Fig. 30.6** Survival in successive 3-year cohorts of UK residents with cystic fibrosis: (a) males; (b) females. (Adapted from Dodge *et al.* [123].)

ileus can occur in infants who are pancreatic sufficient [142].

### Prolonged neonatal jaundice

Prolonged cholestatic jaundice in the neonate may suggest a diagnosis of CF [143]. It is present in about 50% of patients presenting with meconium ileus.

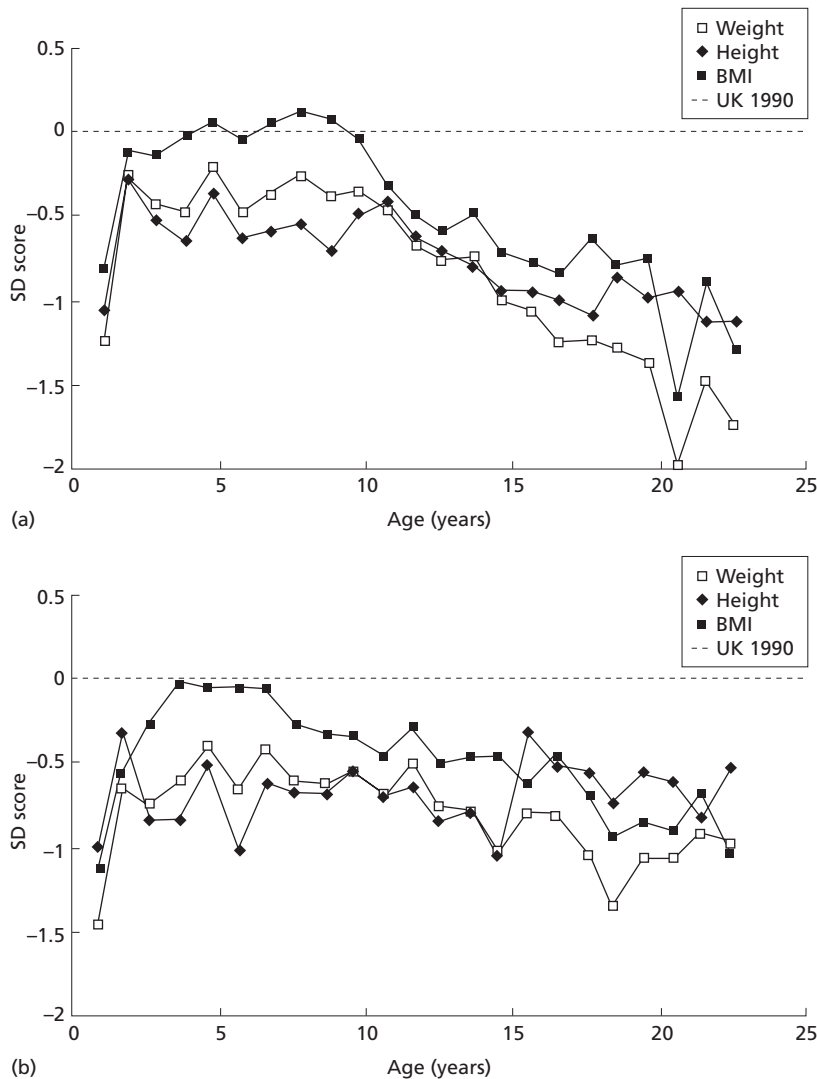
### Failure to thrive

Pancreatic insufficiency should be obvious by age 6 months in 75–80% of individuals [144]. In the absence of respiratory infections the affected infants usually have a voracious appetite but gain weight poorly. Usually the child is underweight and has obvious gaseous distension of the abdomen [145]. The stool may be frequent, bulky and offensive. In about 20% there is associated rectal

prolapse, which may be the presenting clinical problem and can be recurrent [146–149]. Rarer associated presentations include anaemia, hypoproteinaemic oedema and hypochloraemic alkalosis [150].

### Recurrent infections

Respiratory symptoms have a variable age of onset and there is no clear marker for those who present early or late. A persistent cough is usually the first symptom. This is often exacerbated by viral infections and sputum appears loose. However, sputum production is uncommon in infants and young children, who tend to swallow the excessive mucus. A historical assessment from Australia (1955–78) showed that 37% of children presented with respiratory infections [151]. More recent data from the USA give a figure of 45% [121]. Wheezing is common, with up to 50% of cases being affected in some centres [152], and



**Fig. 30.7** (a) Mean weight, height and body mass index by age in patients with cystic fibrosis expressed as SD scores relative to the British 1990 growth reference [136,137]: (a) males; (b) females. (Adapted from Morison *et al.* [135].)

there is a risk that the infant may be misdiagnosed as asthmatic.

### Nasal polyps and sinusitis

Nasal polyps are rare in the infant but increasingly common in preschool and school-age children. Presentation is most common between 5 and 14 years [153]. Polyps recur frequently and rapid growth may be a feature. Occasionally, they may be the only presenting feature of CF. There is a common association between sinusitis and nasal polyposis. Although the sinuses are rarely tender to palpation, over 90% are opacified radiographically [154].

### Neonatal screening

Neonatal screening programmes have allowed the early recognition of CF, before any symptoms may have devel-

oped. Screening programmes and benefits of earlier diagnosis are discussed separately.

## Diagnosis

### Sweat test

The sweat test remains the gold standard for diagnosis, although all methods are uncertain at times. The Gibson and Cooke test of 1959 [8] has stood the test of time well and been examined in detail [155,156]. Sweat is stimulated by pilocarpine iontophoresis (a weak electric current aids the penetration of pilocarpine into the skin) and collected on preweighed filters. At least 100 mg of sweat should be analysed for sodium and chloride. Chloride is more discriminative than sodium and sodium values alone should not be used to diagnose CF [157,158]. It is probably correct to regard ion concentrations of greater than 70 mmol/L for both ions as definitely abnormal and indicative of CF, con-

centrations of less than 50 mmol/L as normal, and values of 50–70 mmol/L as equivocal requiring further consideration [158]. Sweat potassium concentrations are also raised in CF but there is some overlap with normal children. The data reported by Shwachman and colleagues [159] from 252 CF children and controls demonstrate these points (Table 30.4).

The sweat test is a complex procedure and there is room for misdiagnosis [160,161]. A single positive test should always be confirmed by a repeat test or with genotyping. The test should be performed by staff and a laboratory that carry out sweat tests on a frequent basis, not just occasionally. Infants under 4 weeks of age or 3 kg tend to produce too little sweat, and dry skin at any age is a problem. Thus eczema, with a small sweat volume, is a relatively common reason for raised electrolyte values. There are a number of rare conditions that may also cause raised sweat electrolytes: adrenal insufficiency, ectodermal dysplasia, hypothyroidism, familial hypoparathyroidism, nephrogenic diabetes insipidus, glucose 6-phosphatase deficiency, mucopolysaccharidoses, glycogen storage disease type I, anorexia nervosa and severe malnutrition.

Sweat sodium and chloride do show some variation with age; normal teenagers and young adults may have sweat test values, especially for sodium, that are just within the CF range. The effect of pretreatment with fludrocortisone increases the discriminating power of the sweat test in adults [162], since CF patients are relatively more resistant to its suppression of sweat electrolytes.

### Nasal potential difference

If patients have an equivocal sweat test and the full genotype cannot be defined readily, it is worth while measuring the nasal potential difference [95–97], although the technique is difficult to apply in small infants and equivocal sweat tests often mean equivocal nasal potential difference.

### Tests of pancreatic function

A variety of tests of pancreatic function have been

described for patients with CF [163]. A simple screening test has been to look for fat globules in a stool preparation using a microscope. However, this is not specific for CF and false negatives occur. The gold standard is estimation of total faecal fat in stool collected over 3–5 days, a test designed to endear itself to patients, parents and laboratory staff! The daily dietary fat intake over the period must be adequate: 3 g/kg for infants and 30–100 g for older children and adults. Laboratory methods depend on whether medium-chain triglycerides are included in the diet [164,165]. Normal values for daily faecal fat excretion are usually less than 5 g and often less than 3 g [166].

Searches have been made for more pleasant tests. Faecal chymotrypsin concentrations have been suggested as an indicator of pancreatic exocrine insufficiency in neonates and older children [167,168]. The investigators have recommended testing three random specimens and calculating the mean value. Another alternative, the steatocrit test, examines small amounts of homogenized stool sealed into capillary tubes and centrifuged. The fat content is assessed in the resultant layers (basal solid layer, intermediate liquid layer, upper fatty layer) as the ratio of fatty layer to solid plus fatty layers, expressed as a percentage. However, there have been conflicting views of the reliability of this test [169,170].

Two urinary tests have been devised. They are based on the ability of pancreatic enzymes to cleave a compound administered orally, releasing a product that is absorbed from the gut, conjugated in the liver and excreted in the urine. *N*-benzoyl-1-tyrosyl *p*-aminobenzoic acid (NBT-PABA) releases PABA when acted upon by pancreatic chymotrypsin. PABA is then measured in the urine. However, PABA may not be fully absorbed and so a second collection is made after administration of free PABA, allowing a correction to be applied. This test gives incomplete separation between subjects with pancreatic insufficiency and normal function [171]. The pancreolauryl test is similar. On day 1 fluorescein dilaurate is given and hydrolysed to a variable degree by pancreatic arylesterases, with release of fluorescein. Fluorescein alone is given on day 3 and the overall result expressed as a ratio of the two. The test was reported as 97.6% specific for pancreatic insufficiency, and superior to an estimation of faecal chymotrypsin, in a

**Table 30.4** Sweat sodium, chloride and potassium concentrations (mmol/L) for 252 patients with cystic fibrosis (CF) and 252 controls. (Adapted from Shwachman & Mahmoodian [159].)

	CF patients			Control subjects		
	Sodium	Chloride	Potassium	Sodium	Chloride	Potassium
Mean	111.2	115.3	22.9	28.2	28.0	10.3
SD	12.0	12.1	2.5	6.1	6.0	2.4
Minimum	75.4	78.6	13.8	15.9	7.7	6.0
Maximum	144.6	148.2	29.6	45.9	43.4	16.9

variety of patients not including those with CF [172]. It has distinguished between CF children with 'severe' insufficiency and controls [173]. The newest test measures pancreatic elastase in a 'spot' sample of stool. If it proves to give a true quantitative assessment of pancreatic insufficiency, it will be a welcome advance.

### Genetic tests

The use of the polymerase chain reaction allows genotyping on blood spots or mouth rinses. This can be an useful adjunct to other diagnostic tests and to screening programmes. The large number of variants (>600) means that not all genotypes can be tested, although screening for approximately 20 genotypes would encompass 90–95% of all CF genes within discrete geographical populations. Nevertheless, the costs and the logistical effort involved in screening for more than a very small number of genotypes means that at present genetic tests for a diagnosis of CF are complementary to the other methods described.

### Screening

The potential for neonatal screening was realized following the description of increased immunoreactive trypsin (IRT) levels in dried blood spots from infants with CF [174,175]. Possible benefits from screening were deemed to be (i) a favourable alteration in the natural history of the disorder; (ii) availability of genetic counselling to avoid the birth of a second child with CF in a family where the first child remained undiagnosed; (iii) eliminating the period of prediagnosis; and (iv) the prospect of being able to conduct critical studies of new treatments. Disadvantages were thought to include adverse effects on developing family relationships with the new baby, the trauma of false-positive tests and the stigmatization of children who might only have mild disease [176–178].

### Immunoreactive trypsin

Early data that IRT is elevated in CF neonates suggested that the finding was almost always true, irrespective of pancreatic status [179,180]. However, a review of more extensive studies shows relatively high false-positive (up to 1% on the first sample) and significant false-negative rates [181]; the false-negative rate is not dependent on pancreatic function [182]. One problem with the IRT assay is that the level falls variably with age and method of assay [183,184]. Levels are raised two to five fold in the first 4 weeks of life but a negative test after 8 weeks of age is no longer informative. The value of IRT in screening was greatly enhanced by the additional ability to use the blood spots for CF gene screening.

### IRT and DNA analyses

Bowling and colleagues [185] outlined a two-tiered approach of initial IRT assessment and then DNA mutation analysis on those samples with a defined elevated IRT. Similar IRT/DNA protocols have been adopted by most screening programmes and assessments are good [186–191]. The advantage of the combined IRT/DNA method compared with IRT alone is that the number of infants receiving a false-positive screening result is reduced dramatically.

### Is early detection beneficial?

Short-term benefit has been shown for infants with CF who are diagnosed early by neonatal screening. Any evidence of altered long-term outcome is less clear-cut. The earlier reports on the benefits of neonatal screening were flawed in study design, since the outcomes for screened infants were compared with historical controls recognized in previous years [144,192–194]. However, these suggested that screened children at 2 years had spent less time in hospital [192] or gained weight better and had fewer chest infections [194]. Studies by Dankert-Roelse and colleagues [193,195,196] are of longer duration, although again the screened and unscreened populations are not entirely comparable since more of the screened patients were followed in a CF centre. The screened children had better clinical scores and survival and less decline in lung function [195,196]. In Wisconsin also, comparator groups have not been absolutely identical, although there has been evidence of some nutritional advantage (thus far up to the age of 10 years) in the group identified by screening [197]. A better-designed study for true comparison was carried out in Wales and the West Midlands of England between 1985 and 1990, in which screening was carried out only on alternate weeks and where screened and unscreened patients were followed in the same centres and therefore received identical management strategies [198,199]. Data have been recorded annually. Analysis to 4 years of age showed only shorter hospital admission time for the screened children in their first year [199]. By assessment at 8–10 years of age there was evidence that the screened group had (modestly) better lung function and nutrition (Weller, personal communication).

### Antenatal screening

Different approaches have been used in the screening of pregnant women, such antenatal diagnosis being used in hospital and primary care settings. Stepwise screening tests the pregnant woman, and her partner is only tested if she is found to be a carrier of one of the small number of CF genes tested [200,201]. Couple screening requires

mouthwash samples from both parents but only one is tested, unless that is positive, in which case the other is also tested [202,203]. A direct comparison of the two methods [204] found that couple screening allowed carriers to avoid the transient high levels of anxiety caused by stepwise screening, which occurs after the tested woman is found to be a carrier and the result from her partner is awaited. However, couple screening was associated with more anxiety and false reassurance among most screenees, who will test negative. Stepwise screening gave carriers and their relatives informative genetic facts. Population screening has also been tested in general practice [205]. Carrier testing was offered to patients of reproductive age, with an uptake of 66%. However, the cost-effectiveness of this approach is doubtful.

In one large trial when antenatal screening was offered to 8536 couples, the participation rate was 76% [203]. However, with the expected survival times of CF subjects constantly improving and the prospects of newer therapies in the future, the take-up rate is less certain. In 1998, Lothian was the only area in the UK where antenatal screening was routinely offered; neonatal screening is the preferred option of the Cystic Fibrosis Trust and others.

## Childhood management

CF affects several organ systems. Many of the problems pertaining to individual systems apply to children and adults and are considered together. Similarly, the organization of care can be applied to both age groups, although the historical predominance of CF as a paediatric disease means that paediatric centres may be better established. The evidence has been convincing that CF children fare better if their care is coordinated from a specialist centre. Indeed the recommendation of the US Cystic Fibrosis Foundation is that all patients be evaluated at least quarterly at a regional CF centre [206]. In the UK the Cystic Fibrosis Trust, British Paediatric Association and the British Thoracic Society have jointly advocated care in specialist centres. The key factor is to provide care with an experienced team. The core team should include doctor(s), clinical nurse specialists, dietitian, physiotherapist, social worker and psychologist. The addition of a pharmacist is most useful. Access to other specialists and support teams is required and is considered with the specific complications.

## Physical examination

The physical signs depend on the severity of disease. Often there may be no abnormal signs at all. With disease progression the lungs become hyperinflated and if this occurs in infancy thoracic cage deformity appears, revealed as bowing of the sternum (pectus carinatum),

Harrison's sulci and kyphosis. Digital clubbing develops. On auscultation, end-inspiratory and expiratory crackles appear, usually in the upper zones in the first instance. There may be polyphonic wheezes. In the abdomen there may be signs of hepatomegaly, splenomegaly or faecal 'masses'.

## Other assessments

Scoring systems have been established, including clinical and radiographic evidence. Investigations at each visit include lung function, weight and height. Haematological, biochemical and microbiological assessments vary in frequency depending on the patient's condition.

## Scoring systems

Clinical scoring systems in CF became pertinent once survival started to increase. The first, the Shwachman-Kulczycki score, was developed to evaluate a therapeutic programme, determine disease severity and compare one patient with the next [207]. The score is based on history, examination and chest radiograph. Respiratory function tests are not included, since at the time of the original paper these were not universally available. A maximum of 25 points and a minimum of 1 are awarded on a 5-point scale to each of four domains (Table 30.5). The 'Shwachman score' is so entrenched in CF clinical work that it is still applied even though it has been substantially outdated by the advances in CF care and patient well-being over the past 40 years and this should have confined it to historical interest; even so, there have been attempts to update it [208–210].

Other scoring systems have been suggested but also have faults. The Cooperman system [211] is rather too simple and was not really evaluated adequately. The NIH score, reported initially by Taussig and colleagues in 1973 [212], does take into account lung function tests and disease complications that were thought to influence survival (cor pulmonale, haemoptysis, pneumothorax), is reproducible and found to be useful prognostically. Stockrider and colleagues [213] have modified the NIH score in an attempt to refine it as a research tool. They found that five components accounted for 85% of the reliable consistency of the score (general pulmonary, nutrition, disability, psychosocial, acute pulmonary changes), although these had very little correlation with each other. Thus patients with the same total score could have very different component scores. Such differences limit its use as a research tool.

## Chest radiographic scoring systems

Chest radiographic scores are included in the major

**Table 30.5** Shwachman–Kulczycki score: a clinical evaluation score of patients with cystic fibrosis. (From Shwachman & Kulczycki [207].)

Grading	Points	General activity	Physical examination	Nutrition	Radiographic findings
Excellent (86–100)	25	Full normal activity; plays ball; goes to school regularly	Normal; no cough; pulse and respirations normal; clear lungs; good posture	Maintains weight and height above 25th centile; well-formed stools almost normal; good muscle mass and tone	Clear lung fields
Good (71–85)	20	Lacks endurance and tires at the end of the day; good school attendance	Resting pulse and respirations normal; rare coughing or clearing of the throat; no clubbing; clear lungs; minimal emphysema	Weight and height about 15th to 20th centile; stools slightly abnormal; fair muscle tone and mass	Minimal accentuation of bronchovascular markings; early emphysema
Mild (56–70)	15	May rest voluntarily during the day; tires easily after exertion; fair school attendance	Occasional cough, perhaps in the morning on rising; respirations slightly elevated; mild emphysema; coarse breath sounds; rarely localized râles; early clubbing	Weight and height above 3rd centile; stools usually abnormal, large and poorly formed; very little if any abdominal distension; poor muscle tone with reduced muscle mass	Mild emphysema with patchy atelectasis and increased bronchovascular markings
Moderate (41–55)	10	Home teacher; dyspnoeic after a short walk; rests a great deal	Frequent cough, usually productive; chest retraction; moderate emphysema; may have chest deformity; râles usually present; clubbing 2 to 3+	Weight and height below 3rd centile; poorly formed bulky fatty offensive stools; flabby muscles and reduced mass; abdominal distension mild to moderate	Moderate emphysema; widespread areas of atelectasis with superimposed areas of infection; minimal bronchial ectasia
Severe (40 or below)	5	Orthopnoeic; confined to bed or chair	Severe coughing spells; tachypnoea with tachycardia and extensive pulmonary changes; may show signs of right-sided cardiac failure; clubbing 3 to 4+	Malnutrition marked; large protuberant abdomen; rectal prolapse; large, foul, frequent, fatty movements	Extensive changes with pulmonary obstructive phenomena and infective lobular atelectasis and bronchiectasis

clinical scoring systems, although several independent radiographic scores have been developed since and have been used widely in staging disease severity. The most widely quoted was published by Chrispin and Norman in 1974 [214], which was usefully modified, standardized and validated by Brasfield and colleagues [209,215]. Independent assessments of the Shwachman, Chrispin–Norman and Brasfield scores reveal similar interobserver and intraobserver variations [216,217]. However, the rather simpler to apply Northern Score has the advantage of rapid and reproducible scoring by a single observer [218] (Table 30.6).

## Pathophysiology of respiratory disease

The pulmonary disease, by far the principal cause of morbidity and mortality, is suppurative and progressive. Chronic endobronchial infection leads to bronchiectasis and eventually to respiratory failure. The abnormalities of CFTR function result in relative dehydration in the pericellular layer above the epithelial cells. This appears to facilitate bacterial adherence and inhibit mucociliary clearance. This progresses to chronic bacterial colonization with intermittent acute inflammatory responses, and a vicious cycle of further airway damage, further reduc-

**Table 30.6** Northern score: a radiographic scoring system for cystic fibrosis.

Scale	Radiological changes
0	Normal: no cystic fibrosis lung disease evident
1	Mild: minimal increase in linear marking and/or nodular cystic lesions up to 0.5 cm diameter
2	Moderate: more pronounced linear marking and/or more widespread nodular cystic lesions
3	Severe: prominent increase in linear markings, profuse nodular cystic lesions, large areas of collapse/consolidation
4	Very severe: little or no area of normal lung seen, dense infiltration

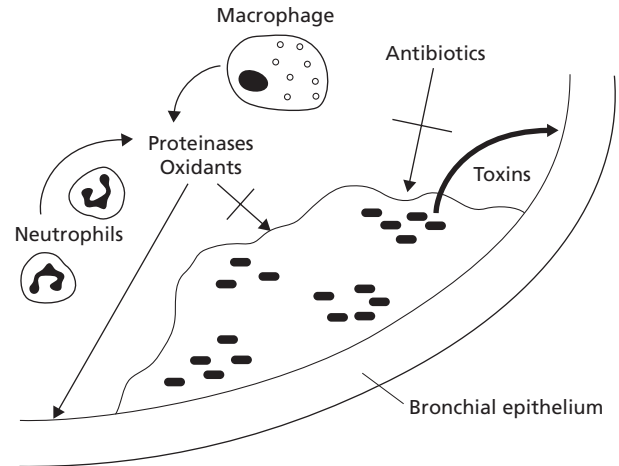
Notes: The lungs are divided into four quadrants by a line drawn outwards from each hilum and each quadrant scored on a 0–4 scale based on increasing severity of chest radiographic changes. A further 0–4 points are allocated according to the observer's perception of overall severity.

tion in mucociliary clearance and further bacterial colonization. While this rather superficial explanation for a progressive, suppurative airways disease may summarize events, it does not really address the underlying mechanisms and CF generally behaves more aggressively than other forms of bronchiectasis. Some genotypes of CF display a much milder form of airways disease. These facts suggest that there are specific biochemical events in CF that determine the inflammatory and infective responses.

Mucins are important for the viscoelastic properties of respiratory mucus. These large glycoproteins, consisting of a protein core that is extensively glycosylated, are in a highly condensed state inside secretory granules of respiratory epithelial cells. During secretion into the airway lumen they undergo rapid rehydration, with a several hundred-fold expansion in volume [219]. The pericellular relative dehydration in CF may affect this process. In addition, the mucins in CF are biochemically abnormal by being oversulphated [220,221], which may result from a defect in acidification of intracellular organelles in CF cells [38] that favours the activity of sulphotransferases over other processing enzymes in the Golgi.

### Bacterial colonization

There appear to be no defects in traditional airway defences in CF. Clearly, however, bacterial colonization does take place and infective exacerbations ensue. Recent data suggest that subtle alterations in the sodium and chloride concentrations of the airway microenvironment may limit bacterial killing [222]. Further, reactive nitrogen species may be important microbicidal agents [223,224] and there is some evidence that inducible nitric oxide syn-



**Fig. 30.8** Diagrammatic representation of *Pseudomonas aeruginosa* having undergone mucoid change and residing as microcolonies within an alginate gel. The alginate provides protection from phagocyte proteinases and oxidants and inhibits antibiotic penetrance. The bronchial epithelium is subject to damage from host defence mechanisms as well as pseudomonal toxins.

thase in the airway epithelium fails to upregulate [225], which could result in relative local deficiency of nitric oxide and its reactive product peroxynitrate. Also, there is new insight into CFTR function and mechanisms relating to bacterial colonization. CFTR functions as a receptor for the binding, endocytosis and clearance of *Pseudomonas aeruginosa* in the normal lung [226], and *in vitro* gene transfer of normal CFTR to CF epithelial cells reduces the binding of *Ps. aeruginosa* to the cells [227]. There is also evidence that the same organism binds to asialo-GM1, which appears to be expressed specifically by regenerating respiratory epithelial cells [228].

Bacterial adaptation can favour persistence even in the face of an active host response. After colonization, *Ps. aeruginosa* tends to undergo mucoid change. Mucoid strains appear among organisms grown *in vitro* under sub-optimal conditions [229], and in CF airways *in vivo* the bacteria appear to be subject to similar nutritional limitations [230,231]. The mucoid change is due to marked production of alginate, which in the presence of calcium forms a firm gel. Microcolonies of organisms then exist in the alginate gel [232], protected from phagocytosis by host defence cells [233] and from antibiotics [234] (Fig. 30.8). The mucoid strains of *Ps. aeruginosa* express a different form of lipopolysaccharide [235] that makes the organism more sensitive to complement-mediated killing [236] and thus limits its ability to cause systemic infection. Indeed, despite the number of endobronchial bacteria, systemic sepsis is very unusual in these patients.

### Infection and inflammation: a vicious circle

Bacterial colonization occurs early in CF patients and is



found even in those who apparently have clinically mild disease [237,238]. The supposition has been that the presence of bacteria stimulates and maintains a host inflammatory response that is unable to eradicate the organisms and therefore persists as a 'chronic' acute inflammatory response. Whilst this is undoubtedly of major importance, bronchoscopies in very young children have revealed the presence of an acute inflammatory response driven by interleukin (IL)-8 in the absence of bacteria [239]. In addition, laboratory-based tests have suggested an intrinsic deficiency of CF epithelial cells and cloned T cells to release IL-10 [240,241]. CF may therefore exhibit an 'intrinsic' alteration of IL-8 and IL-10 responses that would favour the persistence of inflammation.

The persistence of bacteria in the airways generates a continuous antigenic load. Coupled with an exuberant antibody response, this facilitates immune complex formation and amplification of tissue damage [242]. However, most tissue damage is mediated by neutrophils, predominantly via proteolytic mechanisms and oxidants. Neutrophil proteinases are present in substantial excess compared with their inhibitors [243], with elastase occupying a position of importance. Neutrophil elastase not only causes tissue damage but also has proinflammatory activity, activating chemotactic complement components and inducing IL-8 release from bronchial epithelial cells [244]. This aids the establishment of the 'vicious circle' of inflammation, bacterial colonization and progressive bronchiectasis.

## Microbiology

A surprising feature of pulmonary infection in CF is the limited spectrum of pathogens involved, although this is increasing as patients are living longer, presumably related to the more aggressive use of antibiotics helping to 'select' organisms. Another surprising feature is that the organisms involved, which frequently are uncommon respiratory pathogens, do not cause the devastating *acute* illness that they may in other patients.

### *Staphylococcus aureus*

In the earliest microbiological study of postmortem cultures of lung tissue from CF infants, *Staph. aureus* was the predominant organism [245]. Subsequently *Staph. aureus* and *Haemophilus influenzae* were recognized as important CF pathogens, often with repeated exacerbations [246–248]. *Staph. aureus* may cause severe infective exacerbations, although the potential for therapy is greater at present than in earlier times. However, there is an emerging problem with methicillin-resistant *Staph. aureus* (MRSA). This organism does not cause more serious infections but its presence is a major problem for patients with advanced disease, since some transplant centres do not

accept such patients on to their programmes. In some clinics the frequency of patient colonization with MRSA is greater than 10% and a number are employing segregation policies, as with *Burkholderia cepacia* (see below).

### *Pseudomonas aeruginosa*

*Ps. aeruginosa* is generally regarded as the major CF pathogen but usually occurs after repeated infections with other pathogens. The incidence increases with age [249], with about 80% of patients over 26 years in the USA colonized [121], although the same survey showed an incidence of 21% under the age of 1 year. The emergence of colonization by *Ps. aeruginosa* is regarded seriously since it is often associated with an increased rate of decline in lung function. Certainly the organism has a wide range of virulence factors, including pyocyanin, elastase, exotoxin A and exoenzyme S [250–252]. Current practice is to attempt eradication procedures immediately on recognition of colonization. Different approaches include initial oral ciprofloxacin, with or without intravenous antibiotic therapy, followed by a more protracted period of nebulized antibiotics and/or intermittent ciprofloxacin [253].

An alternative, but as yet unproven, strategy to counter chronic pseudomonal infection is immunotherapy. Early attempts at using a *Pseudomonas* vaccine had proved very disappointing. A more recent polyvalent vaccine appears safe [254], and non-colonized patients who maintained high levels of antibodies in response to the vaccine have had a lower rate of infection than non-immunized patients or immunized patients who did not maintain a high-affinity response [255].

### *Stenotrophomonas (Xanthomonas) maltophilia*

Other Gram-negative organisms, such as *E. coli* and *Klebsiella* spp., cause occasional colonization. Yet others are being seen with increasing frequency and may have serious implications for the patient. *Stenotrophomonas maltophilia* [256,257] colonization may follow *Ps. aeruginosa* infections or even occur as the first major Gram-negative problem after *Staph. aureus* and *H. influenzae* colonization. This organism usually displays multiple antibiotic resistances but its effect on the longitudinal health of the patient has to be established.

### *Burkholderia cepacia*

*B. cepacia* has had a major impact in CF clinics. This organism, first identified as causing onion rot [258], was seen from the early 1970s [259] as an occasional colonizer of patients, although the frequency may have been underestimated because of inadequate laboratory culture techniques. During the 1980s and the early 1990s, the

frequency of patient colonization [260–263] increased substantially and it was recognized that certain strains were being transmitted from patient to patient [262–272]. The problems with this organism are its innate resistance to very many antibiotics and the poorer clinical outcomes for many (but not all) patients colonized [273]. A number of patients succumb rapidly to ‘cepacia syndrome’, where severe worsening of pulmonary infection is associated with septicaemia [261,274,275]. These very serious considerations, linked with the transmissibility, have led to segregation policies between colonized and non-colonized patients and bans on summer camps and similar social events for CF patients. The psychological, social and financial implications of these infection control measures have been considerable. Recent work has identified a novel genomic marker that may help differentiate transmissible and non-transmissible lineages [276]. If so, it may prove helpful in the segregation of patients.

### Opportunistic mycobacteria

The frequency of isolation of mycobacteria in the sputum of CF patients probably depends on the diligence with which these organisms are sought. Regular sputum testing and rigorous culture techniques to avoid ‘contamination’ by the organisms discussed above [277] appear to yield isolation rates of 10–20% of patients, with higher or lower rates in some clinics [278–283]. However, the true prevalence and effects of these mycobacteria are poorly understood. *Mycobacterium chelonae* and *M. avium* complex are the organisms reported most frequently to cause true infection (rather than colonization) and the criteria for ‘infection’ are not firm. Anecdotally, it has been difficult to be convinced of overt clinical deterioration in all but one of the Edinburgh Adult Clinic patients (frequency >10%), despite lack of treatment. In some the sputum becomes negative quite quickly and in others the organism persists or rarely the species changes. The one exception has been a patient colonized by *M. fortuitum*, an organism not usually viewed as pathogenic, and a fatality with this has been reported [284]. Occasional cases of *M. tuberculosis* are seen and it is important to maintain regular sputum vigilance, since the presence of such infection may be difficult to recognize clinically or radiologically, particularly in patients with more advanced disease.

### Aspergillus

*Aspergillus* spp. are recovered quite frequently from the sputum of CF patients. The clinical relevance of this is unclear. The presence of a positive sputum culture, high IgE levels, a positive skin-prick test and precipitins are sometimes taken as evidence of allergic bronchopulmonary aspergillosis. In conjunction with new radiological shadowing and a clinical response to steroids, this

may indeed be the case. Allergic bronchopulmonary aspergillosis in CF patients has been reported [285]. One report suggests that the presence of *Aspergillus* spp. in the sputum does not contribute independently to a more rapid deterioration in pulmonary status [286]. At present the best advice is that if a patient is suspected of having clinically relevant lung disease associated with *Aspergillus* spp., treatment with steroids and itraconazole should be considered.

### Viral infections

The precise role of viral infections in initiating respiratory problems or, in particular, promoting lower respiratory exacerbations is uncertain. The balance of data implies that infections with influenza A and B, rhinovirus, adenovirus and respiratory syncytial virus may be important [287–291] and affect mucociliary clearance. It is standard practice to immunize against influenza in the autumn.

## Respiratory complications

### Nasal polyps and sinus disease

The upper respiratory tract holds significant problems for the CF patient. The incidence of nasal polyposis is reported to vary from 10 to 32% [153,292–294]. There are differences between CF and non-CF nasal polyps, including the presence of acidic sulphated mucins in the CF patients [295], fewer eosinophils [296] and more mast cells and lymphocytes. The mast cells may show evidence of degranulation [297]. Approximately 50% of the CF patients appear to be atopic [292], although the relevance of this is uncertain [153,298]. Up to 40% of adults develop polyps [299]. The polyps may be multiple and large enough to cause visible nasal deformity. The presence of nasal polyps bears no relation to the severity of the lung disease.

The sinuses are affected in more than 90% of patients [292,300], involving predominantly the maxillary and ethmoid sinuses. The radiograph may show anything from mucosal thickening to complete opacification. While many patients are asymptomatic, others experience recurrent problems and the sinuses are colonized with the organisms found in the lower respiratory tract. Surgery and parenteral antibiotics may be required.

### Progressive pulmonary pathology

The initial infections favour the development of bronchitis and bronchiolitis. Repeated infection causes ulcerative bronchitis leading to dilatation of the bronchial wall with resultant bronchiectasis. This affects the proximal airways and is usually most marked in the upper zones. The process favours progressive bacterial colonization and

damage to the airways as outlined above. Bronchioles become filled with pus and there is consolidation of the surrounding lung parenchyma. Pneumonia can be seen at all stages of the evolution of the disease. Cysts occur in the lungs, particularly the upper lobes. The progressive lung damage results in deteriorating lung function, the development of pulmonary hypertension and respiratory failure.

### **Atelectasis and collapse**

Segmental atelectasis and even lobar collapse can occur. These are usually associated with thick, retained secretions, often as a consequence of an infective exacerbation. While physiotherapy and antibiotics (see below) would be standard treatment, the importance of re-expanding the lung has led some physicians to have a low threshold for bronchoscopy with suction and even lavage of the involved segment. In the patient with more advanced disease, lavage has greater potential for causing problems and may even promote a worsening inflammatory response.

### **Haemoptysis**

Small haemoptyses are common in CF, particularly in the patient with advanced disease. They are more frequent in the presence of an infective exacerbation and antibiotic treatment may be the appropriate course of action. However, isolated haemoptyses can occur in the stable patient and may simply require reassurance. Massive haemoptysis (>250 mL) is much less common but very disturbing for patient and clinician alike. It almost certainly reflects bronchial artery bleeding. In severe or persistent cases, interventional radiology with bronchial artery embolization may be a necessity [301–303].

### **Pneumothorax**

Spontaneous pneumothorax (Fig. 30.9) is not very common in childhood but the risk increases in adolescence and adulthood. It is commoner in males, in whom an incidence of just under 20% has been reported [304]. Pneumothorax may be associated with a poor prognosis [305] and in our unit has been an event leading ultimately to the death of two patients. While small, asymptomatic pneumothoraces can be treated conservatively, larger pneumothoraces require aspiration or, more commonly, intercostal tube drainage. Lack of resolution results in surgical intervention. The more limited the procedure, the better. A limited abrasion surgical pleurodesis is the preferred option. More extensive pleurodesis or talc or kaolin slurry pleurodesis are less desirable because of increased risk of bleeding at any future transplant. Pleurectomy should be avoided for this reason. The problems associ-

ated with surgical interventions have encouraged us to pursue conservative intercostal tube drainage for significantly longer periods than would be the case for non-CF patients.

### **Pregnancy**

The respiratory complications of pregnancy are considered in the section on fertility (see p. 863).

### **Respiratory failure**

In the later stages of illness patients develop hypoxic respiratory failure, leading to pulmonary hypertension and cor pulmonale. There is usually a progressive rise in carbon dioxide, and early morning headaches are common. Oxygen therapy and nocturnal ventilatory support are valuable aids to symptom control and are described below. These strategies should not be used simply to prolong survival, unless lung transplantation is actively awaited.

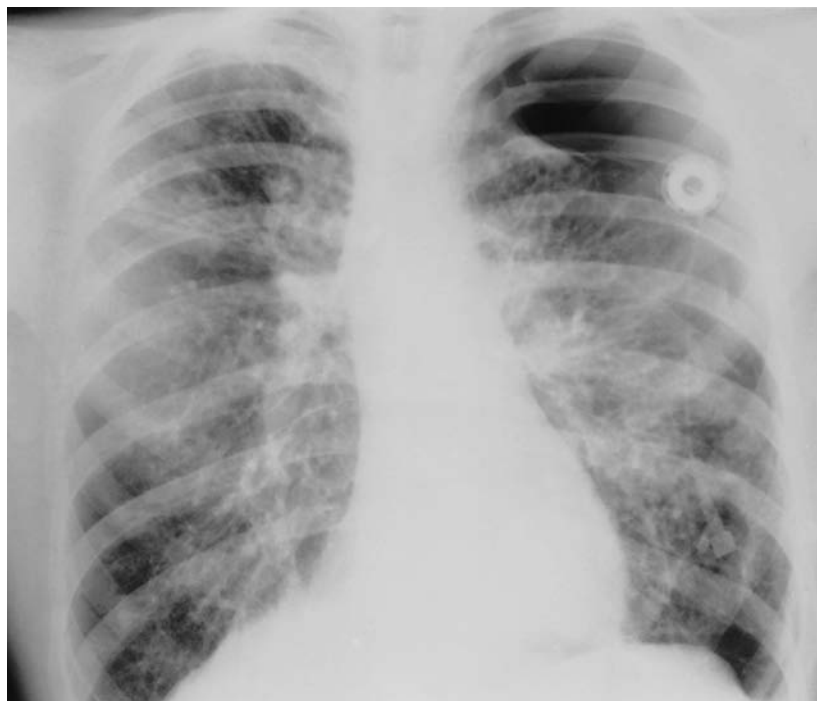
### **Management: lung transplantation**

(see Chapter 59)

Respiratory failure, lung infection and other pulmonary complications account for about 95% of CF deaths. Lung transplantation is the therapeutic option to prolong survival and return physical function and quality of life to satisfactory levels. The shortage of organ donors and the consequent wait for transplantation usually result in the referral for transplant assessment being made when the physician estimates a probable life expectancy of about 2 years. The first successful heart–lung transplant for CF was in 1983 (1985 in Europe) [306,307]. Single lung transplantation is not feasible in CF because of the chronic infection in the native lung, which could lead to fatal infections under immunosuppression. Heart–lung transplantation thus remained the treatment of choice [308] until the successful introduction of bilateral lung transplantation [309–311]. With this technique cardiopulmonary bypass can often be avoided, making it the procedure of choice. To date nearly 400 CF patients in the USA and more than 300 in Canada and Europe have undergone heart–lung or lung transplantation. In 1990 the first living-donor lobar lung transplantation took place and over 50 have now been performed. For patients with marked liver disease in addition to lung disease, heart, lung and liver transplantation may be undertaken, although numbers of such operations are few.

### **Referral and waiting**

In general it is helpful if the referring and transplant centres have a close working relationship. This aids patients in their anticipation of what to expect at assess-



(a)

**Fig. 30.9** (a) Chest film of a male patient with advanced cystic fibrosis. There are extensive bronchiectatic changes with a complicating pneumothorax on the left side. The film also shows a totally implanted venous access device in the upper left anterior chest wall accessed by a 'gripper' needle and standard connector for administration of intravenous antibiotics. (b) Chest film of a female patient with advanced cystic fibrosis. There are extensive bronchiectatic changes with a complicating pneumothorax on the left side. The film also shows a totally implanted venous access device in the right mid-axillary chest wall. The device is not being used so there is no external access needle. The tubing connecting the reservoir chamber and the central veins can be seen. It runs in the subcutaneous tissues upwards across the lateral and anterior chest wall to enter the subclavian vein above the clavicle and downwards within the veins to the superior vena cava.



(b)

ment, and may limit inappropriate referral of individuals. The whole process is very stressful for patients. Most do not believe they are unwell enough for transplantation when the subject is first broached, although once they have accepted the idea the time spent waiting for assessment and placement on the programme seems far too long to them. Once on a programme the usual wait for suitable donor lungs averages well over a year and a substantial proportion of patients die on the waiting list. Many receive 'false alarms', and may even be at the transplant centre awaiting the donor organs only to find them too

damaged for transplantation on arrival. These stresses mean that the support of family and CF unit carers may be invaluable.

### Preparations

CF patients require particular attention in the waiting period. Their general health is, by definition, poor and frequent infective exacerbations are to be anticipated. Indeed many become so unwell that they receive intravenous antibiotics more often than not and undergo multiple

hospital admissions. Nutrition is difficult, since most have no appetite and may become extremely breathless during eating. Nasogastric or gastrostomy tube feeding is usually essential. Supplemental oxygen therapy at night, or usually night and day, is necessary for most patients, and some benefit from nocturnal ventilatory support using BiPAP. Attention should also be paid to the bones, since a significant number of CF patients have reduced bone mineral density or overt osteoporosis. This is probably the result of low vitamin D levels through some or all of childhood combined with low exercise levels because of their respiratory disabilities. The high doses of steroid used in the immediate post-transplant period put the patients at risk of fractures. Assessment of bone mineral density before or at time of transplant referral, followed by therapeutic intervention as necessary, is important. Our policy is to use calcitriol rather than bisphosphonates, but there are no comparative studies.

### Early complications

Early mortality (within 30 days) was as low as 12% even in the earlier days of transplantation and has improved since. The 1-year survival in two large series of heart–lung transplants has been about 70% [307,308], and there are similar figures for bilateral lung transplants [312,313]. Rejection episodes are the most common early complication, with almost all patients experiencing an episode within the first month. Infection is also quite common and it is difficult to distinguish between rejection and infection on clinical grounds; fever, cough, breathlessness and chest radiographic infiltrates are typical of both. In acute rejection radiographic abnormalities are less common after 1 month [314]. Cytomegalovirus (CMV) infections, especially pneumonitis, are common in lung transplantation; ideally, CMV-negative recipients should receive organs from CMV-negative donors. Ganciclovir provides important therapy for such problems. *Pneumocystis carinii* infection is common in patients not receiving prophylactic treatment [315]. The most convenient prophylaxis is with co-trimoxazole on Fridays to Sundays.

### Late results and complications

Survival rates are improving. At present the 3-year survival is in the order of 56%, in contrast to 46% for transplants prior to 1992, and the 5-year survival is 48%. Survival rates are higher at centres that perform more transplants. There do not appear to be significant differences in survival attributable to differences in gender, age group or blood group.

Obliterative bronchiolitis is the most serious late pulmonary complication. Its development appears linked to repeated (perhaps unrecognized) episodes of rejection. Close assessment and treatment of rejection should limit

the frequency of this complication. On the other hand, immunosuppression may allow the development of lymphoproliferative disorders caused by Epstein–Barr virus. The recognition of this requires modulation of the immunosuppressive regimen and treatment with ganciclovir. A careful watch for bacterial infections is required since CF patients have bacterial colonization of their sinuses, a ready source of *Pseudomonas* and other organisms for infection of the lower respiratory tract. The non-CF phenotype of the transplanted lungs seems to help limit permanent colonization in the lower airways.

The immunosuppressive drugs have their own problems. The steroids affect glucose handling, and thus patients already on insulin need their doses modified and other patients not previously on insulin may have to start therapy. In many patients cyclosporin causes hypertension that necessitates treatment. In the long term, cyclosporin-induced renal impairment is important and there should be careful monitoring. Some patients develop a chronic anaemia unrelated to renal impairment that presumably is drug-induced. Azathioprine may be the principal culprit, although the cause is not clear-cut.

Despite the unwanted effects of the immunosuppression, particularly the high doses of steroids in the early days, patients soon observe a dramatic improvement in exercise capacity and loss of the severe problems of chronic sputum production. Despite the very marked improvement in exercise abilities the maximum tolerable exercise capacity in transplanted patients is significantly diminished compared with healthy control subjects. Heart–lung and bilateral lung transplant patients achieve a mean maximum oxygen uptake of 50–60% predicted [316–318].

## Gastrointestinal complications

### Pancreatic insufficiency

Pancreatic disease was recognized before the respiratory component of CF (see above). Pancreatic function declines during the first year of life; 92% of infants diagnosed by neonatal screening were found to have steatorrhoea by age 1 year [319], while 20% of patients found to be pancreatic sufficient at birth became insufficient within 2–12 months of evaluation [320]. Various tests have been used to test pancreatic status (see above). Clinical steatorrhoea is a florid expression of pancreatic insufficiency, occurring only after patients lose greater than 97% of pancreatic lipase and colipase secretory activity [321].

Exocrine pancreatic dysfunction is treated by giving oral pancreatic enzyme supplements. These are extracts of pig pancreas. Initially, powdered extracts were used but these were inactivated by gastric acid and pepsin. In the 1970s, enteric-coated microspheres were developed, the coating not dissolving unless the pH is greater than 5.5,

enabling the enclosed enzymes to escape the acid-pepsin gastric environment. Although pancreatic-insufficient patients have impaired secretion of all pancreatic enzymes, fat malabsorption presents the greatest difficulty. It leads to malodorous bulky stools and flatulence and, because of the calorie content of fat, weight loss. Pancreatic supplements are therefore ranked according to lipase content. The dose of enzyme supplements should be adjusted to the estimated fat content of a meal or snack. In reality most patients are poor at such estimations, and the number of enzyme capsules they use for the average meal is usually achieved by judging the clinical response. If a good clinical response is difficult to obtain or there remains doubt about the patient's level of absorption, a faecal fat balance is the most useful study to optimize enzyme dose [322,323].

With pancreatic insufficiency, the high-volume bicarbonate-rich fluid is not secreted and intraduodenal pH may remain low, since gastric acid is inadequately buffered [324]. When duodenal pH is less than 4, pancreatic lipase is irreversibly inactivated and most bile acids precipitate thus preventing micelle formation; this combination contributes to fat malabsorption.  $H_2$  antagonists and proton pump inhibitors can reduce gastric acid output and enhance the alkalinity of the duodenum [325–327]. This can be a useful adjunct for patients requiring large numbers or increasing doses of pancreatic enzymes in order to control malabsorption.

### **Fibrosing colonopathy**

In 1994 a 'new entity' for CF, fibrosing colonopathy, was reported [328]. This first report highlighted a possible association between colonic strictures and patients' intake of high-strength pancreatic enzyme preparations. It led to a UK survey, which identified 14 cases whose lipase intake was substantially higher than that of controls (46200 units/kg daily vs. 21500 units/kg daily) [329]. Similar cases have been identified in other countries. Although not all such cases had used high-strength enzyme preparations, the more recent USA case-control study has confirmed the association with high intake of enzyme supplements [330]; 29 patients had a mean lipase intake of 50046 units/kg daily compared with 18985 units/kg daily for the 105 controls. This provided a relative risk of 10.9 for patients taking 24000–50000 units/kg daily compared to those taking 0–24000 units/kg daily. In the UK the Committee on Safety of Medicines has recommended a maximum lipase intake of 10000 units/kg daily, even for adults among whom no cases have been described.

The pathology associated with the colonic strictures is that of extensive submucosal fibrosis. Some cases show evidence of mucosal injury and repair, while others show a normal mucosa. Mild infiltration with inflammatory

cells is occasionally seen, and in some there is an eosinophilic infiltrate. The condition comes to clinical attention when the colonic lumen is narrowed to the point where it causes obstruction. At operation the colon wall is thickened and firm. One report has suggested that increased thickness of the colonic wall can be detected by ultrasound [331]. This has not been confirmed by other investigators and barium enema appears a more informative investigation. However, radiological appearances of a featureless and stiffened colon were reported more than 20 years ago as features of CF [145]. This was long before high-dose or even standard-strength enteric-coated microspheres were introduced. It may be unsafe therefore to assume that radiological or ultrasound evidence of a thickened colon is sufficient in itself to suggest early fibrosing colonopathy.

### **Pancreatitis**

Pancreatitis occurs in pancreatic-sufficient patients. Pancreatic-insufficient patients usually have fatty replacement of the pancreas and too little tissue to become inflamed. Pancreatitis is seen in less than 0.5% of CF children but with greater frequency in adults (1.6–2.4% over 30 years) [121]. The diagnosis is easy to miss since pancreatic-sufficient patients are thought to be 'too healthy' or 'too old' to have CF. A sweat test should be performed in any person with unexplained recurrent pancreatitis [332,333]. Perversely, recurrent pancreatitis in pancreatic-sufficient patients may ultimately lead to pancreatic insufficiency.

### **Gastro-oesophageal reflux**

Gastro-oesophageal reflux is common in CF. It appears to be commoner than in the general population, an 'anecdotal' observation supported by a comparative study finding increased frequency in CF patients compared with their siblings [334]. The cause is not clear, although there are probably contributions from the increased abdominal–thoracic pressure gradients associated with coughing and forced expiration during chest physiotherapy and from the postural drainage positions during physiotherapy. This would provide an explanation for the reported association with severer respiratory disease [335]. A significant proportion of patients require therapy with an  $H_2$  antagonist or proton pump inhibitor.

### **Distal intestinal obstruction syndrome**

Distal intestinal obstruction syndrome is an intestinal obstruction in the ileocaecal region unique to CF that occurs after the neonatal period. The true incidence is uncertain. Retrospective case reviews have reported incidences of 12–41% [336,337], with males and females

equally affected. The syndrome almost always occurs in the pancreatic-insufficient patient. Relative dehydration, dietary changes and, in particular, inadequate enzyme supplementation may contribute. Distal intestinal obstruction syndrome occurs with sludging of intestinal contents in the ileocaecal region, with the process extending distally.

Clinically, there is crampy abdominal pain and distension, usually with a palpable mass in the lower right quadrant. Partial obstruction can extend to complete obstruction, with increasing pain and distension plus vomiting. The uneducated patient and the unaware surgeon have conspired occasionally to allow inappropriate surgery and resection of bowel. Successful medical treatment is almost always possible, particularly in the early stages, with repeated oral doses of Gastrografin, a contrast medium that exerts a strong osmotic effect. The consequent movement of fluid into the bowel moves the obstructing ileal contents. Success has also been reported using bowel irrigation with balanced polyethylene-glycol solutions [338]. Contrast enemas may be therapeutic for patients with complete obstruction [339].

## Hepatobiliary complications

The primary liver abnormality of CF affects the cells of the bile ductules, with consequent reduced bile production and altered bile acid composition [340,341]. There is resultant biliary obstruction, portal tract inflammation and eventually portal tract fibrosis and focal biliary cirrhosis [342]. The quoted prevalence of cirrhosis in CF varies from as little as 2% to as much as 25% [121,343,344]. It is extremely difficult to obtain an accurate estimate of bile ductule function and associated focal damage. Plasma hepatocellular enzymes (alanine aminotransferase and aspartate aminotransferase) and biliary enzymes (alkaline phosphatase and  $\gamma$ -glutamyltransferase) are readily measured but give very poor indication of hepatobiliary status. Nevertheless, in the absence of a better measure these are generally used as the monitors of CF liver disease.

There appears to be no relationship to CF genotype, an observation confirmed by formal studies. In one, patients identified with severe liver disease had genotypes that reflected the spectrum of mutations seen in the local population [345]. In another, 29 of 111 children and young adults had severe liver disease with portal hypertension, 19 had biochemical or clinical evidence of liver disease and 63 had no evidence of liver disease. There was no correlation between hepatic disease and CF mutation [346].

Not all liver disease is as severe. In several studies over many years, fatty change has been reported to have a high incidence in CF [2,347,348]. Since CFTR is found only in the bile duct epithelium, the fatty change presumably represents a secondary effect, for example of malabsorption.

Also, there are many case reports of prolonged neonatal jaundice in CF infants. Most appear also to have had meconium ileus, although the mechanism of the jaundice is uncertain. Cholestasis may persist for months but ultimately resolves. It is not clear whether these patients are at increased risk of developing biliary fibrosis and cirrhosis later in life.

## Assessment

Since conventional liver biochemistry appears to underestimate biliary and liver disease, additional assessments should be considered as part of routine monitoring, for example at the annual review. Upper abdominal ultrasound is easy, non-invasive and may be informative. Abnormal liver architecture and splenomegaly are indicators for repeated or additional investigations. In more advanced disease Doppler may reveal reversed portal blood flow. Ultrasound does not always reveal the presence of varices, and in our unit the presence of significant splenomegaly leads to CT contrast scanning to try to identify these.

Biliary scintigraphy often shows delayed excretion in the absence of extrahepatic obstruction, presumably reflecting biliary hypomotility or bile stasis [349]. In one study using endoscopic retrograde cholangiography-pancreatography, all patients had abnormalities of the intrahepatic bile ducts [350].

## Treatment

Medical treatments are distinctly limited. The use of ursodeoxycholic acid has become widespread during the past 5 years, although the evidence for its benefits is, as yet, unclear. Ursodeoxycholic acid is a hydrophilic bile acid that tends to replace the more toxic hydrophobic bile acids [351]. Also, it is able to stimulate bicarbonate secretion directly and thus improves bile flow [352]. The early clinical studies reported improvement in liver function when patients with CF liver disease were given high-dose ursodeoxycholic acid [353–355]. There are no studies to show whether use of this drug prevents the development or progression of cirrhosis, or indeed to identify which patients should be treated.

For established cirrhosis with portal hypertension and varices, traditional treatments such as portosystemic shunting [356] and sclerotherapy [357] have been used. Currently, major operative portosystemic shunts have been superseded by TIPSS (transjugular, intrahepatic, portal systemic shunt) procedures [358]. Patients with severe liver disease are candidates for liver transplantation. A balanced assessment has to be taken with respect to the pulmonary status. Accompanying severe lung disease may indicate the need for heart–lung–liver transplantation. Alternatively, severe liver disease may have sec-



ondary effects on the lungs (e.g. intrapulmonary shunting; diaphragmatic splinting), which would reverse on liver transplantation. Medium-term survival for liver transplantation is good; the Cambridge group reports nine children all alive at 4–55 months (median 30 months) [359].

### **Extrahepatic biliary disease**

Many CF patients have small shrunken gallbladders or bile sludging [360]. Gallstones and symptomatic gallbladder disease are seen frequently, usually in adults, with CF [121,361]. It is thought that the large faecal bile acid losses and decreased bile acid pool cause the bile to become supersaturated with cholesterol, which leads to stone formation [362]. The management for most patients is laparoscopic cholecystectomy.

### **Nutritional consequences of, and implications for, cystic fibrosis**

Clinicians have long recognized that patients who are underweight have a worse prognosis than well-nourished patients, but does poor nutrition cause the decline or is it merely a marker of disease progression? Mortality patterns over a 20-year period obtained from the Canadian Patient Data Registry suggest that being underweight is, at least partly, an independent predictor of mortality [363]. Body cell mass (BCM) is the portion of metabolically active fat-free mass. Assessment of anthropometric parameters, lung function and BCM in 61 patients aged 5–17 years with moderate disease showed that change in BCM was the best predictor of change in forced vital capacity (FVC), and those patients with normal growth in BCM had less decline in FVC than those with retarded growth of BCM [364]. Generally, BCM increases with increasing calorie intake. However, the use of nutrients is controlled hormonally, particularly by insulin. In CF there may be relative insulinopenia (see below), which may contribute to reduced anabolic activity.

The association of poor nutritional status and poor lung function is presumed to be the result of increased energy expenditure from lung infection and inflammation and increased work of breathing. While these have a major effects, it has also been speculated that the CF gene defect itself may elevate energy expenditure, as a result of both abnormal ion channel kinetics and increased activity of mitochondrial electron transport.

The other aspect to consider is the dietary intake. Recommendations for daily intake are between 120 and 150% of normal recommended intake. In practical terms this is not always easy when the patients are relatively fit and well. When they are unwell, the consequent anorexia makes it even more difficult. When patients have moderate to severe disease, they have to contend with a degree of

constant anorexia. At this stage also, poor nutrition has a deleterious effect on the individual's ability to resolve infection and inflammation.

### **Dietetic support**

The dietitian has an important role in the management of CF patients by monitoring body mass index and lean body mass as well as reviewing the average daily calorie intake and pancreatic enzyme use. Dietary advice is important since it is difficult to achieve a high calorie intake without adequate use of fats, and this requires guidance with respect to pancreatic enzymes. In addition, malabsorption results in low levels of fat-soluble vitamins and it is standard practice to advise supplementation with vitamins A, D and E. When patients have difficulty keeping their body mass index in the range 19–20 or better (normal range 20–25), they should receive high energy-containing oral supplements. The newer preparations appear more palatable than some of their predecessors. In the patient with more advanced disease additional measures are often needed. Overnight enteral feeding via a nasogastric tube (passed by the patient every night) or a gastrostomy tube is a very effective way of maintaining reasonable nutrition.

### **Diabetes mellitus and cystic fibrosis**

Changes in glucose metabolism were observed in the very early descriptions of CF [2,365] and the association between CF and diabetes mellitus was first recognized in 1955 [366]. Subsequently, different studies have reported varying prevalences of impaired glucose tolerance and diabetes mellitus, although methodologies have varied [367–373].

The Copenhagen centre has provided some of the more comprehensive data. For a planned longitudinal study over 5 years all 226 patients over 2 years of age were entered; 191 patients completed the 5 years. During the study the prevalence of diabetes increased from 11 to 24%, with an average annual incidence of 3.8%. For those aged 10 years or more the respective figures were 16%, 34% and 5.0% [374]. The median age of diagnosis for diabetes was 21 years (range 3–40); 22% of oral glucose tolerance tests showed impaired glucose tolerance, although the overall picture was complex. Nearly 60% of subjects with impaired glucose tolerance showed normal glucose tolerance at their next annual test. Overall only 37% of patients had a normal test on all five occasions and impaired glucose tolerance gave a higher risk of developing diabetes (odds ratio 5.6). This study highlighted that an oral glucose tolerance test is the gold standard for assessment. Routine assessments of hyperglycaemic symptoms, fasting hyperglycaemia and glycated haemoglobin did not identify diabetes mellitus reliably.

## Pathogenesis

In patients with CF who have diabetes, there are reports of a 30–50% reduction in the number of islets and  $\beta$  cells [375–377]. With the additional observations of fibrotic bands, a shrunken fibrotic pancreas and presumptive distorted blood supply, the prevailing view has been that diabetes develops in CF as a secondary effect of progressive damage to the pancreas as a result of CF-related abnormalities in the exocrine pancreas. However, more recent data have shown that diabetes in CF appears to be type II diabetes [378,379] and that patients often have non-CF relatives with type II diabetes. This has led to the suggestion that CF is a risk factor that interacts with the genetic predisposition for type II diabetes, resulting in clinical disease.

## Management

There is some suggestion that insulin treatment of diabetic patients improves lung function and reduces infective exacerbations [380]. In our own unit we have observed evidence of improved nutrition and body mass index after introduction of insulin treatment. In addition, diabetic patients with CF are probably no less prone to developing late diabetic complications than are other patients with diabetes of similar duration and glycaemic control. An ideal approach appears to be to run a combined clinic with an interested diabetes service. However, the dietetic input is different from that in conventional diabetes management. Since CF patients have such difficult nutritional demands, their diet should be directed accordingly and insulin therapy adjusted to the dietary intake.

## Arthropathy and vasculitis in cystic fibrosis

Acute or subacute arthritis is seen in patients with CF and has been well reported [381–384]. In our own adult unit about 5% of patients have intermittent problems of arthritis, occasionally with the associated symptoms being their principal clinical concern. Usually, there is an adequate response to non-steroidal anti-inflammatory drugs (NSAIDs). However, there are reports of individuals developing persistent synovitis and progressive erosive arthritis [383], and also isolated reports of concurrent arthritis, psoriasis and CF [385] and sarcoidosis, arthropathy and CF [386]. As an additional anecdote, one of our patients with intermittent arthropathy also has biopsy-proven sarcoidosis.

Sometimes episodic arthritis is associated with erythema nodosum or other nodular skin lesions. More commonly, purpura may be seen, particularly on the legs [387–389]. In a report of 12 patients with dermal vasculitis two had evidence of systemic vasculitis [389]. There was

no evidence of autoimmune disease but 40% had antineutrophil cytoplasmic antibodies. Purpuric vasculitis is probably associated with severer lung disease. It is a matter for conjecture as to whether lung-derived immune complexes are part of the underlying mechanism. Anecdotally, some severely ill patients awaiting transplantation experience fevers and arthralgia that are suppressed by systemic steroids.

## Fertility and pregnancy in cystic fibrosis

With the marked improvements over the past 30 years in patients' well-being and survival, 'new' CF-related problems have arisen. Many now have the expectation and wish to have children. Two problems therefore have to be addressed: infertility, especially in the male, and the risks of pregnancy.

### Male fertility

Infertility is almost universal among males (approximately 2% appear fertile [390,391]) as a consequence of a developmental defect of structures derived from the embryonic wolffian duct. This leads to absence, atrophy or various forms of obstruction of the vas deferens, the body and tail of the epididymis, and the seminal vesicles [392–396]. However, testicular histology appears normal and active spermatogenesis occurs, although some abnormal and immature sperm may be seen on testicular biopsy [392,397]. As discussed above, during fetal growth CFTR function appears critical for the normal development of the wolffian duct structures, and congenital absence of the vasa deferentia may be the only manifestation of CF.

The potential for fertility can be readily assessed by checking for azoospermia. It is important to introduce the likelihood of male infertility gently, during adolescence, when the concept is less threatening. However, new techniques of sperm aspiration from the epididymis or vasa efferentia and *in vitro* fertilization [398] are now being introduced in the management of male infertility in CF.

### Female fertility

As a group, females with CF have reduced fertility compared with healthy subjects. The extent of the reduced fertility is unclear, and individual patients have normal fertility, subfertility or absolute infertility. One frequently quoted study, which gives a group estimate of about 20% normal fertility [399], appears flawed in design and details. Primary and secondary amenorrhoea are common [400], often reflecting poor lung health and nutrition [401]. These contribute to overall reduced fertility. Anatomically the female reproductive tract appears normal, although

relative dehydration of the cervical mucus may result in a physical barrier to sperm penetration [399].

In the absence of a simple screening test to assess fertility in women with CF, all patients of child-bearing age should be presumed to be potentially fertile and those wishing to avoid pregnancy for personal or health reasons should be counselled on appropriate forms of contraception. Oral contraceptives generally are effective and in limited-size studies have not shown problems [400,402], although there are potential difficulties. Chronic use of oral contraceptives has been associated with intrahepatic cholestasis and cholelithiasis; some of the progestogens used impair glucose tolerance; and oral contraceptives may deplete vitamin D and E levels. Finally, concern has been expressed over possible antagonistic effects of antibiotics on the intestinal absorption and bioavailability of oral contraceptives. If pregnancy is definitely contraindicated, a more definitive contraceptive measure should be given serious consideration.

### Pregnancy

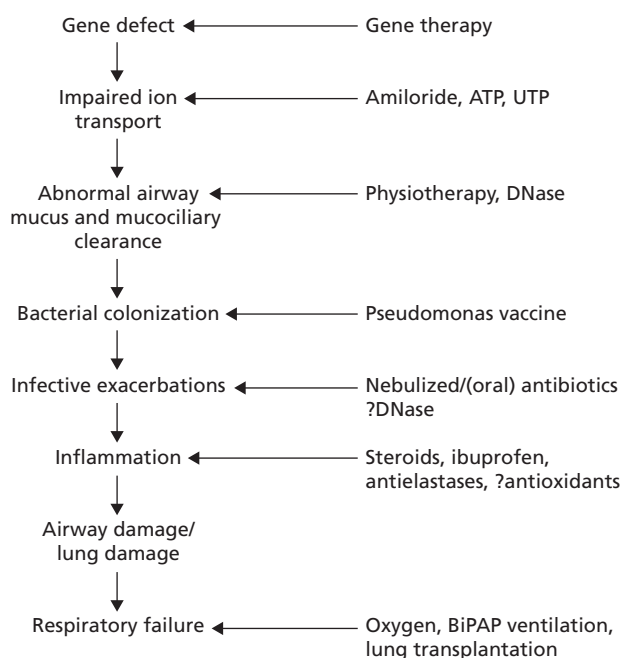
The first documented successful pregnancy in CF was in 1960 [403]. However, the patient died 6 months postpartum. The next report, in 1966, of a survey of 13 pregnancies in 10 patients from 34 CF centres revealed that five women experienced significant pulmonary decline during pregnancy and two died in the immediate postpartum period [404]. A further large survey of 119 CF centres in the USA and Canada, published in 1980, reviewed 129 pregnancies in 100 patients [405]; 75% of the pregnancies were completed, 89% of which resulted in viable infants; 12% of the women died within 6 months of delivery. The women who died were noted to have severe pulmonary disease before pregnancy. A similar association was observed in a smaller report published in 1983 [406]. Supporting this concept, a survey of 38 pregnancies in 25 women, predominantly with mild disease (half were pancreatic sufficient), indicated that pregnancy was well tolerated [407]. In contrast to the preceding studies, a recent UK report of 22 pregnancies in 20 patients recorded lung function before pregnancy, immediately after delivery and after pregnancy [408]; four mothers died up to 3.2 years following delivery. The previous observations were supported but with firmer data. The women with moderate to severe lung disease (forced expiratory volume in 1 s,  $FEV_1$ , <60% predicted) before pregnancy fared worse, producing preterm infants and suffering increased loss of lung function and mortality compared with mildly affected mothers.

Pregnancy is therefore not to be undertaken lightly. There should be very careful assessment of an individual's health and sound counselling provided. Patients whose  $FEV_1$  is less than 60% predicted should be cautioned about the risks. Pregnant mothers, even those with mild CF, should be monitored closely during pregnancy. Maternal

weight gain and uterine fundal height may help assess fetal growth retardation [409]. Antibiotic therapy should be given if needed. However, aminoglycosides and quinolones are potentially teratogenic and are best avoided, although they have been used by pregnant patients without consequences for the fetus [407]. From our own and others' observations, the immediate postpartum period may have its own hazards. We have seen severe respiratory exacerbations occur at this time. The reasons are unclear, although there must have been a release of the upward displacement of the diaphragm and associated possible closure of small basal airways. More importantly, the immunological changes of pregnancy, which are predominantly 'immunosuppressive' and anti-inflammatory, revert to 'normal'.

### Management of respiratory aspects of cystic fibrosis

There are several well-established areas of management of the various respiratory aspects of CF. These can be viewed in respect to the pathogenetic processes involved, as outlined above and as illustrated in Fig. 30.10. Also, there is much active research in CF and new and novel approaches to management are in constant development. In this section, the standard and new management techniques are reviewed.



**Fig. 30.10** A flow diagram outlining the pathogenetic sequence of events causing airways and lung disease in cystic fibrosis. The points of therapeutic interventions, both established and in development, are indicated.

### Physiotherapy

For over 40 years chest physiotherapy has been the principal technique for attempting to remove viscid secretions from the airways and thus interrupt the cycle of infection, inflammation, tissue damage and decreased clearance. First introduced in the 1950s, the combination of postural drainage, percussion, vibration, deep breathing and coughing constitutes 'conventional' chest physiotherapy and for many years has been the gold standard [410]. When introduced, virtually all patients were children and their parents could assume responsibility for performance of the treatment. As survival has improved, more and more adolescents and adults have had to assume responsibility for carrying out their own physiotherapy. Adherence to treatment is often poor among adolescents and adults. Newer techniques have been developed to try to make physiotherapy more patient-centred and to aid compliance. The active cycle breathing technique has been shown to be as effective as conventional physiotherapy in mobilizing secretions [411–413] and is less likely to cause oxygen desaturation [414]. It undoubtedly allows patients more independence. No added benefit to this technique has been provided by a positive expiratory pressure mask or a Flutter VRP1 system [415,416], although both have had their advocates. Autogenic drainage has been reported favourably with respect to both mobilizing secretions and avoidance of oxygen desaturation [417–419]. However, since adherence to treatment is such a problem it is important to select the technique that the patient prefers. There are many likely benefits of regular exercise, including improved cardiorespiratory efficiency, respiratory muscle function, muscle strength and exercise tolerance, as well as improved self-image and well-being. Exercise alone does not appear as efficient as physiotherapy in mobilizing sputum but is a valuable adjunct [413] and to be encouraged.

### Antibiotic treatment

Aggressive antibiotic therapy has probably been the major contributor to the improved survival of CF patients. Use falls principally into two categories: acute treatment for an infective exacerbation and chronic administration as maintenance therapy intended to decrease the bacterial load in the lung and to maintain lung function. Intravenous administration and nebulized antibiotics have their own intrinsic problems. In addition, pharmacokinetics are different in CF patients, who appear to have a larger volume of distribution and increased clearance of aminoglycosides and  $\beta$ -lactams, with a shorter elimination half-time and lower peak plasma antibiotic concentrations [420]. A larger dose and possibly more frequent dosing intervals are necessary to compensate for these differences. Children with CF appear to eliminate ciprofloxacin

more rapidly than older patients and may require higher dosing of fluoroquinolones [421].

### Combination therapy and aminoglycosides

Repeated courses of antibiotics lead to increased bacterial resistance patterns, and this may be an important reason for the emergence of bacterial colonization by organisms with multiple innate antibiotic resistances. Certain principles appear useful. Treatment with combinations of antibiotics appears to combine the additive benefit of two or more drugs, while in one clinic the use of monotherapy has resulted in widespread resistance to the antibiotic by *Ps. aeruginosa* [422]. Aminoglycosides in particular seem to be useful drugs to combine with other agents such as cef-tazidime, aztreonam and meropenem. The ototoxicity of aminoglycosides is an important consideration, since a patient is likely to have multiple courses. Despite rigorous monitoring of blood levels and no record of 'toxic' levels, two patients in the Edinburgh adult clinic have experienced tobramycin-related vestibular problems. Once-daily aminoglycoside dosing has been used increasingly for non-CF-related disease, but in CF there are extremely limited, almost anecdotal, reports. In the Edinburgh clinic, a 6-month period of once-daily tobramycin (5 mg/kg at night) appeared to be associated with a more rapid 'relapse' rate of exacerbation, although the treatment approach has not been assessed in a prospective double-blind fashion.

### Chronic antibiotic therapy

A number of centres treat children with regular anti-staphylococcal drugs, especially flucloxacillin, from the first isolation of *Staph. aureus*. Other centres prefer to treat infections aggressively as they occur, often maintaining treatment for 4 weeks. This has the advantage of including *H. influenzae* in the treatment spectrum. This regular flucloxacillin therapy has had an element of 'tradition' about it. Nevertheless, recent data from a study of infants diagnosed at neonatal screening showed that those who received continuous flucloxacillin had less frequent cough and fewer and shorter hospitalizations compared with infants treated with episodic courses of antibiotics. There was no difference in pulmonary function between the two groups at 1 year [423,424].

The use of regular antibiotics has been applied in older patients colonized by *Ps. aeruginosa*. In this instance, the route of administration has been by nebulizer. There have been differences in frequency of such treatment between the USA and Europe. Regular nebulized colistin is employed frequently in the UK, nebulized gentamicin or tobramycin less often. There are issues of drug-induced bronchoconstriction in patients (sometimes quite a high frequency) and adherence among adolescent and adult

patients to a twice-daily regimen is probably even less good than to physiotherapy. There are numerous published studies with nebulized antibiotics [425] but very few address long-term use and very few are placebo-controlled [426–428]. On balance, treated patients have positive benefits including better lung function and/or fewer hospital admissions. Recent, well-controlled, multicentre studies have been performed in the USA. The first, although short term, showed benefit to lung function [429]. The second, also led by Ramsey, has been in progress for a year and has shown definite benefit [430].

### Intravenous antibiotics

Recurrent infections, particularly after colonization with *Ps. aeruginosa*, require repeated courses of intravenous antibiotics. Traditionally, peripheral intravenous cannulae or long lines have been used for this purpose. However, frequent replacements are often required in a single treatment period and resulting damage to veins makes venous access difficult in the long term. The introduction of the totally implantable venous access device (TIVAD), also known as 'ports', has provided a solution to this problem. A TIVAD usually consists of a silicone septum mounted in a titanium chamber, which is inserted subcutaneously on the chest wall (see Fig. 30.9) or in the arm. The chamber is connected to a catheter, which is tunnelled into a central vein. These devices have proved successful clinically [431–435] and have greatly aided home intravenous antibiotic management. Home treatment is appreciated by patients, who avoid prolonged hospital admissions, but is dependent on adequate support. Clinical nurse specialists can provide that support and train the patients in the aseptic techniques necessary for self-administration of drugs. An important safety proviso is that the initial dose of any course of intravenous drugs is given under supervision in case of an anaphylactic response, which occasionally occurs even if the patient has received the same drugs on numerous previous occasions.

### Therapy with DNase

CF sputum is remarkably tenacious and the physical effort of expectoration, particularly in patients with poor lung function, is substantial. Much of the viscosity is attributable to DNA in the sputum, the source of which appears to be dead neutrophils. In the late 1950s, use of DNase to cleave the DNA was found to be effective at reducing sputum viscosity and aided sputum clearance. Unfortunately, marked allergic reactions occurred after a short while, since the DNase was of bovine origin, and the treatment fell into disuse. More recently, human DNase has been cloned, mass produced and was licensed for use in 1994. It is markedly effective in reducing sputum

viscoelasticity *in vitro* [436] and *in vivo* early trials showed encouraging improvements in spirometry [437,438]. The large, multicentre trial (968 patients) used to support licensing [439] showed that once-daily treatment gave a relatively modest (5.8%) improvement in FEV<sub>1</sub> at 24 weeks, with a small reduction in exacerbations requiring parenteral antibiotics. However, there was wide variability of individual responses to treatment, with a significant proportion appearing to have no benefit. Further studies have shown no significant benefit of short-term use during exacerbations [440], improvements in spirometry but not in antibiotic use in sicker patients [441], and a wide scatter of spirometric responses with a reduction in historical antibiotic use in children [442]. One longer-term study has suggested no benefit for lung function, nutrition or hospitalization rates [443]. However, group mean data may be misleading if 'non-responders' are included in the study group. Anecdotally, in our centre there appears to be a reduction in requirement for antibiotics over about a 2-year period if the drug is targeted to patients who show a definite response to short-term testing [444]. The initial persuasive reason for testing patients' responses to DNase, i.e. to target therapy, was its great expense. The cost of therapy cannot be ignored; at more than £7000 per patient per year for once-daily dosage, it equates broadly to the per capita cost of caring for CF patients in a specialist centre [445] and thus prescription to all patients would nearly double the cost of CF care in the UK. A Scottish protocol has been developed to target the use of DNase [444], and this protocol or similar should be applied before commencing patients on long-term DNase.

### Treatment of the excessive inflammatory responses

Following the recognition that host inflammatory responses are major contributors to the progressive lung damage (see above), therapeutic strategies have been directed towards control of these responses.

### Corticosteroids

An initial trial reported benefit in children aged 1–12 years when given high doses of prednisone (2 mg/kg on alternate days) [446]. The steroid-treated children were said to have had better lung function and growth, and fewer hospitalizations, with no adverse effects. This trial prompted a larger, multicentre study. Two alternate-day dosing regimens (2 mg/kg and 1 mg/kg) were compared with placebo over a 4-year period in 285 children aged 6–14 years. There were benefits to lung function but growth retardation, glucose abnormalities and cataracts occurred even at the lower dose of prednisone, and the treatment limb at the higher dose had to be discontinued early

because of unacceptable side-effects [447,448]. Although long-term steroid therapy is inappropriate because of this, there may be a place for short courses or inhaled treatment. A 12-week course of prednisolone produced improvements in lung function and serum IgG and cytokine concentrations [449]. Early results from trials of inhaled steroids are equivocal but suggest the approach is worth pursuing [450–452].

### Non-steroidal anti-inflammatory drugs

NSAIDs have anti-inflammatory effects, for example ibuprofen can inhibit neutrophil migration and release of lysosomal enzymes. In a rat model of chronic endobronchial infection with *Ps. aeruginosa*, ibuprofen decreased inflammation without increasing the lung burden of organisms, probably in part by interfering with the production of leukotriene B<sub>4</sub> [453,454]. In patients it proved possible to achieve the necessary blood levels without overt side-effects [455]. A 4-year trial of ibuprofen was then conducted in 85 patients with mild lung disease aged 5–39 years. Treated patients had less decline in lung function and chest radiographic scores, preserved body weight and tended to have fewer hospital admissions than placebo-treated patients [456]. However, the effects were most pronounced in the youngest patients (5–13 years), while the data for adults were not impressive. Given that NSAIDs may cause serious problems at times, the case for treatment of adults has yet to be made.

### Antiproteases

Elastase, predominantly from neutrophils, is found in the active state, often in high concentrations, in CF sputum. This implies that the natural inhibitors of neutrophil elastase in the airways,  $\alpha_1$ -antitrypsin, secretory leukocyte protease inhibitor (SLPi) and elafin, have been 'overwhelmed' by the total elastase burden. Elastase has proinflammatory effects as well as tissue-destructive actions. It cleaves complement components to active chemotactic products and induces release of IL-8 from epithelial cells. Antielastases should therefore exert anti-inflammatory as well as tissue-protective effects. The definitive studies have yet to be done but the principles of treatment have been addressed. A preliminary study in 12 patients showed that nebulized  $\alpha_1$ -antitrypsin twice daily for 1 week suppressed elastase activity [457]. Aerosolized recombinant SLPi 100mg twice daily to 16 patients decreased active elastase and IL-8 in the airways [458], although a lower dose failed to decrease elastase [459]. This area of management requires further study. Empirically, an antielastase delivered via the circulation appears to have greater likelihood of action at relevant sites than nebulized drug.

## Newer therapies in development and trials

### Therapies based on CFTR defects

CFTR mutations that involve premature stop codons lead to early termination of CFTR mRNA (class I mutations) (see Fig. 30.2). Some aminoglycoside antibiotics can suppress these nonsense mutations and restore full-length CFTR mRNA protein to the cell [460]. There are a number of current trials of intranasal gentamicin in patients who carry two such mutant alleles (e.g. G542X, R553X, R1162X or W1282X).

Class II trafficking mutations, such as  $\Delta F508$ , are defective with respect to structural assembly in the endoplasmic reticulum and are not efficiently glycosylated or transported to the cell surface. The  $\Delta F508$  protein retains some chloride channel function and may be more readily transported to the cell surface by treatment with 'chemical chaperones' such as glycerol. These are thought to facilitate protein folding and stabilize protein structure, thus promoting processing and trafficking to the cell surface [461]. A number of chaperones are being investigated *in vitro* in order to identify candidates for *in vivo* study. An alternative agent is phenylbutyrate, an oral analogue of butyrate, which was developed to treat urea cycle disorders. Phenylbutyrate regulates the expression of many genes, including CFTR, and promotes trafficking of the  $\Delta F508$  protein *in vitro* and *in vivo*. Encouraging phase I trials have been conducted at Johns Hopkins, Baltimore and been reported at the North American CF Meeting [462].

Class IV mutations have partial responses to cyclic AMP stimulation. A number of agents that may increase CFTR activation are being investigated. Milrinone is a phosphodiesterase inhibitor that improves chloride conductance by  $\Delta F508$  in a mouse model of CF [463]. Genistein is a tyrosine kinase inhibitor that augments chloride channel activity in CFTR via inhibition of protein phosphatase and possibly by a direct effect on CFTR itself [464,465]. The xanthine A<sub>1</sub> adenosine receptor antagonist 8-cyclophenyl-1,3-dipropylxanthine specifically activates the  $\Delta F508$  chloride channel [466] and a phase I trial is in progress. Any of these compounds, or their successors, might be used alone or in combination with other agents.

### Gene therapy

The goal in gene therapy of CF is the replacement of CFTR function at a level that will prevent the progressive damage to the airways. Ideally, this would be targeted at children before the onset of pulmonary disease. The success or failure of gene therapy depends to a great extent on how much transgene expression is needed to correct the phenotype. Some individuals who are phenotypically

normal have up to 92% abnormally spliced mRNA, which results in a defective protein [69]. This suggests that less than 10% of normal mRNA expressed in airway cells may be sufficient. However, since the majority of cells of the respiratory epithelium are terminally differentiated, vectors for CF gene therapy must be able to infect non-dividing cells. Both viral and non-viral strategies have been considered and numerous studies have demonstrated the principles of *in vivo* gene transfer in a variety of animal species.

Adenoviral vectors have been based on adenovirus serotypes 2 or 5, which exhibit tropism for the respiratory epithelium. Potential advantages of adenovirus vectors include this natural tropism for airway epithelium, the ability to transduce non-dividing cells and the capacity to be produced in high titre. Initial animal studies [467] demonstrated that adenoviral vectors could deliver transgene to all major cell types of the respiratory epithelium. However, these preclinical studies also made clear that adenovirus administration is associated with a dose-dependent inflammatory response and a (consequent) loss of transgene expression [468–470].

Adeno-associated virus vectors have also been considered for CF gene therapy. Like adenovirus, they exhibit tropism for the respiratory epithelium and are able to infect non-dividing cells. In contrast, they are naturally replication deficient and are not associated with any known human disease. However, they are small and CFTR cDNA is at the upper limit of packaging size, which places constraints on which promoter and enhancer can be incorporated. *In vivo* studies in rabbits [471] and monkeys [472] have demonstrated that safe and efficient delivery of transgene can be achieved following endobronchial administration, with expression persisting up to 6 months and no evidence of inflammation or other toxicity. On this basis phase I clinical trials have been initiated.

Cationic liposome-mediated gene delivery was first described in 1987 [473] and has been widely used to transfer DNA to a variety of cell types *in vitro* and *in vivo* [474]. Unlike adenoviral vectors, liposomes are non-immunogenic and offer advantages in terms of bulk production and quality control. Cationic liposome-mediated gene delivery to the airway was first demonstrated in mice in 1989 [475], and delivery and expression of CFTR in the airways of normal mice in 1992 [476]. Correction of the cyclic AMP-dependent chloride transport defect in CF mutant mice followed [477,478] and, subsequently, phase I clinical trials.

To date, nine clinical trials involving 78 CF patients have been published [16,479–486] and at least four others are in progress. These clinical trials have progressed from an open, uncontrolled study using the nasal epithelium of three patients to nebulized administration of the vector to the whole airways. They have clearly demonstrated that

the principle of transfer and expression of normal CFTR cDNA to airway epithelium can be achieved by both viral and non-viral approaches. However, in all of these trials there was low efficiency of gene transfer and no ideal method of judging the adequacy of correction of the physiological defect. Furthermore the expression of transgene was transient, lasting less than 2 weeks in most cases, confirming the need for repeated administration. Studies with current adenoviral vectors suggest that the presence of neutralizing antibodies raised against an initial administration severely limits the efficiency of subsequent doses. Clearly, improvements in delivery and persistence of expression are required for any realistic prospect of therapeutic benefit. Attempts have been made to reduce the immune response by modifications of the adenoviral genome, which reduces expression of adenovirus proteins [487], or by interfering with MHC class I expression on the cell surface of infected cells, thus suppressing viral antigen presentation [488,489]. For non-viral delivery systems the most important issue is to improve the efficiency of transfection. Cationic liposome-based gene therapy has the further drawback of being non-specific. Attempts have been made to circumvent this problem by incorporating ligands for cell surface molecules into the DNA–liposome complexes. However, despite initial successes *in vitro* [474], this approach has yet to be proved *in vivo*. Effort has gone into the development of novel cationic liposome formulations and to optimizing formulations of currently available liposomes by mixing with neutral colipids [490]. Some of these novel cationic liposomes appear more inflammatory than the original formulations, raising concerns for clinical safety. The first reports of a phase I clinical trial involving application of the cationic lipid GL67 to the lung supports such concerns.

Thus, after 5 years of clinical gene therapy trials (and only 9 years after identification of the CF gene), trial results hold promise of effective therapy but, realistically, the delivery of that promise appears a further decade away.

### **Holistic care for adults and adolescents with cystic fibrosis**

The idea that the management of CF can be neatly packaged into therapeutic areas (exciting and new though they are) avoids the realities of care. Patients' problems are psychosocial as well as physical and require holistic care provided by a team of experienced people. Adolescents with CF have all the problems of healthy adolescents but compounded by physical limitations and additional requirements. The extra nutritional needs and the time for self-treatment (physiotherapy, nebulized therapies) test patient adherence to the limits. Educational pressures, limitations on close contact with friends with CF (*B. cepacia*



transmission), parental difficulties in 'letting go', and the move from paediatric to adult clinic care all severely test patients' emotional strengths. Transition clinics, with adult clinic team members meeting the patients in their familiar paediatric clinic surroundings, and contact with patients and families in their home surroundings may smooth the passage of patients into adult clinics. Adults too have many psychosocial problems that have to be addressed. These include independent living, establishment of permanent relationships and further education and employment, usually in the face of declining physical health. Generally, carers in CF centres are experienced in the support of patients with regard to employment and education [491].

It remains a little unclear how the health problems of CF

patients influence their quality of life. Often psychological studies find similar quality-of-life scores to people with minor health problems and even healthy controls [492–494]. However, this may reflect the limitations of the tools used to measure quality of life and patients' reduced expectations. Certainly their health perceptions impact on their therapies. One study has suggested that patients who cope well with their disease may be less adherent to their various management regimens than those who worry about their disease and who perceive that they have little personal control over it [495].

All these issues emphasize the need for 'art' as well as 'science' in providing care for CF and the need to be involved in the 'whole' patient contributes to the rewarding nature of CF management.

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# PULMONARY FIBROSIS

ANTHONY SEATON

Pulmonary fibrosis is the end-result of a multiplicity of pathological processes, from infections to autoimmune diseases. Many of these are of unknown aetiology but have characteristic features that allow them to be classified as distinct disease entities. Among them is one that typically occurs in older males, is slowly progressive, poorly responsive to therapy and has well-defined clinical, radiological, pathological and functional characteristics, known as idiopathic pulmonary fibrosis or cryptogenic fibrosing alveolitis. The latter term, coined by Scadding [1], is probably to be preferred as it emphasizes the inflammatory reaction in the alveoli that precedes the fibrosis. The danger implicit in either term is that all patients with pulmonary fibrosis are labelled 'of unknown aetiology' and the doctor forgets that all diseases must have a cause that is worth seeking. As with cardiac failure, the term 'pulmonary fibrosis' describes a clinical end-point of many different pathological processes, and the adjective 'idiopathic' or 'cryptogenic' should only be applied after appropriate thought.

In fact, the first description of the idiopathic condition concerned a rather atypical and acutely progressive variant, which still sometimes goes by the names of the original authors, the Hamman-Rich syndrome. They described five patients with progressive dyspnoea, following a fulminant course and leading to death with cor pulmonale or respiratory failure within 6 months [2,3]. It subsequently became apparent that this form of the disease was uncommon and that the majority of patients pursue a more chronic course lasting for several years [4-6].

Cryptogenic fibrosing alveolitis is a progressive fibrosing inflammatory disease of the lung of unknown aetiology. Most patients present with dyspnoea, although some are detected at an asymptomatic stage by the coincidental finding of clubbing, crepitations or radiological changes. Bilateral pulmonary crepitations are almost always audible and finger clubbing is often present. In the author's experience, very marked clubbing denotes a more chronic process. Lung function testing shows a

restrictive defect with diminished gas transfer, and inflammation and fibrosis are evident distal to the terminal bronchioles on lung biopsy. Similar clinical, radiological and pathological findings may occur in pulmonary fibrosis associated with connective tissue diseases (see Chapter 53), asbestosis (see Chapter 54) and certain drugs (see Chapter 55).

## Aetiology

By definition, cryptogenic fibrosing alveolitis is of unknown aetiology. However, this should not close the clinician's mind, since the disease must have some cause or causes, be they genetic or environmental. As with most diseases it is likely that there will eventually prove to be several contributing environmental causes operating in someone who is genetically susceptible. There are now some clues relevant to both factors.

The evidence for a genetic cause is not strong, most cases occurring quite sporadically. However, many familial cases have been described [7-11], including the finding of subclinical disease in relatives of patients [12]. Occasionally the occurrence of the condition in monozygotic twins separated from birth has suggested a genetic influence [10,13]. When the condition occurs in families it is probably transmitted as an autosomal dominant with incomplete penetrance. No consistent association with human leucocyte antigen (HLA)-A or HLA-B foci has been found [14-16], although one study has recorded an increased frequency of the B-cell alloantigen HLA-DR2 in patients (65%) compared with controls (26%) [17]. Studies of gene loci in patients with familial disease have also been confusing, in some subjects pointing to loci on chromosome 14 and in others to chromosome 6 [11,18]. Evidence from animal studies and from studies of human responses to fibrogenic stimuli due to drugs suggests that individuals differ on a genetic basis in their lung fibrogenic responses, although it is likely that these differences are mediated by complex mechanisms that probably differ from person to person. They presumably involve the

genotypic control of HLA type or of any one or more of the large number of cytokines and receptors involved in the processes between the environmental stimulus and the deposition of collagen [19,20].

The more likely primary causes in most cases are environmental. This is supported by the considerable similarities between the cryptogenic disease and pulmonary fibrosis caused by asbestos and cytotoxic drugs, by the increasing evidence that the condition is becoming more prevalent and by the differences in trends in different countries, evidence not wholly explained by changes in diagnostic preferences [21–23]. It has been suggested that there is an association with infection by Epstein–Barr virus, although studies of viral genes have shown markedly different frequencies [24,25]. Nevertheless, patients not infrequently give a history suggestive of viral infection prior to the development of the disease [26]. Diffuse fibrosis has also followed infection by *Mycoplasma* [27], and a study in rats has suggested that adenovirus gene products in type II alveolar cells may be capable of promoting type I collagen formation [28].

Infectious causes aside, a case–control study has suggested that in up to about 20% of patients with the disease, exposure to wood or metal dust at work may have been an aetiological factor [29]; a recent British study of 588 patients has shown 47% to have had a history of a dusty occupation [30]. Recent work suggesting that the toxic effects of the ultra-fine fraction of particulate air pollution may lie in the transition metals on the particle surface (see Chapter 11) points towards what may be an interesting line of future research in this area [31]. Further evidence for an environmental factor comes from another case–control study in which it has been shown that cigarette smoking is a risk factor [32]. Another important clue to the aetiology is the occurrence of pulmonary fibrosis in rheumatoid and other collagen diseases. In the absence of the clinical manifestations of these diseases, rheumatoid factor and antinuclear factor are found in a proportion of patients with cryptogenic fibrosing alveolitis, suggesting a spectrum of response to whatever it is that causes these diseases. Again, the association of collagen diseases with quartz exposure [33] (see Chapter 54) serves as a reminder that these may also have environmental causes.

## Epidemiology

Cryptogenic fibrosing alveolitis is a disease affecting males rather more frequently than females, the median age at diagnosis being in the seventh decade. However it may occur in either sex at any age. The prevalence has been estimated, using somewhat different methods, to be about 6 per 100 000 in England and Wales and 20 per 100 000 in the USA [34,35]. It is the cause of some 2000 deaths annually in the UK and 10 000 annually in the USA. It appears to be becoming a more frequent cause of death

in the UK, Australia and Canada, and this may reflect a real rise in incidence as well as greater diagnostic awareness [21,23]. It seems to show no racial preference and is diagnosed in developing as well as developed countries [36].

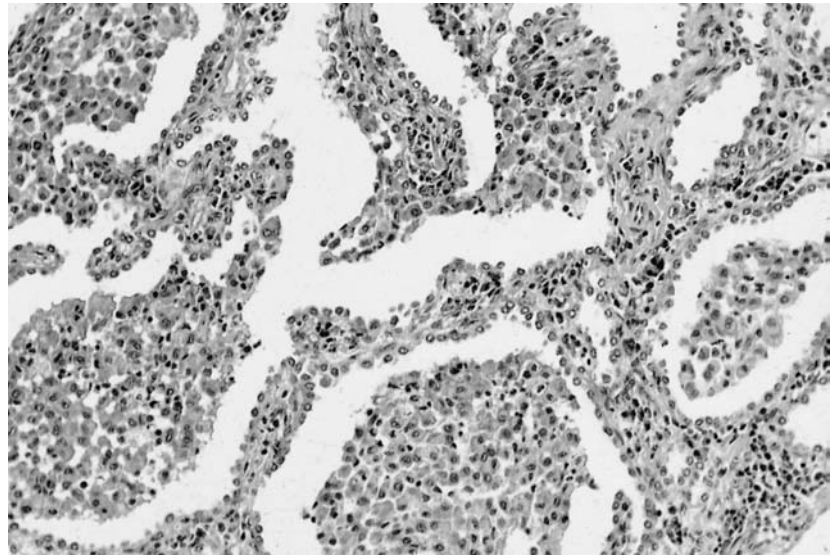
## Pathology

In many patients with features suggesting a diagnosis of cryptogenic fibrosing alveolitis, a lung biopsy is carried out to provide both diagnostic and prognostic information prior to the initiation of therapy. Transbronchial lung biopsy is not suitable for establishing this diagnosis and open, trephine or, most frequently nowadays, thoracoscopic lung biopsy should be employed to obtain satisfactory tissue specimens [37–41]. There are two principal features of the disease identifiable on the biopsy: (i) cellular thickening of the alveolar walls with a tendency to fibrosis and (ii) the presence of large mononuclear cells within the alveolar spaces. The more prominent the second feature and the thinner the alveolar walls, the better the response to corticosteroid drugs [5,39,42]. In early disease, proliferation of type II alveolar epithelial cells and loss of type I cells may be seen [43]. The intra-alveolar mononuclear cells, once thought to be type II alveolar cells, are now known on the basis of ultrastructural and cytochemical studies to be predominantly alveolar macrophages [44–48]. Other cells, including lymphocytes, eosinophils, neutrophils and plasma cells, may be seen both in the interstitium and the alveoli. At an early phase, there may be fibrinous exudate in the alveoli with hyaline membrane formation. In the later stages, the lung architecture is distorted by fibrosis and there may be hyperplasia of the bronchiolar epithelium to line the residual airspaces. Interestingly, the collagen content of the lung does not differ from that found in controls but the ratio of type I to type III collagen is increased from 2:1 in controls to 4:1 in fibrosing alveolitis, reflecting increased production of type I collagen by the fibroblasts [49,50]. Release of fibronectin and alveolar macrophage-derived growth factor is not suppressed by corticosteroid therapy in these patients, which may explain the relatively poor response to such therapy [51]. Haemosiderosis and squamous metaplasia of bronchiolar and alveolar epithelium may occur [52,53], and occasionally deposits of bone may be found [54,55]. B-lymphocyte follicles with occasional germinal centres and containing helper T cells may be seen and indicate a local B-lymphoid immune response [56]. Occasionally when a particular cell type predominates, for example the lymphocyte, giant cell or plasma cell, the terms lymphocytic, giant cell or plasma cell interstitial pneumonia are used, although this differentiation is probably not clinically useful since all are likely to progress to end-stage fibrosis.

Livingstone and colleagues [57] divided their cases



**Fig. 31.1** Open lung biopsy from patient with a diffuse pneumonitis on radiography showing thickened alveolar walls lined by hyperplastic type II cells. The alveoli are filled with a mixture of macrophages and desquamated type II cells. This is the pattern of 'desquamative interstitial pneumonitis' (haematoxylin & eosin  $\times 150$ ).



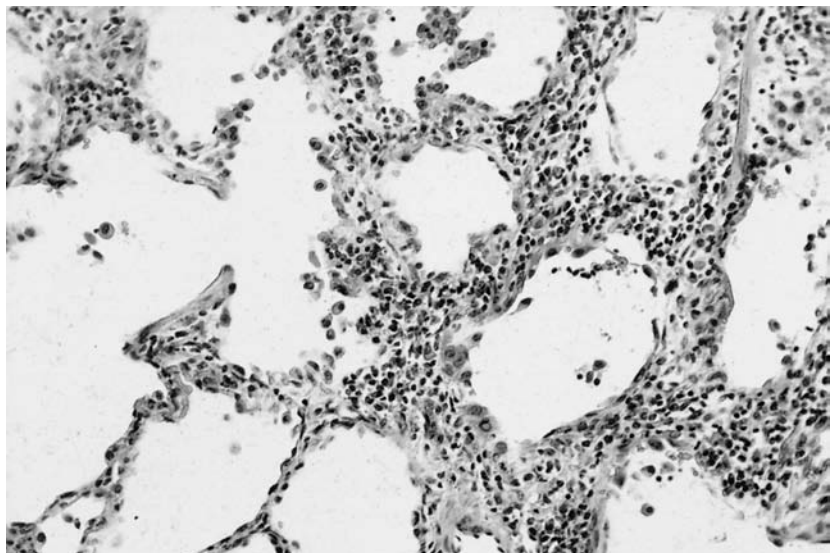
pathologically into five grades according to the amount of disruption of lung architecture. Grade I is the mildest stage, in which change is confined to the alveolar walls, the alveolar spaces being empty. In grade II, the architecture of the lung is still intact, although the alveolar space is now filled with fluid or cellular exudate. In grade III, the alveolar architecture is becoming blurred and perhaps lost altogether, though bronchioles may still be recognized. Elastic fibre staining shows that the alveolar pattern is no longer intact. In grade IV, the normal lung structure is distorted by fibrosis, although remnants of bronchiolar epithelium and muscle may still be recognized. In grade V, the lung is converted to cystic spaces varying in diameter up to 1 cm or more. Grades IV and V commonly coexist and correlate with the presence of honeycombing on the chest radiograph, whereas grades I and II more often show

fine and coarse mottling on the chest film and a ground-glass appearance on high-resolution CT (HRCT).

The terms 'usual' and 'desquamative' interstitial pneumonitis have been used by pathologists to describe discrete pathological and clinical entities [6,58,59]. Most workers now consider 'desquamative' change to indicate the early stage of the disease with active alveolitis and minimal fibrosis (Fig. 31.1) and 'usual' change to indicate the late stage of the disease when fibrosis is established and alveolitis is minimal (Fig. 31.2) [1,60,61].

Injection studies have shown a dramatic increase in bronchial arteries with numerous precapillary bronchopulmonary anastomoses. In contrast, pulmonary angiograms show the peripheral pruning characteristic of pulmonary hypertension [62]. Pulmonary muscular hyperplasia may occur in some patients, resulting in

**Fig. 31.2** Open lung biopsy from patient with a familial type of interstitial lung disease showing expanded alveolar walls containing an interstitial infiltrate of chronic inflammatory cells and some fibrosis. A few hyperplastic alveolar lining cells are visible. This is the pattern of 'usual interstitial pneumonitis' (haematoxylin & eosin  $\times 150$ ).



pathological descriptions of 'bronchiolar emphysema' or 'muscular cirrhosis of the lung' [63–65]. Most such examples are probably variants of fibrosing alveolitis and radiologically honeycombing is common.

## Pathogenesis

The pathogenesis of cryptogenic fibrosing alveolitis is not understood. This statement is intended to prevent the reader feeling discouraged when confronted by all the trees and wondering where the wood is. After a promising start, most reviews of the subject finish as an enumeration of cytokines that may or may not be important, leaving the reader somewhat bewildered, as one might perhaps feel from trying to appreciate a symphony by studying small collections of notes played by individual instruments.

It may be helpful to think of the condition as an aberrant defensive reaction at the alveolar level, these defences having evolved specifically to deal with invading airborne microorganisms. The unknown initial stimulus, candidates for which have been discussed above, appears to initiate an uncontrolled inflammatory reaction that involves recruitment of macrophages, neutrophils and smaller numbers of other cells including lymphocytes, eosinophils and mast cells. This inflammatory reaction leads in turn to 'healing' by inappropriate alveolar wall fibrosis and destruction of the normal alveolar wall of type I and endothelial cells, with proliferation of type II cells, the normal progenitors of the type I cell. It is noteworthy that emphysema, which often accompanies fibrosis in sarcoidosis, allergic alveolitis and mineral pneumoconioses, is not a common feature of the cryptogenic disease but that late development of carcinoma is — this is the wood.

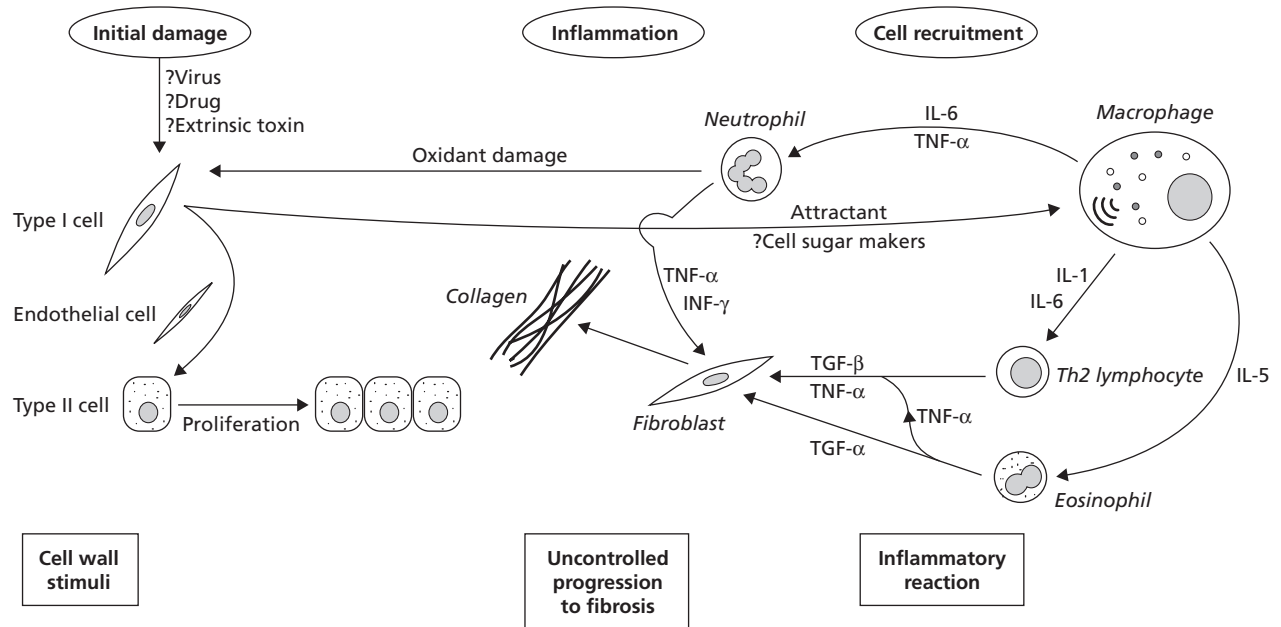
Whatever triggers the process, mystery number one, seems to be responsible for attracting the greatly increased numbers of alveolar macrophages, which in turn attract other inflammatory cells, leading to the alveolar wall damage. Mystery number two is why this process continues and is not checked, as it is in almost all infective alveolar inflammatory conditions. The answer to this is likely to be that the triggering stimulus remains *in situ*, perhaps as a consequence of virus-induced genetic change in epithelial or endothelial cells. This would be analogous to the pathogenesis of asbestosis, where the fibres remain embedded at alveolar level and continue to stimulate macrophage ingress, and consistent with bleomycin-induced fibrosis that generally arrests when the drug is stopped. However, another possibility is that the lungs in some people lose their ability to downregulate the inflammatory response, making them unable to control the process once initiated. This would be consistent with the studies of familial fibrosis and with the observation that the disease occurs only in relatively few of those people treated with bleomycin. It is possible, indeed likely, that

both mechanisms may operate together in those unfortunate enough to develop the disease.

Research intended to elucidate the pathogenetic mechanisms has studied both these possibilities. Less effort has been expended on what at first sight might appear more fundamental, the initial triggering factors and possible alterations in alveolar cells. The majority of the effort seems to have been devoted, perhaps understandably, to a search for cytokines that may be present to excess and therefore possibly amenable to drug therapy [66,67]. With respect to the former, the most promising research relates to alteration of cultured rat alveolar cells by adenovirus infection, leading to increased type I collagen production [28]. Viral alteration of the genetic material of alveolar cells could lead not only to uncontrolled fibrosis but also to the development of carcinoma, which is a feature of the condition.

The aspect of pathogenesis that has attracted most attention is the link between inflammatory cells, once recruited, and the deposition of fibrosis. Studies have concentrated on the demonstration of the actions of an increasingly large number of cytokines and cell receptors able to stimulate fibrogenesis, in the hope that an understanding of these mechanisms may lead to the development of drugs able to block them. Of the cytokines, those currently attracting most interest are transforming growth factor (TGF)- $\beta_1$  and tumour necrosis factor (TNF)- $\alpha$  [68]. TGF- $\beta_1$  has been shown to be able to cause expression of the gene for procollagen in fibroblasts, increase protein synthesis and inhibit breakdown of collagen. TNF- $\alpha$  has also been shown to cause increased collagen formation and is released in increased amounts from macrophages of patients with fibrosing alveolitis. In the case of both cytokines, there is experimental evidence that their fibrogenic action may be inhibited by antibodies, thus raising hopes of possible future therapeutic options [69,70]. Other cytokines that may play a part in fibrogenesis include platelet-derived growth factor and insulin growth factor 1. Endothelin 1, derived from capillary endothelial cells, may have a similar effect [71]. Finally, there is increasing interest in the presence of coagulation activity in the lung, based on the production by alveolar macrophages of thromboplastin and factor VII [72,73]. The very number of substances thought to be of interest in the genesis of lung fibrosis, and the fact that all are inflammatory cell products normally available and controlled by homeostatic mechanisms, indicate the difficulties that still lie ahead of those who hope to discover a curative treatment.

To pursue the symphonic analogy, the cytokines are the notes while the instruments are the inflammatory cells. Typically, in active cryptogenic fibrosing alveolitis, the total number of cells obtained at lavage is increased, with significant increases in percentages of neutrophils and eosinophils and occasionally a small increase in percentage of lymphocytes. Although the macrophage percent-



**Fig. 31.3** An outline scheme for the pathogenesis of cryptogenic fibrosing alveolitis. The initial stimulus to inflammation, acting through macrophage recruitment, and the reasons for uncontrolled progression to fibrosis are unknown.

age is usually decreased, the absolute numbers of macrophages are much increased [74–76]. A scheme, necessarily simplified, of some of the roles of each cell type in the pathogenesis of the disease is discussed below (Fig. 31.3).

### Alveolar macrophages

Not only are the alveolar macrophages increased in numbers in cryptogenic fibrosing alveolitis but the macrophages are activated, as demonstrated by increased surface expression of markers [77,78]. They have been shown to secrete a large number of cytokines, including interleukin (IL)-1, IL-6 and IL-12, interferon (IFN)- $\gamma$ , granulocyte-macrophage colony-stimulating factor (GM-CSF), TGF- $\beta$  and TNF. Mechanisms promoted by these substances are able between them to explain attraction and activation of further macrophages, neutrophils and lymphocytes [79–83]. However these mechanisms are all designed for anti-infection purposes and why they go awry in pulmonary fibrosis remains unknown.

### B lymphocytes

Although the percentage of lung B lymphocytes is not usually increased in cryptogenic fibrosing alveolitis, the absolute number is increased because the total number of lymphocytes is increased several-fold. B-lymphocytic fol-

licles with germinal centres have been identified in lung tissue from patients with cryptogenic fibrosing alveolitis [56] and the number of B lymphocytes producing immunoglobulin, particularly IgG, is increased [84]. In keeping with these observations, IgG levels in bronchoalveolar lavage (BAL) fluid of fibrosing alveolitis patients are increased, suggesting that there is active local production of immunoglobulins [85,86]. Coupled with the finding of immune complexes in BAL fluid, this suggests that immunoglobulins are produced locally in the lung and combine with antigens to form complexes that may subsequently be demonstrated both in the lung and in circulating blood. The antigen or antigens against which the antibodies are directed have not been identified but the observation that blood lymphocytes from patients with fibrosing alveolitis release lymphokines on exposure to type I collagen suggests one possible antigenic site in the alveolar wall [87].

### T lymphocytes

The percentage of T lymphocytes is not increased in BAL fluid of patients with cryptogenic fibrosing alveolitis but the absolute numbers are, under the control of macrophage-derived cytokines including IL-6 and IL-12. There is a suggestion that a shift from the Th1 subtype (which produces IFN- $\gamma$ , a cytokine that suppresses fibroblast proliferation and collagen synthesis) towards the Th2 subtype (which produces IL-4 and IL-5, both of which have been implicated in fibrogenesis) may be relevant to the production of fibrous tissue [88]. IL-5 is an eosinophil chemoattractant, and the presence of eosinophils in pulmonary fibrosis is an indicator of poor prognosis.



## Neutrophils

As already noted, the percentage and total number of neutrophils have been shown to be increased in BAL fluid of patients with fibrosing alveolitis, though not all studies are consistent in this respect [74–76]. However, tissue concentrations of these cells and evidence of their elastase activity are considerably increased from normal [89]. Their presence is probably a response to macrophage-derived attractants, including IL-6, IL-8, GM-CSF and TNF- $\alpha$ . When activated, they can perpetuate the inflammatory response by producing IL-1, IL-8, IFN- $\gamma$  and TNF- $\alpha$  themselves. These neutrophils are cytotoxic to normal lung parenchymal cells and their cytotoxic properties are related to the release of reactive oxidant species [90,91]. This is consistent with the demonstration of myeloperoxidase in BAL fluid of patients with the disease [92]. In addition, one neutrophil protease, a collagenase, has been found in lavage fluids from patients with the disease and shown to be cytolytic to normal lung explants [93,94]. The damage to alveolar walls may therefore be secondary to release of reactive oxidant species and proteases from neutrophils. The identification of fibronectin fragments in lavage fluid from patients with cryptogenic fibrosing alveolitis suggests that fibronectin degradation may also be occurring *in vivo* [95].

## Eosinophils

Eosinophils are often increased in percentage and total numbers in BAL fluid of patients with cryptogenic fibrosing alveolitis, attracted by macrophage-derived cytokines particularly IL-6. They may damage normal lung parenchymal cells by release of cytokines, including TGF- $\alpha$  and TNF- $\alpha$ , and also release a collagenase capable of cleaving types I and III collagen [94,96,97]. Their presence is generally taken to indicate a poor response to treatment.

## Conclusion

The pathogenesis of cryptogenic fibrosing alveolitis appears to hinge around activation of alveolar macrophages. The triggers of this reaction are unknown but could be infections, environmental pollutants or both. The activated macrophages produce chemotactic factors leading to accumulation of increased numbers of neutrophils and eosinophils which, by the generation of reactive oxidant species and proteases, produce local lung damage. The generation of cytokines promoting fibrosis by these cells and by lymphocytes promotes the collagenous scarring found in association with the lung tissue destruction characteristic of this disease. The condition is characterized by a failure of control

mechanisms that would normally be expected to halt the repair process, and this may have a partly genetic aetiology.

## Clinical features

Cryptogenic fibrosing alveolitis [1,3,30,53,57,98] is approximately twice as common in males and most commonly presents in older patients, the mean age in the largest survey reported being 67 years [30]. It commences in some 90% of patients with progressive dyspnoea on exertion. A non-productive cough is present in 75% at presentation. About 5% of patients are discovered at an asymptomatic stage by an incidental chest film or by a doctor hearing crepitations at the bases. The subacute, rapidly progressive type of the disease originally described by Hamman and Rich is much less common than the more slowly progressive chronic form of the disease, and may declare itself as an illness with systemic symptoms such as fever, weight loss, fatigue, myalgia and arthralgia

Finger clubbing is found in about half the patients, while auscultation of the chest reveals bilateral, gravity-dependent, inspiratory crepitations. With progression of disease, cyanosis becomes a feature and evidence of pulmonary hypertension may be found. In some patients, signs of connective tissue disease, such as rheumatoid arthritis, systemic lupus erythematosus or scleroderma, may coexist (see Chapter 53). Subgroups of patients with associated digital vasculitis or peripheral neuropathy have also been described [99,100], and rare associations with chronic active hepatitis and autoimmune haemolytic anaemia have been reported [101]. Hypertrophic pulmonary osteoarthropathy and spontaneous pneumothorax may occasionally occur [102,103]. Bronchogenic carcinoma is 14 times more common in patients with cryptogenic fibrosing alveolitis than in a control population [104]. In one series, carcinoma showed the usual distribution of histological types and was found in 13% of 155 patients followed to death [104].

The course of the disease is very variable. It ranges from an acute, rapidly progressive condition that may progress to death within months to a very slowly progressive or even apparently arrested pulmonary fibrosis. Most patients fall between these extremes and show gradual deterioration over 3 or 4 years. It is not uncommon in such circumstances to find that chest films taken several years before symptoms developed show early changes of fibrosis. In general, the younger the patient and the more acute the history, the more likely is the condition to respond to treatment. However, in an initial report of the large UK study 47% of patients had died within 2–4 years of enrolment, indicating a poor overall prognosis with or without treatment [30].

## Radiology

### Chest radiography

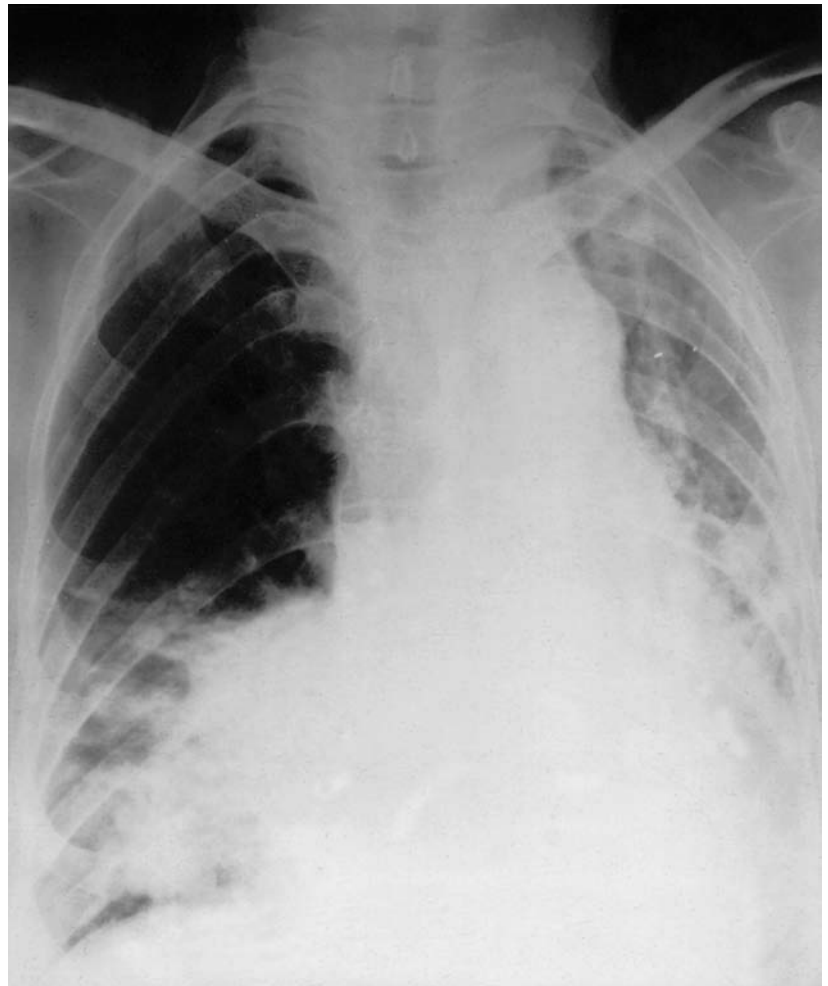
In the early stages the chest film can be normal despite the presence of dyspnoea. In one study of lung biopsies in breathless patients, 26% of 47 with a 'desquamative' histological picture had normal films compared with only 7% of 68 with the 'usual' type of alveolitis [105]. In the subacute type of disease, the initial chest radiograph may resemble bronchopneumonia with extensive patchy shadows, confluent in places, and more extensive in the lower zones (Fig. 31.4). In the commoner chronic type, mottling may give rise to a ground-glass appearance, although more often individual shadows up to 2 mm in diameter may be identified and these may later increase in size (Fig. 31.5). In the majority of patients the shadowing is predominantly in the lower zones. As the shadowing coarsens, translucencies up to 3 mm in diameter may appear, and this may finally develop into classical honey-comb lung (Fig. 31.6). Larger translucencies may also

occur and, in the later stages of the disease, emphysematous bullae and irregular streaky fibrosis may be seen [106]. Shrinkage of the lungs occurs, with progressive elevation of the diaphragms. In the presence of cor pulmonale the proximal pulmonary artery shadows increase in diameter.

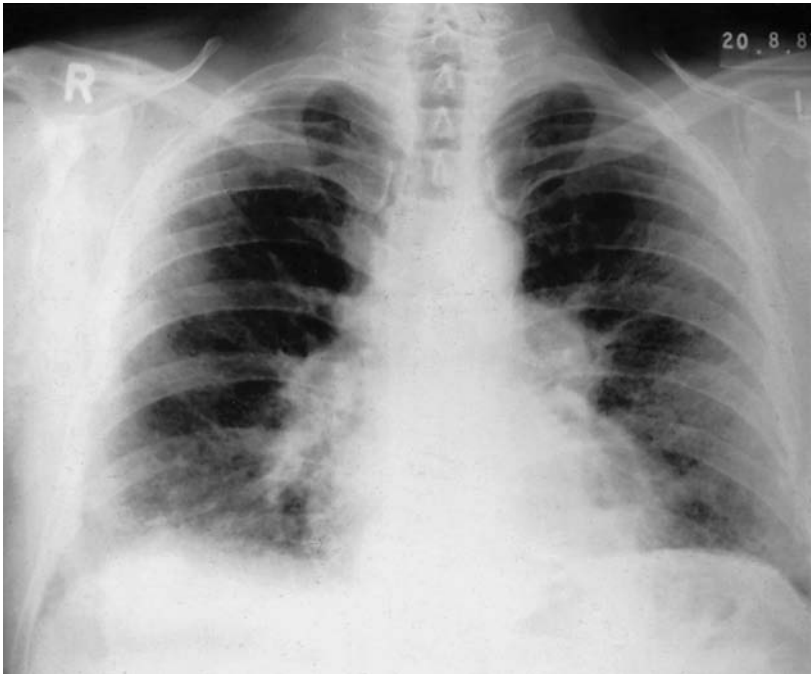
When the disease is advanced, bronchograms may show shrinkage of the lung and bronchial dilatation. In the late stages, the distortion of lung architecture is reflected in bronchiolectasis and bronchial distortion [57]. In one reported case, diffuse dense mottled opacities seen on the chest film proved to be deposits of bone, some containing marrow cavities [55].

### Computed tomography

Because of the risks associated with lung biopsy and the generally poor response to treatment, non-invasive diagnostic methods find favour with most clinicians, especially in older patients. The dilemma regarding the decision to investigate has been made less taxing by the



**Fig. 31.4** Chest film of a female with a relatively rapid onset of pulmonary fibrosis. The patient presented with increasing breathlessness over 9 months. After 2 months of treatment with corticosteroids, the left lung remained unchanged but much clearing had occurred in the right lower zone.

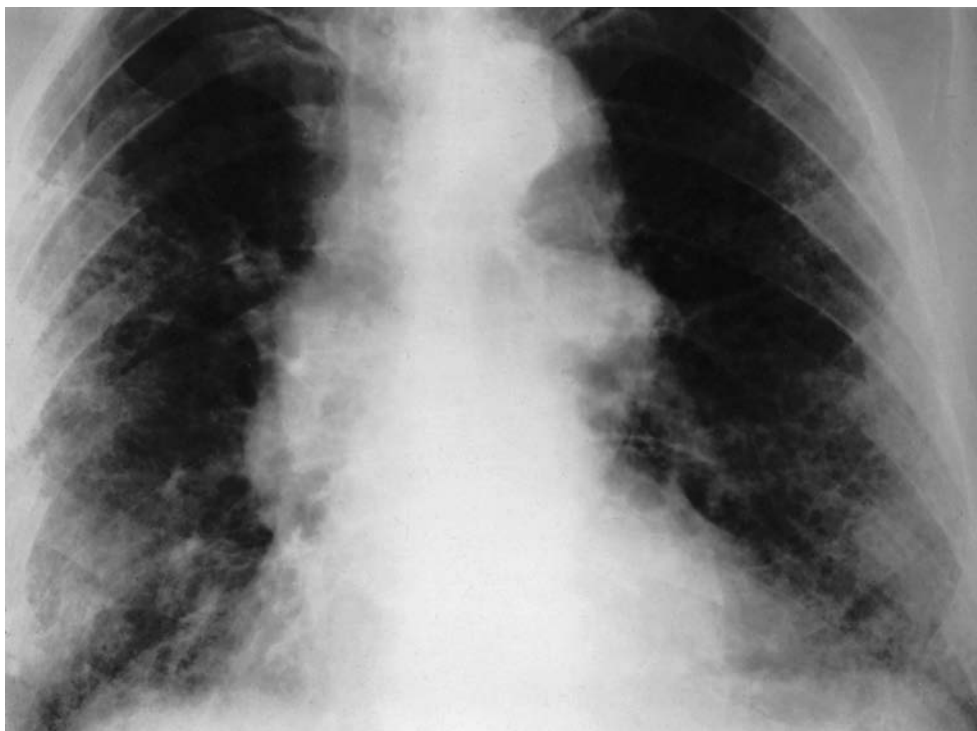


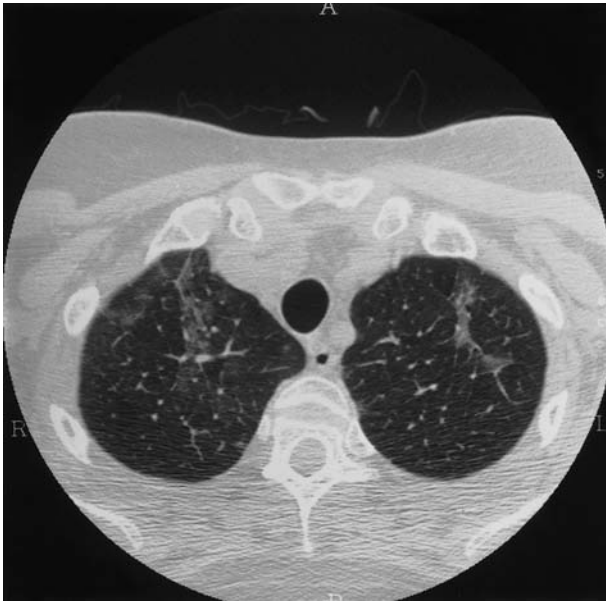
**Fig. 31.5** Chest film of a patient with early fibrosing alveolitis showing diffuse, predominantly lower zone, micronodular infiltrates. This patient made a good response to corticosteroids.

advent of HRCT [107,108]. The features found on HRCT reflect histopathology quite well [109] and three types of shadow may be recognized. Early, active inflammatory disease is characterized by a ground-glass appearance,

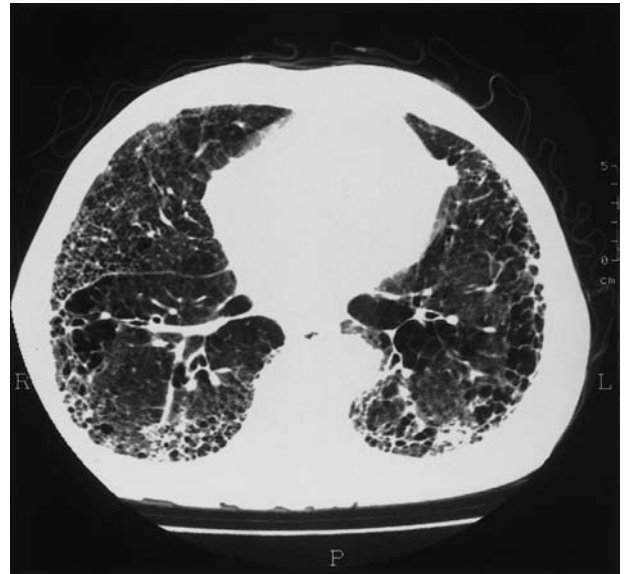
**Fig. 31.6** Extensive honeycomb change in a patient with slowly progressing, irreversible fibrosis.

with hazy attenuation of the normal lung parenchyma but preservation of vascular shadows (Fig. 31.7). Usually such appearances coexist with areas of more mature fibrosis in the same film, and if biopsy is to be carried out it should be directed at an area of ground-glass opacity. As fibrous tissue is laid down, the appearances are of thickened interlobular and intralobular septa, giving a reticular pattern





**Fig. 31.7** High-resolution CT of patient with predominantly 'desquamative' alveolitis, in this case associated with rheumatoid disease, showing patchy ground-glass appearances. (Courtesy of Dr Lesley Gomersal.)



**Fig. 31.8** High-resolution CT of patient with 'usual' type of fibrosing alveolitis showing reticular pattern of interlobular and intralobular fibrosis. (Courtesy of Dr Lesley Gomersal.)

(Fig. 31.8); the distribution of shadows is predominantly lower zone and subpleural initially, though as the disease progresses it becomes more generalized. Finally, mature fibrosis with bronchial ectasia and destruction of lung architecture is represented by thick-walled cystic changes 5–10 mm in diameter, so-called honeycombing (Fig. 31.9). In smokers, emphysematous changes in the upper zones often coexist with the fibrosis [110].

These appearances are reasonably characteristic and, taken with the clinical features, allow a confident diagnosis to be made in most cases. They do not differ in any important respects from the changes seen in systemic sclerosis or asbestosis, although the differentiation from these diseases is made on other clinical grounds and, in the case of asbestosis, by the frequent presence of associated pleural lesions. In younger patients, differentiation from the rare diseases, Langerhans' cell histiocytosis and lymphangioleiomyomatosis, is aided by the more generalized appearances, nodular change and thinner-walled cysts in these conditions.

### Gallium-67 lung scanning

Pulmonary uptake of gallium occurs in many diffuse interstitial lung diseases, including cryptogenic fibrosing alveolitis [76]. The pattern of uptake is usually diffuse and confined to the lung parenchyma. Such scans are positive in about 70% of all patients with cryptogenic fibrosing alveolitis [76,98], and the intensity of gallium



**Fig. 31.9** High-resolution CT of patient with advanced disease showing honeycomb pattern of fibrosis with destruction of normal lung architecture. (Courtesy of Dr Lesley Gomersal.)

uptake correlates well with the degree of alveolitis on open lung biopsy and the percentage of polymorphonuclear leucocytes present in BAL fluid [111]. However, this technique does not make a major contribution to the clinical assessment of patients with cryptogenic fibrosing alveolitis.

## Pulmonary function

The lung volumes may be normal in early cryptogenic fibrosing alveolitis but as the disease progresses all the compartments of lung volume decrease, with a relatively greater reduction in vital capacity [98,112,113]. In the absence of extensive emphysema the forced expiratory volume in 1 s ( $FEV_1$ )/forced vital capacity (FVC) ratio is normal, although abnormalities in sophisticated tests of small airways function (e.g. frequency dependence of compliance, the terminal portion of the maximum expiratory flow–volume curve and the maximum flow–static recoil curve) correlate with morphological evidence of small airways disease [114,115].

The single-breath diffusing capacity for carbon monoxide is reduced early in cryptogenic fibrosing alveolitis [76,112]. In the early stages of the disease,  $Pao_2$  may be normal at rest but falls during exercise when the alveolar–arterial  $PO_2$  gradient is increased [76,116–119]. With progression of disease, resting hypoxaemia develops. The major part of this hypoxaemia can be explained by mismatching of ventilation and perfusion [120–122]. During exercise, because of the reduced transit time of erythrocytes in the pulmonary capillaries, up to 20% of the exercise-induced widening of the alveolar–arterial  $PO_2$  difference may be due to impaired oxygen diffusion [123]. Hypoxaemia in fibrosing alveolitis worsens during sleep, particularly in the rapid eye movement stage [119,124].

Lung compliance is reduced in fibrosing alveolitis, with greater transpulmonary pressure changes on breathing and consequent increase in the work of breathing, which may be responsible for the sensation of dyspnoea. Exercise tolerance is reduced and there is an increased heart rate and ventilatory response to exercise compared with normal individuals [125]. The maximal achievable exercise ventilation correlates with lung volumes. The tidal volume is reduced in proportion to the reduction in vital capacity and increased ventilation during exercise is achieved by increases in respiratory rate rather than by the predominant increase in tidal volume seen in normal subjects [125,126]. The 12-min walking test provides a useful measure of limitation of exercise tolerance in these patients [127].

## Bronchoalveolar lavage

BAL fluid usually shows an excess of neutrophils and eosinophils compared with normal non-smokers. There is considerable overlap, making this little use as a diagnostic test; it is more informative in a prognostic sense, in that high proportions of neutrophils (>4%) or eosinophils (>3%) are indicative of a poor response to steroids. A relative lymphocytosis (>11%) may also be an indicator of active alveolar inflammation and a better response to steroid treatment [128,129].

## Other investigations

The erythrocyte sedimentation rate is usually elevated in this disease, but apart from the occasional detection of antinuclear antibodies, rheumatoid factor, cryoglobulins or other autoimmune phenomena, no other abnormalities are found in the peripheral blood [98,130,131].

## Diagnosis

The diagnosis is suggested by the clinical features of dyspnoea, cough and bilateral basal crepitations in an elderly or middle-aged individual, the presence of reticulonodular shadowing predominantly at the lung bases on the chest film in the absence of a known cause, the typical findings on HRCT, and appropriate pulmonary function findings. In most cases these investigations are sufficient to make a confident clinical diagnosis, although differential cell counting of BAL fluid may assist in indicating likely response to treatment. The main decision required is whether to proceed to lung biopsy, which provides definitive proof of the diagnosis and somewhat better prognostic evidence. It has been established that the small specimens obtained by transbronchial biopsy through the fiberoptic bronchoscope are not suitable [37] and open or thoracoscopic lung biopsy, guided by HRCT to areas of active alveolitis if present, is preferred [37–41]. This therefore subjects the patient to some risk and discomfort and should be undertaken only if it is considered that knowledge of the histological appearances would influence the physician's treatment regimen. Thus the serious possibility of some other disease, more acute presentations or a relatively young patient in whom a very persistent trial of treatment, often including consideration of transplantation, is likely to be considered are usually influential factors in coming to a decision to proceed to biopsy. With appropriate ethical safeguards, biopsy would also usually be advised if the patient has agreed to participate in a trial of new therapy. Physicians differ in their practices but ultimately rather fewer than half of all patients are biopsied in the UK. In the majority of patients the clinical findings, including HRCT, give sufficient diagnostic information to justify a therapeutic trial monitored by response in terms of change in lung function. However, patients with an acute or rapidly progressive presentation in whom HRCT suggests active disease should almost always have early biopsy if considered fit enough, since the differential diagnosis of such patients is wide and treatment may well be influenced by the histological findings.

## Treatment

It is disappointing to record that the prognosis of this condition appears not to have altered appreciably nor has any important advance in treatment occurred since the first

edition of this book in 1969. The mainstay of therapy in cryptogenic fibrosing alveolitis remains corticosteroids, prednisolone being the drug of choice. Since occasionally the disease is very slowly progressive, or has even arrested, it is wise in patients suspected of such a course to allow a period of several months to elapse, monitoring the patient's lung function and exercise performance carefully in order to assess whether treatment is likely to be necessary. In fact, the major recent UK study showed that the option not to treat was taken in over 50% of cases [30]. After the diagnosis has been established and baseline measurements of pulmonary function (i.e. lung volumes, *DLCO* and exercise tolerance) have been obtained, treatment is usually initiated with prednisolone in a dose of 40–60 mg daily for at least 4 weeks. This is followed by a graduated reduction in dosage over 2–3 months to the lowest maintenance dose capable of sustaining any objective improvement in chest radiograph, lung volumes, exercise tolerance or *DLCO* that has been achieved. Objective improvement is most likely to be found in those with histological evidence of early disease with marked cellularity and little fibrosis on the lung biopsy [6,39], in younger patients and in those with recent onset of disease [39,132], and in those with less severe radiographic and functional abnormality [132].

Although it is common (almost 60% in one series [133]) for patients to report some subjective improvement with corticosteroid therapy, objective evidence of improvement is found relatively rarely (17% in the same study). Clearly, many patients with established fibrotic disease do not respond, although a trial of therapy is often warranted. BAL studies suggest that high eosinophil or neutrophil counts or low lymphocyte counts predict a poor clinical response to corticosteroids, whereas a lymphocyte count of greater than 11% appears to be related to improvement [128,134–136]. Serial lavage studies suggest that objective improvement is associated in general with return of elevated cell counts towards normality; however, there is no indication at present that such studies, although interesting from the research point of view, influence the clinical management of patients [136]. Indeed, striking decreases in neutrophil counts in BAL fluid occasioned by high-dose parenteral steroid therapy have resulted in no greater changes radiologically and functionally than occurred in a conventionally treated group [137]. Also, confusingly, corticosteroid therapy may lead to an increase in lavage neutrophils in smokers with fibrosing alveolitis [138].

In patients who do not respond to corticosteroids or for whom steroid therapy is contraindicated, immunosuppressant drugs such as azathioprine 150 mg daily or cyclophosphamide 100–120 mg daily may be tried. There have been reports of successful treatment with these agents, which may also be employed for their steroid-sparing effect [136,139,140]. Patients treated with a combi-

nation of cyclophosphamide or azathioprine and prednisolone fare little if any better than those treated with prednisolone alone [141,142], although there is a case for considering such a combination for its steroid-sparing properties. No other drugs have proved of clinical value, but it is to be hoped that the new understanding of pathogenetic mechanisms discussed above will lead to therapeutic trials of specific cytokine antibodies or receptor antagonists that may eventually prove of more promise. Possible new therapeutic options have been discussed in detail [67,68].

The author's approach is to make an initial assessment of likelihood of response, based mainly on HRCT and either biopsy or BAL findings. In the presence of evidence of active alveolitis, combined steroids and cyclophosphamide are started immediately and continued until it becomes apparent that no physiological response is occurring or side-effects become intolerable. In the absence of such evidence, a judgement is made as to whether treatment is justified after several months of follow-up with repeated lung function and exercise tolerance tests. Old radiographs are particularly helpful in assessing progression if they are available. The patient's age and general condition are also taken into consideration; most important are the views of the patients themselves, after explanation of the chances of response, the likely prognosis and the side-effects of treatment. Many older patients prefer to wait and see when presented with this information.

In younger non-smoking patients without systemic disease, there is now the option of lung transplantation [143,144] (see Chapter 59) and pulmonary fibrosis is responsible for 20% of transplants done currently [145]. The results indicate a 50% survival at 3 years [146].

Since only a small minority of patients with chronic disease respond in any worthwhile way to steroids or immunosuppressants and many find the side-effects of the former intolerable, the drugs are usually discontinued after a trial of several months and (except in younger patients intended for transplantation) efforts should be made to relieve the symptoms as far as possible. In some cases, small doses of benzodiazepine may help relieve the intractable breathlessness. In the later stages of the disease, oxygen therapy and treatment for right heart failure may be required. Appropriate sedation with opiates should be given in the terminal stages of the disease to relieve the intense distress occasioned by dyspnoea.

## Prognosis

The duration of the illness is variable but may range from a few months in patients whose disease follows a fulminant course to over 20 years. In several large series the average duration of survival from diagnosis has been 4–5 years [39,57,133]. Carrington and colleagues [6] found

5-year mortality in the 'desquamative' type of disease to be 27.5% with a mean survival of 12.2 years compared with 66% and 5.6 years in the 'usual' type. Only the 'desquamative' type improved spontaneously (22%). With corticosteroid drugs, 61.5% of the 'desquamative' but only 11.5% of the 'usual' type improved. In Stack's series the 5-year survival was 43% in those responding to corticosteroids compared with only 20% for those who did not respond [147]. As already mentioned, survival is longest in those with the most cellular and least fibrotic lung biopsies. Wright and colleagues [39] showed that patients with little fibrosis on lung biopsy had a 5-year survival of 90% compared with a 25% 5-year survival in those with severe fibrosis on biopsy. Most patients die from respiratory or cardiac failure, although there is a significant excess of lung cancer in patients with cryptogenic fibrosing alveolitis [104].

## Differential diagnosis of diffuse interstitial lung disease

Contrary to the impression conveyed by accounts of the differential diagnosis of diffuse interstitial lung disease (Table 31.1), the diagnosis of the usual type of cryptogenic fibrosing alveolitis is quite straightforward. A good history and examination, coupled with some experience of the more usual radiographic and HRCT appearances of given diseases makes the task of differential diagnosis easy. The most important aspect of diagnosis is to exclude both more readily treatable causes of the radiological appearances and also conditions with different prognoses. Thus, in practice, sarcoidosis, pneumoconioses (especially asbestosis), extrinsic allergic alveolitis and, most importantly, adverse reactions to drugs need to be considered. The more acute form of the disease, with ground-glass HRCT appearances, has a wider differential diagnosis that is usually only resolved by lung biopsy, a procedure that should not be delayed in such cases.

## Clinical features

### History

Cough productive of sputum is suggestive of airway involvement, and diffuse shadowing on the chest film with associated cough and purulent sputum would suggest pneumonia in relation to underlying airway disease, such as might be found in chronic bronchitis, bronchiectasis and cystic fibrosis. Cough with purulent sputum may also be features of allergic bronchopulmonary aspergillosis, tuberculosis and chronic eosinophilic pneumonia.

Wheeze is a usual accompaniment of acute allergic bronchopulmonary aspergillosis and chronic eosinophilic

**Table 31.1** Some causes of interstitial lung disease.

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<i>Occupational and environmental (Chapter 54)</i>
Asbestos
Quartz, cristobolite, silicates
Beryllium
Bauxite
Coal, graphite
Cobalt, antimony
<i>Organic dusts (Chapter 37)</i>
Microorganisms
Fungal spores
Actinomycetes
Animal protein
Bird bloom
Small mammal protein
<i>Collagen diseases (Chapter 53)</i>
Rheumatoid
Systemic sclerosis
Lupus erythematosus
Sjögren's syndrome
<i>Inherited disorders (Chapter 53)</i>
Tuberous sclerosis
Neurofibromatosis
Ankylosing spondylitis
Familial pulmonary fibrosis
Weber-Christian disease
Hermansky-Pudlak syndrome
<i>Vasculitis/granulomas (Chapter 40)</i>
Churg-Strauss syndrome
Polyarteritis nodosa
Wegener's granulomatosis
<i>Toxic fumes and vapours (Chapters 54, 55)</i>
Oxygen
Chlorine, fluorine and other gases
Nitrogen dioxide
Lipids
<i>Drugs (Chapter 55)</i>
Cytotoxics
Nitrofurantoin
Sulfasalazine, salicylates
Gold
Penicillamine
Amiodarone
<i>Poisons (Chapter 55)</i>
Paraquat
Toxic oil syndrome
Radiation
<i>Infections (Chapter 13)</i>
Viral pneumonias
<i>Mycoplasma pneumonia</i>
HIV-associated disease (Chapter 52)
<i>Unknown aetiology</i>
Cryptogenic fibrosing alveolitis
Sarcoidosis (Chapter 39)
Langerhans' cell histiocytosis (Chapter 42)
Haemosiderosis (Chapter 51)
Amyloidosis (Chapter 51)
Lymphangioleiomyomatosis (Chapter 42)

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pneumonia and is also found in the pulmonary vasculitides and pulmonary oedema. Dyspnoea is a common presenting symptom in diffuse interstitial lung disease. When acute in onset and associated with fever, infection should be suspected although in some instances a connective tissue disorder such as disseminated lupus erythematosus is responsible. Acute dyspnoea is of course commonly due to left ventricular failure. Episodic acute dyspnoea is a feature of extrinsic allergic alveolitis, when a history of exposure to the relevant antigen will be obtained and influenza-type symptoms may be associated. Slowly progressive rather than acute dyspnoea suggests a chronic progressive disease. The rate of progression of dyspnoea varies widely between different processes. Slow progression over a decade or more is usual in asbestosis and some other pneumoconioses and is also found in pulmonary sarcoidosis evolving to fibrosis. In contrast, in some of the complications of human immunodeficiency virus (HIV) infection, including *Pneumocystis* pneumonia, or the more acute cryptogenic fibrosing alveolitis, dyspnoea may progress more rapidly, often over a few months. The relative severity of dyspnoea in relation to the radiographic extent of disease is also important, for example sarcoidosis may cause minimal dyspnoea despite substantial radiographic extent of disease, whereas in cryptogenic fibrosing alveolitis dyspnoea may be disproportionately severe.

Chest pain of a pleuritic nature may suggest a diagnosis of connective tissue disease or pleural involvement in, for example, rheumatoid arthritis or sarcoidosis. Acute pleuritic pain due to pneumothorax may be consequent on rupture of bullae or blebs in chronic fibrotic processes, such as cryptogenic fibrosing alveolitis, or be a manifestation of less common diseases, such as Langerhans' cell histiocytosis or lymphangioleiomyomatosis.

Haemoptysis may occur in left ventricular failure and is a feature of less common conditions such as idiopathic pulmonary haemosiderosis and Goodpasture's syndrome.

As is apparent from Table 31.1, an occupational and environmental history is of cardinal importance. Not only the present occupation but previous occupations should be documented and explored for possible exposure to inhaled agents. If necessary, the workplace should be visited and possible agents obtained for challenge tests if indicated. A domiciliary visit may be required in some cases. The author has seen extrinsic allergic alveolitis in a patient who persistently denied keeping birds until a home visit revealed the offending budgerigars, which an astute ward sister had overheard twittering during a telephone call from the patient's husband. In a similar case, bird fanciers' lung was diagnosed in a patient who eventually revealed that he was keeping doves in his kitchen.

A drug history should be vigorously pursued. Many cytotoxic drugs cause pulmonary fibrosis. Nitrofurantoin, still frequently prescribed for recurrent urinary tract infections, and sulfasalazine (sulphasalazine) for ulcerative colitis are not uncommon causes of pulmonary eosinophilia or chronic progressive fibrosis. The problems of differential diagnosis of diffuse pulmonary shadowing in the immunosuppressed host are discussed in Chapter 52.

Extrapulmonary symptoms may suggest systemic disease. Arthralgia and skin lesions are found in sarcoidosis, connective tissue disease and Wegener's granulomatosis. Eye and skin symptoms are common in sarcoidosis and upper respiratory tract symptoms in Wegener's granulomatosis. Bone lesions may be found in Langerhans' cell histiocytosis and chronic sarcoidosis. Increasingly in the UK, and to a much greater extent in Africa and parts of Asia and the USA, it is necessary to consider HIV infection as a cause of interstitial lung disease, either infective or infiltrative, and some of these manifestations, such as *Pneumocystis* infection or lymphocytic interstitial pneumonitis, cause diagnostic difficulties. A history designed to elicit risk factors and HIV testing should now be considered in all patients with diffuse lung disease of obscure aetiology.

### Examination

Finger clubbing is a feature of cryptogenic fibrosing alveolitis and asbestosis and may also be found in bronchiectasis and cystic fibrosis. Bilateral crepitations on auscultation are a feature of pulmonary oedema, cryptogenic fibrosing alveolitis, extrinsic allergic alveolitis and asbestosis. Crepitations are not a feature of the other pneumoconioses or sarcoidosis (except in the late fibrotic stages). A full examination of all systems should be undertaken in a search for relevant signs, with particular attention being paid to bones and joints, the skin and the eyes.

### Other investigations

The routine full blood count may be diagnostically useful. A neutrophil leucocytosis suggests bacterial infection, while eosinophilia is found in pulmonary eosinophilia of whatever cause (see Chapter 38). A very high erythrocyte sedimentation rate may be found in connective tissue diseases, Wegener's granulomatosis, Goodpasture's syndrome and in chronic eosinophilic pneumonia. Sputum examination may reveal bacterial or fungal infection or malignant cells. Iron-laden macrophages are found in the sputum in idiopathic pulmonary haemosiderosis and PAS-positive material in alveolar proteinosis. Sputum eosinophilia may suggest pulmonary eosinophilia and

bronchial casts may be found in allergic bronchopulmonary aspergillosis.

Precipitins to the causative antigen may be detected in extrinsic allergic alveolitis. Antinuclear antibodies and anti-DNA antibodies are found in disseminated lupus erythematosus; antinuclear and rheumatoid factors may also be found in cryptogenic fibrosing alveolitis and antineutrophil cytoplasmic antibodies in Wegener's granulomatosis. Serological evidence of HIV infection should be sought where relevant and after appropriate discussion with the patient.

BAL may be of value in diagnosing infection and differential cell counting may suggest diagnoses of fibrosing alveolitis, extrinsic allergic alveolitis or sarcoidosis. Birbeck (or X) bodies may be found in Langerhans' cell histiocytosis, and evidence of HIV-related infection may be found with appropriate stains. Transbronchial biopsy is of value in diagnosing infection, malignancy, alveolar proteinosis, haemosiderosis and sarcoidosis but open lung biopsy may be necessary to establish a firm diagnosis particularly in cryptogenic fibrosing alveolitis.

Chest radiograph

The radiographic appearances of specific conditions are described in detail in the relevant chapters. In many conditions the distribution of pulmonary opacities is characteristic and examples of generalized, upper, middle and lower zone opacities are listed in Table 31.2.

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Table 31.2 Patterns of distributions of pulmonary opacities on the chest radiograph.

Upper zones
Tuberculosis
Chronic sarcoidosis
Extrinsic allergic alveolitis
Langerhans' cell histiocytosis
Subacute silicosis
Progressive massive fibrosis
Middle zones
Pulmonary oedema
Alveolar proteinosis
<i>Pneumocystis carinii</i> infection
Lower zones
Cryptogenic fibrosing alveolitis
Asbestosis
Bronchopneumonia
Collagen diseases
Tropical eosinophilia
Generalized
Pneumoconioses
Miliary tuberculosis
Sarcoidosis
Cystic fibrosis
Complications of human immunodeficiency virus infection
Metastases
Lymphangitic carcinomatosis
Adult respiratory distress syndrome
Drug reactions
Haemosiderosis
Microolithiasis

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# ASTHMA: EPIDEMIOLOGY

PETER G. J. BURNEY

Asthma is an important condition with a very variable prevalence that has become an increasing burden on health in both developing and market economies. The condition is associated with atopy, although its causes are otherwise poorly understood. Most people with asthma have mild disease with occasional exacerbations but some develop chronic airflow obstruction and patients with diagnosed asthma have a reduced expectation of life.

## Definition and presentation

Asthma remains undefined. In 1958 a CIBA guest symposium set out to define chronic lung diseases and provided a definition of asthma as 'the condition of subjects with widespread narrowing of the bronchial airways which changes its severity over short periods of time either spontaneously or under treatment' [1]. This remains the benchmark definition, and several groups have refined or altered it to suit current hypotheses from time to time. However, it was pointed out soon after the publication of the symposium that this was less a definition than a description of the condition [2]. A true definition provides unambiguous criteria for deciding whether an individual has asthma or not. Despite this we are no nearer a definition and one recent attempt is perhaps even vaguer than the original on which it is based:

a chronic inflammatory disorder of the airway in which many cells play a role, including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli [3].

Because asthma is used to convey a complex idea, a simple definition is probably not possible and clarification has generally come through restricting the use of the term. For instance, 'renal asthma', a term used at the beginning of the century, is now not recognized and it is increasingly archaic to talk of 'cardiac asthma'. The utility of discussing

all obstructive lung disease as a spectrum of disease with common aetiology (the Dutch hypothesis) is still debated [4]. Against the hypothesis, smoking and atopy are independent risk factors for bronchial hyperresponsiveness and appear to have their effects through different mechanisms [5,6]. The hyperresponsiveness associated with cigarette smoking only emerges in middle life and is more strongly associated with low lung function, whereas the hyperresponsiveness associated with atopy is seen much earlier in life. A number of people develop a condition very similar to atopic asthma, although they are not atopic in the conventional sense of having specific IgE to common inhalant allergen. Nevertheless these 'intrinsic asthmatics' have a histology similar to that of atopic asthmatics and it is speculated that the mechanisms are also similar [7].

In studying asthma, working definitions are required and a number of inconsistent methods have been used; the most common are given in Table 32.1. A clinical diagnosis of asthma is often used in clinical research. However, there is evidence for important differences, at least between countries, in the way that doctors identify patients with asthma [8], and the implicit lack of standardization in this method is unacceptable in epidemiological studies even when the study is small enough for the method to be feasible.

Patients' own reports of whether they have asthma are closely related to their reports on taking treatment for asthma and are largely determined by a doctor's diagnosis. This therefore has the same problem of poor standardization. In addition patients may not always know the doctor's diagnosis [9], and the diagnosis depends on the accessibility and quality of the local health services. This is a particularly severe restriction where surveys are being used in part to assess the quality of healthcare.

Questions concerning symptoms are less prone to these problems and as such are preferable, though they also have their limitations. There is no clear-cut symptom or symptom complex that is pathognomonic of asthma [10] and perception and reporting of symptoms

**Table 32.1** Common methods for identifying asthma in surveys.

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Clinical
Doctor's assessment
Patient's report of asthma
Symptomatic
Wheeze
Physiological
Peak flow variability
Bronchial response to stimulus
Direct: histamine, methacholine
Indirect: cold air, exercise, adenosine
Bronchial response to bronchodilators
Bronchial response to steroids

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may be affected by a number of psychological and cultural factors. Nevertheless there are now some well-standardized, symptom-based questionnaires that can be used [10–12].

Where questionnaires are potentially cheap and quick, physiological measures tend to be expensive to undertake in large surveys. Nevertheless they are less open to cultural influences and are a useful adjunct in epidemiological surveys. Once again, however, there is no physiological measure that is pathognomonic of asthma as it is generally understood and the different tests do not give closely related answers [13].

Improved lung function following administration of a bronchodilator is a useful clinical test but is probably less useful in surveys where 'asthmatic' subjects may have good lung function prior to the medication and therefore may not respond.

Bronchial challenge tests using bronchoconstrictor agents are now commonly used in surveys and simplified dosage schedules have been introduced [14]. Indirect challenge with cold air, non-isotonic saline, exercise or adenosine may be more specific for asthma, although there is less experience with adenosine in large surveys and standardization of the other methods is even more difficult. Extensive use has been made of histamine and methacholine challenge in surveys and there is now a great deal of experience with these. However, patients with cigarette-induced airway damage also respond to these tests. Challenge tests also tend to be relatively poorly standardized, as the effective dose delivered depends on the nature of the aerosol and this may vary considerably from one machine to another. Using the slope of the dose-response curve as the measure of responsiveness mitigates this problem and has the additional advantage that it provides a continuous measure of responsiveness [15].

In reality, the distinction between the normal and the abnormal is somewhat arbitrary and the level of abnormality selected as being significant is as important as the method of detection. In general it can be shown that specific tests give less misclassification, while the best test depends on the circumstances in which it is being used

and on the prevalence of disease in the population under study.

## Distribution

### Geography

Asthma is widely distributed but very variable in its prevalence. The use of standardized methods ensures that even though the absolute prevalence of the disease is unknowable, because the disease is undefined, the relative prevalence of the condition can be studied. It appears from surveys of children [16,17] and young adults [18] that the disease is more common in the English-speaking world and in some other areas such as France, of relatively lower prevalence in Scandinavia and in most of southern and eastern Europe, and very low in prevalence in some parts of rural Africa and other areas with markedly undeveloped ways of life [19–22]. There is some broad correlation between the prevalence of asthma and the prevalence of IgE antibodies to common inhaled allergens [23].

### Age and sex

The incidence of diagnosed asthma as recorded in the USA is highest in the first year of life. In childhood the incidence is higher in boys than girls but reverses in the age group 15–50 years and reverses again in the older age group when the incidence among men increases once more [24]. The prevalence of bronchial responsiveness has been shown to follow a similar pattern, with boys having greater responsiveness than girls but adult women having higher levels than men and older men having similar levels of hyperresponsiveness as older women [25].

Women have lower levels of total and specific IgE than men and cross-sectional surveys show an increase in prevalence of sensitization during childhood and a marked decline with age in adult life [26,27]. However, cohort studies suggest that at least part of this later decline is due not to ageing but to the year of birth, implying that people who were born longer ago were less likely to become sensitized in the first place [28].

### Ethnicity

Differences in atopy and asthma have been reported between different ethnic groups but whether these are due to genetic, environmental or cultural differences is unclear.

In the UK, there is greater respiratory morbidity in inner city areas, particularly among Afro-Caribbean and white children, although Afro-Caribbean children report slightly less asthma [29–31]. Black British and Caribbean children have also been found to have more atopic dermatitis [32,33], though in one of the surveys this was not



true of black children from Africa [33]. In the USA, both serum IgE levels [34] and the prevalence of skin sensitivity [26] are slightly higher in African-Americans. Schwartz and colleagues [35] also found a significantly increased prevalence of diagnosed asthma (and to a lesser extent wheeze) in black children in the NHANES II study.

By contrast, in Southern Africa there was no difference in the prevalence of exercise-induced bronchoconstriction between black and white children living in the affluent northern suburbs of Harare [22].

In the UK, children from the Indian subcontinent tend to report fewer symptoms [36–38] but have been estimated to have either a greater prevalence of exercise-induced responsiveness [37] or equal prevalence of methacholine-induced responsiveness and a greater prevalence of atopy [38]. They have also been reported to have an increased tendency to respond to food additives, particularly fizzy drinks [39].

In New Zealand [40], European children have a higher prevalence of bronchial responsiveness than the Maoris, who in turn have a higher prevalence of responsiveness than the Pacific Islanders. However the Maoris report more symptoms than either the Europeans or Pacific Islanders. In young adults the Maoris also report more symptoms, though this is largely due to higher prevalence rates in those aged 30–44 years and the Maoris have lower rates of hay fever and are heavier smokers than the Europeans, suggesting that their increased symptoms may not be due to asthma.

### Poverty/social status

The relation between poverty and wheezing is strongly confounded by exposure to cigarette smoke. Children from the 1958 birth cohort whose fathers were of higher social class were more likely to have hay fever and atopic dermatitis [41] and were more likely to be sensitive to common allergens at 33 years old [42], though there was no association with wheezy illness at that age when other factors had been taken into account [43]. The children of fathers of higher social class studied in the 1970 birth cohort were more likely to have persistent wheeze at the age of 16, though they had had less wheeze at the age of 5 [44]. Much of the excess risk of asthma in Baltimore could be explained better by poverty than by ethnicity alone [45]. In England and Wales more severe asthma has also been reported among adults from lower social classes [46].

### Time

There is good evidence that the prevalence of wheezy illness has been increasing over the last couple of decades at least. Indirect evidence suggests that this may have been happening in some places from the early part of the

century, at least in those countries with high prevalence rates. It appears that this has been accompanied for the most part by changes in the prevalence of other atopic conditions [47,48] and in the prevalence of sensitivity to common aeroallergens [49,50]. It would be natural to conclude that much of the increase was secondary to this change in the prevalence of atopy. However it is likely that other factors are also involved and these would have to explain the changes in Australia, where there is evidence for an increasing prevalence of asthma but for a constant prevalence of atopy as measured by skin tests [51].

Admissions to hospitals with asthma have been increasing at approximately the same rate as the increase in the prevalence of disease. There is good reason to believe that hospital admission rates are affected by both health service factors and local prevalence rates [52,53], and the recent slowing down in the increase of admission rates in several countries may be due to health service pressure on costs and, in particular, financial pressure to reduce the use of inpatient facilities [54,55].

The major changes in mortality during the latter half of the twentieth century probably have little to do with changes in prevalence, although it is likely that mortality rates have been affected by changes in prevalence and this may be what is implied by the weak cohort effects found in mortality trends [56]. The changes in prevalence that have almost certainly occurred make it difficult to assess any long-term changes in the case fatality of the disease. Although evidence from life assurance companies, mostly in the USA, suggests that these have been relatively constant over the century, their interpretation is difficult [57].

Although the changes reported here are widespread, it should not be assumed that they have been universal. Trends are more likely to be studied where there is a prior belief that the rates are rising. Only a more systematic estimate of trends would allow generalizations to be made about such changes. The question of whether the same upward trends in prevalence are continuing is difficult to answer.

### Early life

There are several characteristics of early life that predict atopy and asthma later in life. However, it is possible that these are, at least in some cases, predictors of continuing exposures that also persist into adult life. In the case of asthma at least, there is evidence for continuing plasticity as evidenced, for instance, in the effect of migration. In the UK, where there is regional variation in the prevalences of wheezy illness, children at the age of 5 or 7 years have prevalences of wheezy illness closer to those of the regions to which they have migrated than to those in the regions where they were born [58].

There are consistent reports that children from larger

families have less hay fever and atopy than those from smaller families. There is more debate as to whether this is an effect of large families or whether it is more specifically related to the number of older siblings. This finding has not generally been replicated when looking at the prevalence of asthma [59], although Seidman and colleagues [60] have described a similar relationship for asthma in Israeli military recruits.

Younger mothers have been noted to have infants with more wheezy lower respiratory tract infections [61] and 3–4 year olds with more asthma [62]. In the 1970 British birth cohort, children at the age of 16 were more likely to have persistent wheeze if their mothers were younger, but this was not the case at the age of 5 nor was it the case in the 1958 birth cohort. On the other hand, adolescents in Sheffield were found to have rather less hay fever if their mothers were younger [63].

Children who are born prematurely have a greater prevalence of sensitization to allergens [64]. They are also more likely to have wheezy illness [35,65,66] and asthma [67] at primary school age. However, prematurity was not associated with wheezy illness in either the 1958 [43] or 1970 [44] birth cohorts and Olesen and colleagues [68] concluded that atopic dermatitis was more common in postmature children. Bertrand and colleagues [69] hypothesized that both children who were born prematurely and their mothers might be more likely to have airway hyperresponsiveness, though others [70], while confirming the association between low birthweight and later airway responsiveness, were unable to link this with maternal airway responsiveness.

Low birthweight children have been reported to have a greater risk of having asthma and wheeze in childhood [35,70], asthma or wheeze at 16 [71] and asthma as young adults [60] and a lower lung function as primary school children [65] and adults [72]. However, others have reported no greater risk of asthma in childhood [65,67,73] and a reduced risk of atopic dermatitis in low birthweight babies [68].

## Exposure to allergens

Exposure to allergen is necessary for sensitization and for subsequent expression of disease, although as allergens are widespread other factors may well be more important in determining whether sensitization takes place. Some studies have shown that sensitivity to house-dust mite is rare among children where antigen levels are less than 2 pg/g of dust but is increasingly likely as levels rise above this value [74,75]; areas with low levels of dust mite antigens have low prevalence of sensitivity to the allergen [76,77]. Studies have also suggested that cat ownership is associated with sensitization to cats in children [64,78]. However, others have shown very little relation between domestic levels of allergen and sensitivity to mites [79,80]

or cat [79] and Rugtveit [81] was unable to find an association between pet ownership and sensitization to cat or dog.

There is considerable interest in the possibility that early exposure to allergen may be particularly important. The evidence for this is based largely on the association between sensitization to particular allergens and month of birth. A number of studies have shown a strong association between mite allergen sensitivity and birth in the latter part of the year [82–85]. However, in the UK at least, mite is not a strongly seasonal allergen, and there is only very inconsistent evidence that pollen allergen is related to month of birth.

It is unlikely that increased exposure to allergen has led to the increase in sensitization mentioned earlier. Although insulation of housing has increased and it has been shown that reduced ventilation leads to increases in levels of both cat [86] and mite [87] allergens in the home, the two studies that have documented increases in sensitivity to allergens [49,50] have shown that the increase is not due to increases in indoor allergens alone and there is little evidence for an increase in other allergens [88].

Exposure of sensitized subjects to allergen increases bronchial reactivity and this increase is associated with the late asthmatic response [89]. In the USA the increase in emergency room visits with asthma that occurs in the spring has been associated with raised IgE to grass pollen allergen [90] and several studies have shown an association between indoor mite allergen levels and clinical disease [80,91]. There is further evidence that acute severe asthma may be associated with exposure to high ambient levels of indoor allergen [92].

Epidemics of asthma are rare but those that have been recorded have mostly been associated with allergen. The best documented of these were the epidemics of asthma in Barcelona associated with the release of soybean allergen [93]. Other epidemics have been associated with castor bean allergen [94,95] and possibly grass allergen released from pollen during thunderstorms [96,97].

Mortality among young asthmatics also shows a seasonal variation and this is particularly marked in those who die suddenly [98,99]. Increases in acute severe asthma and asthma deaths have been reported following exposure to moulds [100–102] and to soybean dust [93]. The role of indoor allergen in asthma deaths is poorly understood.

## Smoking

Smoking has frequently been associated with higher levels of total serum IgE [103–106]. Although adjustment for age and gender, which are important confounders, reduces the size of this association, the association is not entirely explained by these [107,108].

Allergy to occupational allergens has been found to be

increased in smokers compared with non-smokers [109–111], though the same studies often showed no increase in the sensitivity to common inhaled allergens among smokers. In contrast, a number of studies have shown that the sensitivity to common allergens is reduced among smokers [42,104,107,108]. In two of these studies [107,108], the response to mite allergens was apparently dissimilar to that of the other common inhaled allergens including grass and cat. All these studies are cross-sectional and might be biased by the tendency of those who are sensitized to avoid smoking. However, evidence from the Tucson study suggests that this is not the explanation [28].

The effect of maternal smoking on sensitization is disputed. Magnusson reported an increase in cord IgE and subsequent infant allergy in the children of mothers who smoked during pregnancy. However subsequent investigators have generally not been able to replicate this [112].

Smoking causes a temporary increase in airway responsiveness [113], although smokers also develop a more persistent airway hyperresponsiveness [5,114,115]. This is associated with a fall in baseline airway function and does not reverse on quitting smoking [6], suggesting that it is secondary to structural damage to the lung. Patients with asthma who give up smoking experience a reduction of airway responsiveness [116], but there is little evidence that smokers are at any increased risk of developing asthma [117].

Since Colley [118] first drew attention to the effects of 'passive' smoking on the respiratory health of infants, a large body of literature has grown up to support his conclusions [119], although this effect is generally less marked after the first year of life [120]. Some studies have shown an increase in airway responsiveness in the children of mothers who smoke [121,122] but others have found either inconsistent [123,124] or negative [125–127] results. In Saskatchewan, non-allergic children and adolescents exposed to smoking had an increased prevalence of 'asthma' that was not found in the allergic children [128]. Evans and colleagues [129] found that asthmatic children from families that smoked were more likely to use emergency rooms, though this may have been due to unresolved confounding by other social factors. In contrast, Ehrlich and colleagues [127] found an increased prevalence of asthma in the children of mothers who smoked but were unable to show an increased risk of acute attacks of asthma.

## Air pollution

Air pollution is frequently cited as an important cause of asthma and its exacerbation. There is no good evidence that air pollution in general causes asthma, though it has been hypothesized that traffic pollution may be a cause of

the increased prevalence noted recently in the market economies. The pollution traditionally associated with cities, where coal burning was a major source of sulphur dioxide and particulates, has largely disappeared from the countries that have experienced the major increase in asthma prevalence.

Changes in symptoms and lung function have been noted in both normal and asthmatic populations in relation to increases in air pollution, although these have been for the most part relatively mild changes. Studies of mortality and admissions for asthma in relation to air pollution episodes have generally shown equally small and inconsistent effects. Several investigators have been surprised by such findings. During the famous London smog of December 1952 John Fry, a general practitioner in south London, reported that there was almost no effect of the smog on his young asthmatic patients [130]. In the air pollution episode that affected a large part of central Europe in 1985, admissions rose in affected areas compared with unaffected areas for stroke, ischaemic heart disease and chronic obstructive pulmonary disease but, if anything, fell for asthma [131]. These findings seem to bear out the observations of Henry Hyde Salter that 'it is, one may almost say, a *law* of asthma for it to be better in the air of great cities' [132].

On the other hand, there have been major [133] and some less extensive [134] episodes in which asthma has been reported to have been a problem, and the APHEA studies in Europe showed a modest increase in asthma admissions related to increases in nitrogen dioxide and, in children, with increases in sulphur dioxide levels [135].

One complicating factor in all of this is the role that might be played by allergen. The dramatic effects of exposure to allergen have already been described and the question arises whether allergen may play a role also in more normal circumstances. It is notable that the epidemics in Barcelona that were eventually shown to be due to the release of soybean allergen were at first attributed to oxides of nitrogen [136]. The reason for this is that the same weather conditions that lead to the build-up of one type of pollution may also lead to the build-up of another. The problem has been that there is no way of monitoring allergen, only a limited range of allergenic particles, such as pollens and molds, or specific allergens that have been identified and are under suspicion. However, the data from Barcelona suggest that low levels of allergen can contribute to asthma admissions without producing epidemics [137] and other allergens such as latex have been demonstrated in respirable particles from ambient air [138]. Such confounding could explain the relatively weak and inconsistent effects of air pollution on asthma.

## Infection and infestation

Frick [139,140] suggested that viruses could potentiate

sensitization to aeroallergens. Some bacterial antigens can act in the same way and pertussis vaccine can enhance IgE responses in animals [141], though natural pertussis infection does not lead to persistent respiratory disease [142,143].

As many as 70% of children respond to respiratory syncytial virus (RSV) with specific IgE, although those that have persistent anti-RSV IgE tend to have a family history or a personal history of wheeze [144]. This suggests that response with IgE may be normal but that persistence of the response is dependent on some other personal characteristic, possibly a genetic susceptibility. While it is true that children who develop RSV bronchiolitis are more likely to go on to develop episodic airways obstruction [145], it is not clear that this is cause and effect; it may simply be that those who are going to develop asthma and who become infected with RSV are more likely to have a severe episode of bronchiolitis. It has been shown, for instance, that children who are born with small airways are more likely to develop wheezing when they contract a lower respiratory tract infection [146]. The principal evidence against this interpretation in the case of RSV is the coincidence between the month of birth of those who develop asthma severe enough to be admitted to hospital and the month of birth of those who develop bronchiolitis [147]. It has also been suggested that persistent steroid-resistant asthma may be induced by chronic adenoviral infection [148].

On the other hand, there are alternative theories that suggest that early infection may suppress allergic responses and even the development of the atopic phenotype. In West Africa, a history of severe infection with measles was shown to be associated with a reduced prevalence of atopy, particularly sensitivity to mite allergen [149]. A strong response to tuberculin in Japanese school-children who had received bacille Calmette–Guérin (BCG) vaccine was also inversely related to atopy [150]. Serological evidence of infection by hepatitis A has also been shown to be inversely related to the prevalence of atopy in Italian military recruits [151]. All of these studies have been used to argue the case that early infection may affect the development of the immune response from one characterized by T lymphocytes producing interleukin (IL)-2, interferon  $\gamma$  and tumour necrosis factor to one characterized by T lymphocytes producing IL-4, IL-5, IL-6 and IL-10. At least in the second of these studies it is likely that those who respond to BCG with a tuberculin response are less likely to respond to allergen with an atopic response, rather than that BCG infection itself alters the immune response [150].

The simple view that any early infection reduces the risk of atopy is not well substantiated. Although Martinez and colleagues [152] have found that children experiencing non-wheezing lower respiratory tract infections in early life have a lower prevalence of atopy, Strachan and col-

leagues [63] found no association between early infection and subsequent atopy. Nor is there evidence of an inverse relationship between atopy and the common childhood infections [153].

There is much better evidence that acute viral infections of the respiratory tract, particularly rhinovirus and parainfluenza virus infections, cause acute exacerbations of asthma. Viruses cause exacerbations of asthma in both children [154] and adults [155] and infections are the commonest reported cause of exacerbations of asthma at all ages [27]. It seems likely that there is an interactive effect of viral infections and allergy in causing severe episodes of respiratory disease in children [156].

## Diet

Until the introduction of effective treatments for managing asthma, there was considerable interest in the effects of diet on the condition, and early in the twentieth century there were already hypotheses that food might induce asthma by anaphylaxis or by pharmacological means. The resulting fashion for restrictive diets was reversed in the middle of the century following increasing concern over the effects of these diets on nutrition and the introduction of double-blind food challenge as the criterion for assessing hypersensitivity to food. Although food sensitivity is common in children, and as many as 13% of adults complain of food-associated symptoms, current estimates of true food sensitivity in adults lie between 1 per 10000 and 2.3 per 1000 [157].

## Infant feeding

There is some evidence that allergy in early life may be reduced by breast-feeding and allergen avoidance. A randomized controlled trial of breast milk in premature neonates found less allergy in the treated children, but only among those who had a family history [158]. Zeiger and colleagues [159] also found a reduction of atopic disease in breast-fed babies where both mother and baby avoided allergen in the diet, but were unable to show a reduction in either rhinitis or asthma or in sensitization to inhalant allergens. Although Burr and colleagues [160] were able to show a reduction in wheezy illness early in life in those babies who had been breast-fed on any occasion, most studies show little difference in the incidence of asthma in those who were breast-fed and those who were not [161]. This is the conclusion from the two large British birth cohorts [162,163] and the Melbourne cohort in which the subjects with the longest history of breast-feeding had the worst asthma [164].

## Overall nutrition

There is little evidence on the effects of overall nutrition on

asthma, although there is some evidence that children with protein-calorie malnutrition are less likely to show skin sensitivity to common allergens [165]. At an ecological level, Keeley showed that the response to exercise in African children was related to body size, with the communities with smaller and lighter children having the least response to exercise. Such ecological data are hard to interpret, but Sommerville and colleagues [166] have also shown that children who are heavy for their height are more likely to have wheezy illnesses and in the Second National Health and Nutritional Examination Survey in the USA a two standard deviation increase in triceps skin-fold thickness increased the prevalence of frequent wheeze by 60% [167].

### Lipid

The Victorians believed in the efficacy of cod liver oil for asthma [168] and interest in this was revived by a corresponding interest in the role of lipid mediators in asthma. Clinical studies showed that fish oil in the diet could reduce the production of lipid mediators and blunt the late allergic response [169] but this had little influence on clinical asthma and aspirin-sensitive asthmatic patients deteriorated [170]. More recently interest has returned to this mechanism, with some epidemiological evidence that those who eat a diet rich in fish are less likely to have asthma [171]. However, others have been unable to demonstrate any difference in the  $\omega$ -3 fatty acid content of the diet of women who became asthmatic in middle life [172].

### Antioxidants

The lung has elaborate defences against oxidant damage and these are likely to be stressed in patients with asthma. Some of these defences are dietary in origin and Seaton has suggested that the increase in asthma may be due in part to a change in the diet with, in particular, a decline in the consumption of vitamin C. Trials of vitamin C in patients with asthma were first undertaken in the 1930s, with little success [173,174], and trials since that time have had mixed results. While neither Kreisman and colleagues [175] nor Malo and colleagues [176] were able to demonstrate any effect on either symptoms or hyperresponsiveness, others have reported reductions in the number and severity of attacks, the response to exercise and the response to methacholine. There are moreover several studies that have demonstrated lower levels of vitamin C in asthmatic patients [177–180] and those with hyperresponsiveness [181]. Low levels of vitamin C have also been associated with low lung function in men [182] and symptoms of chronic bronchitis [167].

In addition to the effects of vitamin C, there is suggestive evidence that vitamin E may also protect against the

onset of asthma in mid-life [172]. Selenium is a further micronutrient that has an important role in antioxidant activity in the lung. A number of studies have demonstrated a low level of selenium in patients with asthma [183–186]. One small randomized controlled trial has shown a clinical improvement in those taking selenium supplements but no change in lung function or airway reactivity [187].

### Electrolytes

Two electrolytes have received most attention with regard to their effects on asthma. Magnesium has been used for a long time as a bronchodilator [188], although it has disappointing results in acute severe asthma. A number of studies have shown that dietary magnesium is associated with lower prevalence of airway hyperresponsiveness in population surveys [181,189], though experimental studies have not suggested a strong effect on airway responsiveness [190]. Dietary sodium has been associated with increased bronchial responsiveness in one study [191], while other cross-sectional studies have shown weak or negative effects [192,193]. Experimental studies have suggested that a high sodium load does increase airway responsiveness in men [194,195] but not in women, and this is consistent with a finding that regions of England with high sales of table salt had an increased mortality from asthma for men and children but not for women [196]. The mechanism is unknown but it has been shown that serum from men with asthma increased sodium influx into donor cells and that this influx and dietary sodium were independently related to the airway responsiveness [197].

### Prognosis

#### Symptoms and lung function

A high proportion of children wheeze, though relatively few persist with severe respiratory problems. In the 1958 birth cohort, of all the children whose parents had reported wheeze in the first 7 years of life, only 50% were still wheezing at 7 years, 18% at 11 years and 10% at 16 years. At 23 years, this figure was still only 10% but by 33 the figure had risen again to 27% [43]. During childhood the reduction in symptoms with age is paralleled by a fall in airway responsiveness [198]. A relatively poor prognosis is associated with the presence of atopy and severity of disease, which is itself associated with atopy. Of those with persistent symptoms in childhood, relatively few are symptom-free in adult life [199].

A low lung function and bronchial responsiveness in childhood are predictive of low lung function and bronchial responsiveness in adult life [200]. Furthermore, those who have persistent wheeze during childhood and

are still wheezing in adulthood have low lung function that is not fully reversed by salbutamol. However, although symptomatic children have low lung function, the growth of their lung function with age is normal [201]. It seems likely therefore that asthma does not have an adverse effect on lung growth in childhood. In adulthood the effects of asthma on decline in lung function are unclear. Poor lung function is clearly associated with severe asthma [202] and is also associated with an increased mortality both in those with asthma [203] and others [204]. However, although two studies have reported a more rapid decline in lung function in patients with asthma [205,206], others have not [207] and Burrows and colleagues [208] found a normal rate of decline in lung function in those who had an unequivocal diagnosis of asthma with evidence of atopy and no history of smoking.

### Mortality

Follow-up of representative populations in the UK [209] and the USA [210] has shown an excess of mortality in those with diagnosed asthma. This excess increases with age and is negligible under the age of 45 years. Evidence from the life assurance companies also suggests that there is a small excess of mortality in those with a diagnosis of asthma, but this source also identifies a reduced mortality in those with other allergic diseases. This latter observation may explain why there is no excess of mortality in younger age groups although deaths from asthma do occur.

### Recording

Most studies of the validity of mortality statistics in asthma have studied the certificates and circumstances of death of those who have been certified as dying of asthma. These have generally concluded that, at least in younger subjects, the certificates are fairly accurate [211,212] though others have suggested that the certificates overestimate the number of deaths due to asthma [213]. For a clear view of accuracy, a study needs to assess both false-positive and false-negative rates. Where this has been done it has been found that the false-positive certificates are likely to balance or outweigh the false-negative certificates [214–216].

Vagueness in the definition of asthma and the presence of multiple pathology in older subjects inevitably leads to some uncertainty in ascribing any death to asthma in this age group. However, it also seems likely that there are more systematic biases in the variation in certification from country to country. Kelson and Heller [217] sent case histories to samples of doctors who had signed death certificates in eight European countries and asked them to complete death certificates for each of the cases. There was

considerable variation between countries and these differences related to the recorded mortality rates from asthma for the countries in the study [8].

### Trends

Overall mortality rates from asthma in England and Wales have not changed greatly over the course of the century. However this has not been consistent in all age groups. While mortality from asthma in the older age groups has declined throughout the century, that in adolescents and young adults has tended to rise [99]. In addition, there have been increases in mortality in the 1960s [218] and the 1980s [219].

### Overtreatment

Possibly because the early writers on asthma assumed that it was a largely benign condition that did not kill patients, much of what has been written on the subject since has related to iatrogenic causes of death. Early case reports concentrated on the dangers associated with respiratory depressants [220,221], while in more recent times the dangers of aspirin and other non-steroidal anti-inflammatory drugs have been emphasized. Of greater concern, however, has been the possibility that the drugs used to treat asthma might themselves be responsible for the deaths.

The first to suggest this were Benson and Perlman [222] who noticed that patients using epinephrine (adrenaline) sprays, mostly sold by door-to-door salesmen, had a seven-fold risk of death from asthma. The problem that was unresolved by this study was whether those taking the sprays had more severe disease. The hypothesis was revived in the 1960s when there was an increase in mortality from asthma in a number of countries that had licensed high-dose isoproterenol inhalers for the management of asthma. Early enquiries showed that a high proportion of the asthmatics who died were using these [223], while other studies showed a close association between the time course of the deaths and the use of these medications [218,224].

A further epidemic of deaths from asthma in New Zealand in the 1980s led to renewed interest in this hypothesis, in this case implicating the drug fenoterol. This was another potent bronchodilator prescribed in high doses and widely used in New Zealand. Case-control studies identified patients treated with fenoterol as being at increased risk, and the time course of the epidemic of deaths was interpreted as being compatible with fenoterol having been responsible. Despite this, a prospective study in Canada was unable to confirm the finding, though it showed that both salbutamol and fenoterol were prescribed in increasing amounts prior to the death of an asthmatic patient. The question of how far fenoterol was to

blame for the increase in asthma deaths in New Zealand in the 1970s and 1980s is still controversial. However, it is clear that there were less spectacular increases in deaths in other countries such as the USA at the same time where fenoterol was not licensed.

### Undertreatment

Another line of inquiry into asthma deaths has focused on undertreatment. Historically, much of the evidence for undertreatment being associated with death has come from uncontrolled enquiries into asthma deaths [225–229]. More recently, however, there has emerged more specific evidence that treatment with steroids may reduce mortality substantially [230,231]. Those treated with regular

inhaled steroids appear to have approximately one-third the risk of death of those who are not.

### Summary

Asthma is a disease that has become increasingly common over the last century. Although it is very variable in its severity, it is now a common cause of disability. The causes are still unknown. It has a genetic component although this cannot explain the increase in the disease or much of the variation in prevalence. It is associated with atopy but only a minority of atopic individuals are asthmatic. The major questions remain what circumstances lead to an increase in the disease and what factors lead to a deterioration in the condition.

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# ASTHMA: CELLULAR AND HUMORAL MECHANISMS

CHRISTOPHER HASLETT

The cellular and mediator mechanisms of asthma must be considered in relation to the clinical definition and classification. The widespread acknowledgement that asthma is caused by a chronic inflammatory response in the airways has been arrived at as a result of information gained from histological studies in autopsy specimens (and more recently bronchoscopic bronchial biopsies in patients), the study of mediator and cellular interactions in allergen-challenged atopic patients and, to a lesser extent, the study of experimental animal models. In this chapter, the cellular and mediator mechanisms likely to underlie the asthmatic state and the effector mechanisms that may explain the pathological features are described.

## Clinical definition and classification

A full understanding of basic mechanisms must ultimately explain the clinical picture of airways obstruction that is variable (or reversible) as a result of therapy or spontaneously. It should also account for the propensity of asthmatic patients to show markedly heightened responses to direct bronchoconstrictor agents, or indirectly to triggers such as exercise and cold air. It is now widely considered that in many or most cases, the syndrome of asthma or the asthmatic state arises from a number of poorly understood inducing stimuli, such as allergens and chemicals, in a group of patients who are in some way genetically predisposed. The patient with asthma is 'primed' or at risk of severe bronchospasm if exposed to trigger factors, which may be specific allergens or non-specific trigger factors such as viruses or exposure to cold air (Fig. 33.1).

## Pathology

The macroscopic and histological appearances of the airways of patients dying from status asthmaticus show quite clearly that severe asthma involves much more than simple bronchoconstriction. Naked eye examination shows that many airways are blocked with thick, tenacious mucus [1].

Histological analysis reveals that airway narrowing is not just brought about by shortening of the airway musculature but also by inflammatory oedema of the whole airway, particularly the submucosal layer [2]. There is often marked thickening of the epithelial basement membrane and in many patients, particularly those with severe asthma, the bronchial epithelial lining is damaged, with evidence of epithelial injury, desquamation and even large areas of complete epithelial denudation and exposure of the epithelial basement membrane (see Fig. 34.6) [3,4]. In keeping with the excessive mucus production, there is marked hypertrophy and hyperplasia of submucous glands and goblet cell hyperplasia [5]. There is also evidence of smooth muscle cell hypertrophy and hyperplasia in the muscularis layer, and microvascular vasodilatation in the adventitial layer of the airway. Throughout the layers of the airway there is an intense inflammatory and immunological cellular infiltration, with large numbers of granulocytes (particularly eosinophils) in the submucosa and within the epithelial layer and mucous plugs [5,6], together with evidence of eosinophil degranulation and disgorgement of highly histotoxic products, e.g. major basic protein (MBP), on histochemical staining [7]. Elsewhere in the airway there are heavy infiltrations of chronic inflammatory mononuclear cells, including large numbers of T lymphocytes, particularly CD4<sup>+</sup> cells [8].

Although it may have been thought that these features were predominant only in the catastrophic forms of asthma, early studies of sputum, necropsy studies on patients dying from unrelated causes (e.g. road traffic accidents) and the application of bronchoscopic biopsy techniques in asthmatic patients have clearly demonstrated that many are also found in the background histological picture of asthma [9–14] and in atopic patients challenged experimentally with relevant antigens [15–17].

## Atopic asthma and allergen provocation

Atopic asthmatics constitute the larger subgroup of

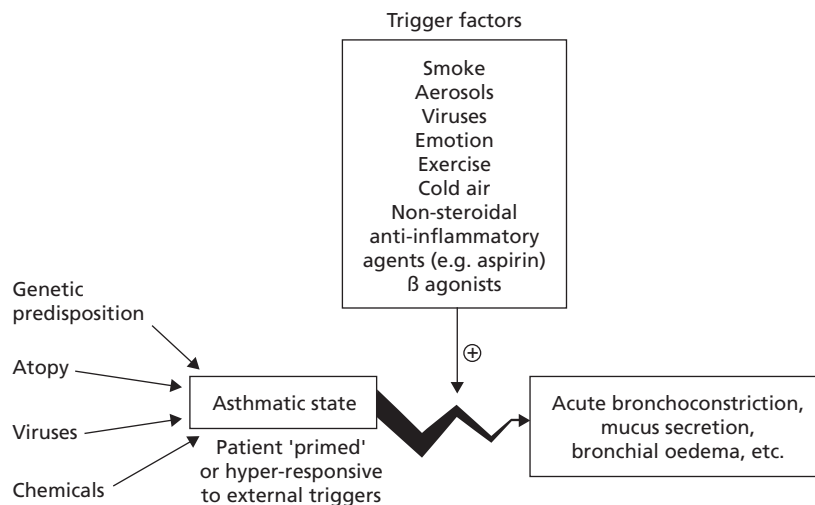


Fig. 33.1 The asthmatic state.

patients, and the study of their bronchial secretions (by bronchoalveolar lavage) and histology (by bronchial biopsy) at various times after deliberate antigen challenge has led to important insights into the mechanisms of asthma. While this experimental approach does not compare exactly with natural exposure to allergens, it has been extremely useful as a human model of asthma, providing much valuable information on the likely pathogenesis of allergic asthma and in the design and testing of new therapeutic agents. When the airways of most atopic asthmatic patients are challenged with specific allergen, the bronchial responses occur in two phases. The first rapid phase of bronchoconstriction (the early asthmatic response) reaches a peak within 20 min of challenge and recovers spontaneously within 60 min or so [18]. This response is thought to resemble a type I anaphylactic response, occurring as a result of IgE-triggered mast cell secretion of histamine and other rapidly acting bronchoconstrictor agents [19,20]. It can be prevented by prior treatment with the mast cell-stabilizing agent sodium cromoglicate (cromoglycate) and abrogated by  $\beta$  agonists [21]. This response is not significantly influenced by a single treatment with corticosteroids. The late asthmatic response occurs in around 50% of atopic individuals. It begins 4–6 h after challenge and persists for 12 h or more [18]. The mast cell is again likely to play an important role in this phase of bronchoconstriction since it is also attenuated by sodium cromoglycate. However, cytological and histological studies also show submucosal oedema, vascular dilatation and a complex cellular infiltration of granulocytes (especially eosinophils) and CD4<sup>+</sup> T lymphocytes, which are linked to a Th2-type cytokine secretion profile including interleukin (IL)-3, IL-4 and IL-5 [22].

The distinction between the early and late phases, which is a useful simplification in research, is of little value in the clinical context as most cases of severe asthma are likely to involve a multiplicity of mechanisms combining

elements of both the acute and chronic inflammatory responses.

## The cells

In this section the role of important cell types in asthma is considered. Although it is a somewhat artificial separation they can be segregated into the following groups.

1 Constitutive or resident cells of the airway, including tissue macrophages, dendritic cells and mast cells. These resident airway cells generally function to initiate the inflammatory and immune responses, although the mast cell clearly has many important effector functions in asthma.

2 Inflammatory/immune blood-borne cells, including the granulocytes and lymphocytes recruited to the inflamed asthmatic airway and which are likely to play additional important pathogenetic roles.

## Resident cells

### Cells of the monocyte/macrophage series and dendritic cells

By far the most numerous cell in the airway is the resident tissue macrophage. Under homeostatic conditions in healthy airways this population of cells is continuously replenished by bone marrow-derived, blood-borne monocytes. The resident macrophage expresses the low-affinity IgE receptor and can secrete a wide range of proinflammatory cytokines and chemokines [23]. These cells perform a key sensing and regulatory function in the inflammatory response, particularly in its initiation phase, although their precise contribution to the pathogenesis of asthma is uncertain. They rapidly secrete cytokines (Table 33.1) such as IL-1 and tumour necrosis factor (TNF)- $\alpha$  that act on microvascular endothelial cells [24,25], causing them to express

**Table 33.1** Some important cytokines: their source and major function.

Cytokine	Source	Functions
IL-1	Macrophages and other cell types	Activation of endothelial cells and macrophages, fever, T cell co-stimulation
IL-2	T cells	T-cell growth factor, NK cell activation
IL-3	Bone marrow stromal cells, T cells	Growth factor for neutrophils, eosinophils, mast cells
IL-4	T cells (Th2) and mast cells	B-cell IgE isotype switching, growth factor for B cells and T cells
IL-5	T cells (Th2) and mast cells	Eosinophil differentiation, recruitment activation and inhibition of apoptosis. Growth factor for B cells
IL-6	Macrophages, T cells and other cells	Acute-phase protein production, B and T cell growth and differentiation
IL-7	Bone marrow stromal cells	Growth factor for pre-B and T cells
IL-8	Reclassified as C-X-C chemokine	
IL-9	T cells	Mast cell activation
IL-10	B cells and macrophages	Inhibits macrophage function
IL-11	Bone marrow stromal cells	Growth factor for haematopoietic stem cells
IL-12	Macrophages and B cells	Promotes differentiation of Th1 cells, activates NK cells
IL-13	T cells (Th2)	B-cell IgE isotype switch, B-cell growth factor
IL-14	T cells	Development of memory B cells
IL-15	Macrophages and other cell types	Growth factor for T cells
IL-16	T cells (CD8 <sup>+</sup> )	Chemoattractant for CD4 <sup>+</sup> T cells and macrophages
TNF- $\alpha$	Macrophages, monocytes and T cells	Activates endothelial cells, stimulates release of IL-8 and other chemokines from resident cells
TNF- $\beta$	T and B cells	Activates endothelial cells, CD8 <sup>+</sup> -mediated cytotoxicity
IFN- $\alpha$	Macrophages, T and B cells	Antiviral activity, increased MHC class I expression
IFN- $\beta$	Fibroblasts and other cells	Antiviral activity, increased MHC class I expression
IFN- $\gamma$	Macrophages, T cells and other cells	Activates macrophages and CD <sup>+</sup> T cells, antiviral activity
TGF- $\beta$	Macrophages, monocytes and T cells	Inhibits macrophage function, promotes fibrosis and wound repair
GM-CSF	Monocytes, macrophages and T cells	Growth factor for myeloid cells, primes macrophages, primes and inhibits apoptosis in neutrophils and eosinophils
PDGF	Macrophages and platelets	Growth factor for fibroblasts, repair, fibrosis
FGF	Macrophages	Growth factor for fibroblasts, repair, fibrosis

FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; NK, natural killer; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TNF, tumour necrosis factor.

the adhesion molecules (Table 33.2) required for leucocyte trapping and emigration. They also secrete certain chemokines such as IL-8 and gro- $\alpha$  that are specifically chemotactic for neutrophil granulocytes [26,27], whereas others such as RANTES and monocyte chemoattractant protein-1 (MCP-1) attract eosinophils and monocytes [28,29]. Macrophage-derived IL-1 and TNF- $\alpha$  can also act on other resident tissue cells, for example fibroblasts and epithelial cells, inducing them to secrete IL-8 and other chemokines [30,31] and thus amplifying the inflammatory response.

In the development of an acute inflammatory response, the initial emigration of granulocytes from blood into tissues is followed by a wave of monocyte emigration. These cells rapidly mature into inflammatory macrophages, which can also secrete cytokines and chemokines and amplify the inflammatory response. However, these cells possess much more effective mechanisms for the secretion of enzymes and reactive oxygen species than do resident macrophages and may thus play an important role in the effector limb of asthma. Macrophages also secrete the cyclooxygenase products thromboxane (TX) $B_2$  and prostaglandin (PG) $E_2$ , the 5-lipoxygenase product leukotriene (LT) $D_4$  and platelet-activating factor (PAF), which are capable of inducing many of the features of

asthma [9,32,33]. Cells of the monocyte/macrophage series are also able to influence T-lymphocyte function through the secretion of cytokines, and while resident macrophages are poor presenters of antigen, monocytes and immature inflammatory macrophages are more effective. Although there is little direct evidence for the macrophage in the pathogenesis of asthma *in vivo*, the circumstantial evidence is impressive and it is hard to believe that it does not play an important role.

The lung dendritic cell is likely to play the major role in antigen presentation to T lymphocytes. These cells are prominent in the submucosal layer of the airway, particularly beneath the epithelial lining.

### Mast cells

These highly granular tissue cells have long been implicated in the pathogenesis of allergic conditions, particularly asthma. Ultrastructural examination (Fig. 33.2) reveals large numbers of cytoplasmic granules with a characteristic morphology. Reports vary as to whether there are increased numbers of mast cells in the asthmatic airway, although most ultrastructural studies show that those present display an activated, degranulated



**Table 33.2** Some surface adhesion molecules controlling leukocyte–endothelial interactions.

Family	Receptor	Distribution	Ligand/counter-receptor	Promotes adhesion to
Integrin family	LFA-1 (CD11a/CD18)	All leucocytes	ICAM-1, ICAM-2, ICAM-3	Endothelial cells
	Mac-1/CR3 (CD11b/CD18)	Granulocytes Monocytes Lymphocytes	ICAM-1, C3bi, factor X	Endothelial cells Opsonized particles
	P150.95 (CD11c/CD18)	Granulocytes Monocytes	Endothelial ligand?	Endothelial cells
Selectin family	L-selectin (CD)	Neutrophils Monocytes Lymphocytes	?E selectin ?P selectin CD15 C5(ex)	Endothelial cells
	P-selectin (CD62)	Endothelium	Sialyl Lewis X (CD15)	Neutrophils
	ICAM-1 (CD54)	Endothelium Epithelium	LFA-1 (CD11a/CD18) MAC-1 (CD11b/CD18)	All leucocytes
Immunoglobulin superfamily	ICAM-2	Monocytes Lymphocytes Endothelium	LFA-1 (CD11a/CD18)	All leucocytes
	VCAM-1	Activated endothelium	VLA-4	Monocytes Eosinophils

ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; VLA, very late antigen.

appearance. Being the most important cellular source of histamine, it has been clear for some time that the mast cell plays a key role in the effector limb of asthma. In addition to secreting preformed mediators such as histamine, mast cells can also synthesize other mediators in the cyclooxygenase pathway, especially PGD<sub>2</sub>, and 5-lipoxygenase arachidonic acid pathways that exert rapid effects on the airway [34–37]. Another important granule component is tryptase, which besides exerting a number of effects on the airway also activates the kinin cascade. Mast cells may be triggered by direct binding of IgE via their high-affinity surface receptors or by cross-linking of these receptors but can also be triggered indirectly by cold air or by changes in tonicity of the fluids in the airways [38,39]. Recent studies suggest that the mast cell, like the resident macrophage, is an important regulatory cell: when atopic airways are challenged with specific allergen, airway mast cells rapidly generate mRNA for IL-3, IL-4 and IL-5, the Th2-type cytokines [40,41]. This cell is clearly a major player in the pathogenesis of asthma (Figs 33.2 and 33.4).

### Basophils

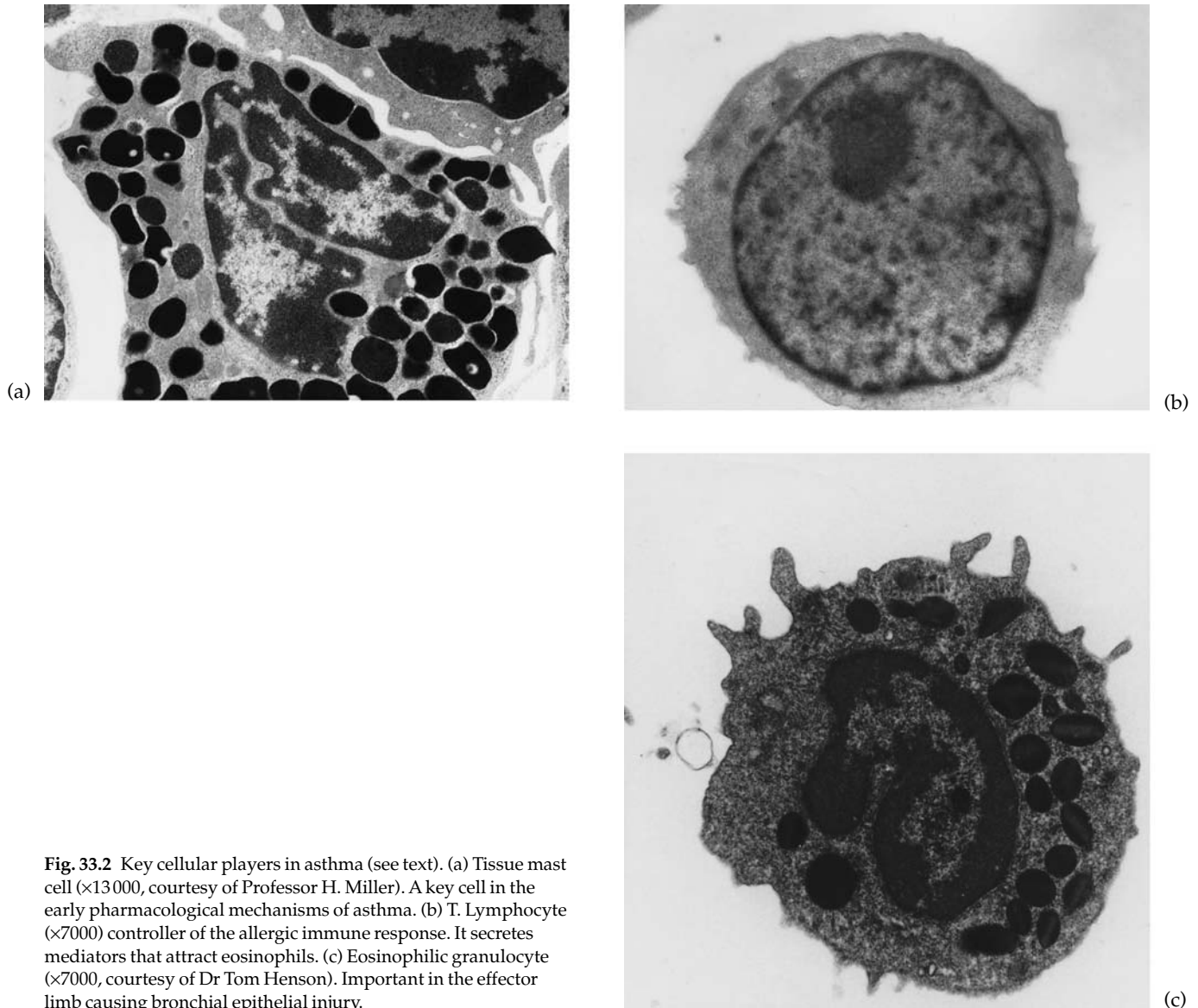
The role of these cells in asthma has been difficult to establish, partly because they lack specific surface markers that would aid histological identification and purification for detailed *in vitro* study. While there is uncertainty about whether increased numbers are present in asthmatic airways, they can be found in the blood during the asthmatic response [42,43]. Like mast cells, basophils possess

the high-affinity IgE receptor and when triggered can secrete histamine and a wide range of other mediators relevant to the pathogenesis of asthma [44–48]. Unlike mast cells they can also be stimulated by the cytokines IL-1 and IL-3 and by the chemokines IL-8 and RANTES.

### Circulating leucocytes

#### Eosinophils

Eosinophils are bone marrow-derived, blood-borne polymorphonuclear leucocytes, the cytoplasmic granules of which stain a deep pink with haematoxylin/eosin; hence the name and their distinction from the neutrophil granulocyte. Ultrastructural examination (see Fig. 33.2) reveals large angular granules possessing the dark, crystalline core that characterizes this cell type. Eosinophil granules contain not only many of the potentially histotoxic agents found in the neutrophil but also a number of eosinophil-specific agents, including major basic protein (MBP) and eosinophil cationic protein (ECP) that help identify the cell and provide evidence of its secretory activity *in situ* [7,49,50]. Atopic asthmatics have long been recognized to display high circulating levels of eosinophils in the blood and large numbers of eosinophils and Charcot–Leyden crystals (lyssolecithin from degraded eosinophils) in their sputum [51,52]. Histological studies of severe asthmatics reveal heavy infiltrations of the airways with eosinophils [6,53,54], many of which show evidence of degranulation on electron microscopy, together with evidence of dis-



**Fig. 33.2** Key cellular players in asthma (see text). (a) Tissue mast cell ( $\times 13\,000$ , courtesy of Professor H. Miller). A key cell in the early pharmacological mechanisms of asthma. (b) T. Lymphocyte ( $\times 7000$ ) controller of the allergic immune response. It secretes mediators that attract eosinophils. (c) Eosinophilic granulocyte ( $\times 7000$ , courtesy of Dr Tom Henson). Important in the effector limb causing bronchial epithelial injury.

gorged MBP and eosinophil peroxidase (EPO) in tissues [7]. These cationic products are highly toxic to epithelial cells *in vitro*, and eosinophils are widely considered to be responsible for much of the epithelial damage described in cases of severe asthma. Eosinophils possess functional low-affinity IgE receptors and can synthesize PAF and other important lipid mediators [55–65]. They can also secrete a variety of cytokines, including IL-4 that is so important in IgE secretion [66,67], and their reputation as a centrally important cell in the pathogenesis of asthma seems fully justified. Airway challenge of atopic patients with specific allergen results in eosinophil accumulation in the airways and bronchoalveolar lavage fluid, together with evidence of extracellular secretion of ECP and MBP. The characteristic eosinophil accumulation in the tissues in an allergic response is probably brought about by the local

secretion of specific chemokines (MCP-1 and RANTES) and cytokines (IL-5) that attract eosinophils, together with the expression of specific components of the adhesive molecule repertoire that trap them in local microvessels prior to their directed emigration. CD4<sup>+</sup> T cells and mast cells are probably responsible for most of the IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 necessary for eosinophil production, recruitment and activation. Extravasated eosinophils are much longer-lived in tissues than are neutrophils, and cytokines such as IL-5 and GM-CSF that are important in the 'supply side' of eosinophils also have major effects in prolonging the functional longevity of these cells in tissues by exerting major inhibitory effects on eosinophil apoptosis, the process of natural cell death that controls the ultimate removal of extravasated granulocytes [68].

### Neutrophils (neutrophilic polymorphonuclear leucocytes)

The importance of these cells in human asthma is uncertain at present. In a number of experimental animal models of asthma there is a relationship between neutrophil influx and airway hyperresponsiveness, and the *Alternaria*-rabbit model appears to be neutrophil-dependent [69]. In equine 'heaves', a syndrome very like asthma that is due to exposure to allergens in mouldy hay, the disease is associated with neutrophil, not eosinophil, accumulation in the airways. However, in established human asthma, eosinophils rather than neutrophils are usually the dominant granulocyte in histological sections of the airway, although neutrophils are certainly present in significant numbers in most cases. In dynamic studies of allergen-challenged atopic patients, a wave of neutrophil migration precedes eosinophil migration. The neutrophil contains an enormous armamentarium of preformed agents in its granules (see Chapter 27) and is able to rapidly synthesize a range of agents, including PAF and cyclooxygenase products that are important in the effector limb of asthma pathogenesis. It is perhaps also worth considering that because the neutrophil lives for a much shorter time in tissues than do the eosinophil, lymphocyte and macrophage, the comparative paucity of neutrophils on histological sections could in fact represent a major tissue throughput and the neutrophil may play a more important role than has hitherto been thought.

### Lymphocytes

Lymphocytes are blood-borne leucocytes responsible for the classical immune response. They can also be regarded as tissue cells since, in the process of lymphocyte recirculation, they pass through the high endothelial venules of organs including the lung, transit the tissues and return to the bloodstream via the lymphatics. The expression of clonally distributed specific receptors for antigen is characteristic of both B and T lymphocytes, although the function of B lymphocytes is generally restricted to immunoglobulin synthesis and, in the lymph nodes, antigen presentation. T cells can be separated broadly into helper or regulatory (CD4<sup>+</sup>) cells and effector/cytotoxic (CD8<sup>+</sup>) cells based on their surface expression of CD4 or CD8 coreceptors. The important role of allergen-specific B lymphocytes in synthesizing IgE has long been recognized as a key mechanism in allergic asthma, although it is now clear that the T cell also plays a vital role in this response by acting as a helper cell and by secreting IL-4, which is responsible for switching B-cell immunoglobulin secretion from IgG to IgE.

However, it is now becoming apparent that CD4<sup>+</sup> T cells may play a number of other important roles: they are the only cells that can recognize and directly respond to

processed antigen on the surface of antigen-presenting cells (APC) and they are likely to represent the major airway tissue source of IL-5, GM-CSF and IL-3, which promote eosinophil recruitment, activation and longevity. In mice, antigen-activated CD4<sup>+</sup> T-cell clones can be divided broadly into two functional phenotypes [70,71]:

1 Th1: secretes IL-2, interferon (IFN)- $\gamma$  and TNF- $\alpha$  (*not* IL-4, IL-5, IL-6);

2 Th2: secretes IL-4, IL-5 and IL-6 (*not* IL-2, IFN- $\gamma$ , TNF- $\alpha$ ).

However, both types of cell secrete IL-3 and GM-CSF. It is not yet certain how directly applicable this subdivision is to humans, but it is clear that Th1 and Th2 patterns of cytokines may be dominant in different circumstances. A Th2 type of response would favour IgE synthesis (which is also inhibited by IFN- $\gamma$ ) and activation of mast cells and eosinophils, and there is preliminary evidence for this pattern of response in human asthma [72–75]. Bronchoalveolar lavage fluid from asthmatics contains increased concentrations of Th2 cytokines and the mononuclear cells from bronchoalveolar lavage fluid contain mRNA for IL-4, IL-5 and GM-CSF [76–78]. However the exact role of CD4<sup>+</sup> cells and possible regulatory role of CD8<sup>+</sup> cells require further clarification.

### Mediators

Hundreds of mediators have been implicated in the inflammatory and immunological processes that contribute to the pathogenesis of asthma, and it is difficult to know how best to categorize them, whether as biochemical groupings or under headings relating to their biological effects. One of the problems with the latter approach is that single mediators may possess a number of very different actions. Furthermore, for a single key function there are usually many different mediators, often from different biochemical cascades, that exert the same action. For example, there are a large number of agents that are chemotactic for neutrophil granulocytes, such as C5a in the complement cascade, LTB<sub>4</sub> in the prostanoid cascade and a variety of chemokines from the C-X-C subclass including IL-8, ENA-78 and gro- $\alpha$  (see Table 33.3). There are numerous examples of this type of redundancy, which probably evolved as an important part of the inflammatory and immune responses against microorganisms, for example should a bacterium develop an escape mechanism against a particular mediator, then there are a number of different back-up mediators to perform that action. Thus the mediators to be described should perhaps be considered as a network or web rather than as a series of pathways. Rather like a spider's web, if one strand is lacking this does not necessarily impair its overall integrity. This remarkable redundancy is undoubtedly of enormous value in antimicrobial host defence. However, when this same concept is considered from the perspective of designing effective mechanism-based therapy in inflammatory and immuno-

**Table 33.3** Some members of the chemokine family of small peptides. ENA, epithelial neutrophil-activating protein; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; NAP, neutrophil-activating peptide.

C-X-C subgroup
IL-8 (NAP-1)
NAP-2
ENA-78
gro- $\alpha$ 1
Platelet factor 4
C-C subgroup
MIP-1 $\alpha$
MIP-1 $\beta$
RANTES
MCP-1
MCP-2
MCP-3

logical diseases such as asthma, where these complex networks are part of the disease pathogenesis, the prospects are indeed daunting. Although, intuitively, it would seem futile in established inflammatory/immunological diseases to adopt a single mediator strategy, there have indeed been attempts to do just this. To exemplify this problem, PAF can provoke virtually all the features of asthma (see below), yet when an extremely effective PAF antagonist (WEB2086), which blocks almost all its effects in model systems, was assessed in human asthma it was found to have no beneficial effects [79]. Glucocorticoids are likely to be effective in most cases of asthma because they have multiple actions at different points in the cellular and mediator events, yet unfortunately they also cause adverse effects. It seems likely that unless we are fortunate to identify key anchor strands of the spider's web of mediators, therapeutic strategies will need to be directed at more than one mediator or mechanism.

In this section the important mediators are described under the headings histamine, kinins, lipid mediators, cytokines and chemokines. The mechanisms whereby these agents might cooperate in the integrated cellular and mediator responses that characterize the asthmatic state are then considered.

### Histamine

The main source of histamine is the mucosal mast cell, although eosinophils may also contribute. Via the airway H<sub>1</sub> receptors, histamine causes rapid bronchoconstriction and induces dilatation and leakage of microvessels, which results in airway oedema and further narrowing of the bronchial lumen [80,81]. Histamine is thought to stimulate secretion of mucus in human airways via the H<sub>2</sub> receptor [82]. While it is likely to be an important mediator in all stages of asthma and particularly the early response, anti-histamines have proved disappointing in the treatment of human asthma, perhaps because of the redundancy factor

since prostanoids, leukotrienes and PAF can mimic most of its actions.

### Kinins

Bradykinin is detected in the bronchoalveolar lavage fluid of atopic patients after allergen challenge of the airways [83]. It acts as a potent constrictor of human airways *in vivo* [84], perhaps acting by indirect mechanisms such as the release of sensory neuropeptides and lipid mediators. Bradykinin is probably generated from preformed kininogens in plasma as a result of the action of kallikrein and mast cell tryptase. In addition to its action on smooth muscle and airway sensory nerves, it is a potent vasodilator and inducer of microvascular leakage and airway mucous secretion [85,86].

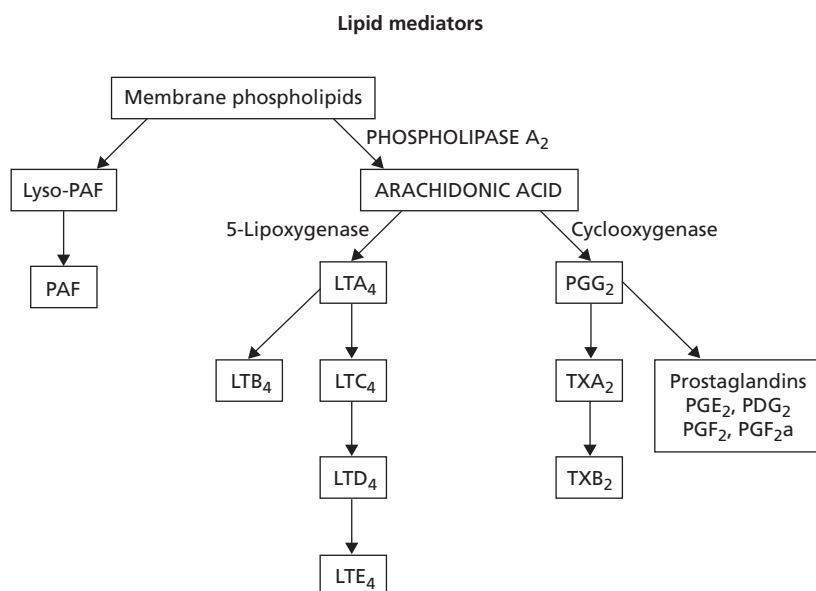
### Lipid mediators (Fig. 33.3)

#### Cyclooxygenase products

A wide range of inflammatory cells are able to synthesize the cyclooxygenase products (or prostanoids, i.e. prostaglandins and thromboxane) from membrane phospholipids; certainly macrophages and granulocytes are potent in this regard. Recent research has identified two forms of cyclooxygenase: COX1, a constitutive form present in unstimulated cells; and COX2, a form induced by TNF- $\alpha$  and other proinflammatory cytokines [87]. Unlike COX1, COX2 is inhibited by corticosteroids [87] and is likely to be responsible for the increased level of prostanoids found in the airways of asthmatic patients and atopic patients challenged with allergens [88,89]. PGD<sub>2</sub> and PGE<sub>2</sub> cause constriction of the airways by activating thromboxane TP<sub>1</sub> receptors, as do TXA<sub>2</sub> and its more stable metabolite TXB<sub>2</sub>. PGD<sub>2</sub> also primes or enhances the airway bronchoconstrictor response to histamine in asthmatic patients. Other prostanoids, including PGE<sub>2</sub> and PGI<sub>2</sub> (prostacyclin), may exert bronchodilator effects. The prostanoid family is likely to contribute to the bronchoconstrictor effect *in vivo*, as do many other redundant mediators, although potent cyclooxygenase inhibitors alone do not exert major beneficial effects on asthma *in vivo* [90].

### Leukotrienes

Activation of 5-lipoxygenase, particularly in macrophages, mast cells and granulocytes, results in the synthesis of LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>. Raised levels of these agents are found in bronchoalveolar lavage fluid after allergen challenge of atopic subjects [89,91]. LTB<sub>4</sub> is a potent neutrophil chemoattractant that has little effect on eosinophils and its role in asthma is uncertain. The sulphidopeptide leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>) are potent



**Fig. 33.3** Lipid mediators derived from membrane phospholipids that have a role in the inflammatory processes involved in asthma.

bronchoconstrictors and can induce bronchial hyperresponsiveness [92,93]. They can also exert potent effects on airway microvascular leakage and airway mucous secretion. It is possible that these agents may play a centrally important role in asthma and new 5-lipoxygenase inhibitors are being developed commercially, particularly directed against 5-lipoxygenase-activating protein (FLAP) [94]. Preliminary studies with LTD<sub>4</sub> antagonists show effectiveness against exercise- and aspirin-induced asthma.

#### Platelet-activating factor

This lipid mediator is synthesized by inflammatory macrophages and granulocytes. It was originally discovered through its action on platelets [95], although it has now become clear that it can mimic many of the features of asthma, including; bronchoconstriction and mucous secretion [93,96,97], and is a potent inducer of microvascular leakage [98]. It has also been found to exert important influences on inflammatory cells, including eosinophil recruitment, endothelial activation and eosinophil degranulation [99–102]. While it is likely that PAF makes important contributions to the mediator network in asthma, it does not seem to have a unique role because the powerful PAF antagonists (e.g. WEB2086) that block the effects of PAF *in vitro* and *in vivo* [103,104] are of little benefit in human asthma [79].

#### Cytokines and growth factors

The cytokines are a family of peptides secreted by inflammatory cells (and also some resident tissue cells) that cooperate to orchestrate the initiation, amplification and,

finally, cessation of the inflammatory and immune responses, plus the regulation of repair responses required to restore tissue integrity. The family now exceeds 50 members (see Table 33.1 for some of the more important ones), which are involved in a complex interplay with each other and with a variety of cells types in the regulation of these important tissue responses. Full understanding of the roles of the cytokine network has been hindered not only by the discovery of new family members almost weekly but also by the facts that (i) there is marked redundancy in many of the mechanisms (a variety of cytokines may exert the same action), (ii) the same cytokine may have multiple effects including different effects on different cells and (iii) some cytokines may require prior interaction with other cytokines before their own effects are revealed.

#### Interleukin 1

IL-1 has important direct actions on microvascular endothelial cells, activating them and upregulating their expression of adhesion molecules necessary for leucocyte trapping and emigration. It exerts important secondary effects by stimulating resident cells, such as fibroblasts and airway epithelial cells, to secrete IL-8 and GM-CSF [105,106]. Thus it is considered to be a key mediator in the control of the early-release mediators involved in the initiation of the inflammatory response, although it is not specific to the allergic response seen in asthma.

#### Tumour necrosis factor $\alpha$

There is much evidence for the release of this peptide and expression of the TNF- $\alpha$  gene in asthmatic tissues and in

allergen-provoked atopic patients [107,108]. It is secreted by macrophages and other inflammatory cells and also by bronchial epithelial cells. Like IL-1, it is likely to play an important role in the initiation of inflammation because it is a potent inducer of GM-CSF and IL-8 secretion by epithelial cells and fibroblasts and it activates microvascular endothelial cells to express intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 [105,106,109,110].

### **Interleukin 3**

IL-3 is centrally important in haematopoiesis, particularly the growth and differentiation of neutrophil and eosinophil granulocytes, mast cells and basophils. At the inflamed site it is likely to promote eosinophil survival.

### **Interleukin 4**

Like IL-3, IL-4 is one of the Th2 group of cytokines produced by a subpopulation of CD4<sup>+</sup> T lymphocytes, although it can also be produced by mast cells in asthmatic patients [40]. Together with CD40L it is likely to play a critical role in switching B-lymphocyte immunoglobulin secretion from IgG to IgE [111]. It may also be important in inducing the expression of endothelial adhesion molecules (e.g. VCAM-1) that are important in monocyte and eosinophil emigration [112].

### **Interleukin 5**

IL-5 is produced by the Th2 subpopulation of CD4<sup>+</sup> lymphocytes and can also be secreted by mast cells. This cytokine is likely to be centrally important in asthma because of its major effects on various aspects of eosinophil function. It is necessary for the final differentiation of eosinophils in the bone marrow, their recruitment to the inflamed site, their activation [113] and, by inhibiting their inherent rate of apoptosis, is likely to exert important inflammatory amplification effects by prolonging their tissue longevity [68]. Raised levels of IL-5 have been found in the bronchoalveolar lavage fluid of asthmatic patients and atopic patients who have been challenged with allergens [114,115].

### **Granulocyte-macrophage colony-stimulating factor**

GM-CSF is produced by macrophages, granulocytes, lymphocytes and airway epithelial cells. It is important in the haematopoiesis of inflammatory cells, in priming macrophages, neutrophils and eosinophils for subsequent secretory responses and, by inhibiting apoptosis, in prolonging the functional lifespan of neutrophils and eosinophils. Once again, there is evidence for the expression and secretion of this important cytokine in asthma

and in allergen-induced bronchoconstriction in atopic patients.

### **Growth factors**

Attention has recently been drawn to the possible importance of thickening of the subepithelial basement membrane and the subepithelial fibrosis that has been observed in necropsy studies of asthmatic patients. Platelet-derived growth factor (PDGF), which in spite of its name is mostly derived from macrophages, exerts potent effects on fibroblast functions, including proliferation and collagen synthesis. Transforming growth factor  $\beta$  (TGF- $\beta$ ) and fibroblast growth factor (FGF) also stimulate fibroblast replication and collagen secretion. These cytokine growth factors may also promote smooth muscle proliferation and vascular remodelling in the chronic asthmatic airway.

Most cytokines so far discovered exert proinflammatory or profibrotic effects, yet in the healthy individual the beneficial inflammatory response to injury or infection is exquisitely controlled, with minimal damage to host tissues, prompt resolution and a fibroproliferative response (see Chapter 27) just sufficient to complete the minor repairs necessary to restore tissue integrity. It is possible that this tight regulation is achieved at the level of synthesis and secretion, although analogies in other cascades such as blood coagulation suggest that there are likely to be numerous inhibitory cytokines or partner molecules that keep cytokine responses in check. IL-12 exerts a number of inhibitory influences, particularly on macrophages, and the soluble form of the IL-1 receptor inhibits several early events in the initiation of inflammation; there are probably many more inhibitory cytokines to be discovered, some of which may yet be of therapeutic value.

### **Chemokines**

The comparatively recent discovery of this family of small peptides, many of which exert powerful and specific chemoattractant influences, has generated much interest. Until now there has been no really plausible explanation for the attraction of specific cell types at different stages of the inflammatory response and in different types of inflammation. Furthermore, the molecular characterization of specific chemokine receptors may lead to incisive therapeutic approaches in allergic inflammation. This family of mediators has been broadly divided into the C-X-C subgroup, in which the cysteine residues of the peptide are separated by an interposed amino acid, and the C-C subgroup where this is not the case (Table 33.3). In humans, the genes encoding the C-X-C group are located on chromosome 4 and those encoding the C-C group on chromosome 17. The C-X-C group contains the neutrophil

chemoattractants IL-8, neutrophil attractant protein (NAP)-2, gro- $\alpha$  and ENA-78. Platelet factor 4 is closely related molecularly but is not a chemoattractant. Lung macrophages are extremely potent producers of IL-8, which was originally classified as a cytokine but molecular characterization resulted in its reclassification as a chemokine. It is specifically chemotactic for neutrophils, although it is thought that in the presence of IL-4 it may also attract eosinophils. It also has important but poorly understood roles in neovascularization. In contrast, the C-C chemokine RANTES is a potent and specific chemoattractant for eosinophils [116,117], whereas its close relative macrophage-inhibitory protein-1 $\alpha$  (MIP-1 $\alpha$ ) is involved in monocyte and eosinophil chemoattraction.

### Orchestration of cellular and mediator events in the pathogenesis of asthma

As mentioned above, most asthma attacks in human disease probably involve elements of both the early and late responses observed when atopic individuals are exposed to airway-delivered specific allergens. Nevertheless, as a simplification of the very complex events *in vivo* it is helpful to consider each separately.

#### Early asthmatic response

In the sensitized individual, mast cells and perhaps also basophils are triggered by IgE, which binds via the high-affinity IgE receptor (Fc $\epsilon$ R1), causing prompt degranulation and secretion of preformed granule contents including histamine and tryptase (Fig. 33.4). Histamine causes rapid airway responses, including bronchoconstriction, vasodilatation/oedema and mucous secretion. Mast cell tryptase exerts direct actions on the airway but also activates the kinin system to generate bradykinin, a

powerful bronchoconstrictor. Activated mast cells also synthesize potent vasoactive and bronchoconstrictor agents, including PGD<sub>2</sub> and LTC<sub>4</sub>/LTD<sub>4</sub>/LDE<sub>4</sub>. The IgE that triggers mast cells is generated by T lymphocytes that have been activated by processed antigen on the surface of antigen presenting cells (APCs). Mast cells can also be triggered by cold air or by changes in the osmolality of the local tissue fluids. In the complex inflammatory picture of the chronic asthmatic airway, other cells including macrophages and granulocytes that display the low-affinity IgE receptor may also contribute to the synthesis and secretion of important vasoactive and bronchoconstrictor agents, including leukotrienes, prostanoids and PAF.

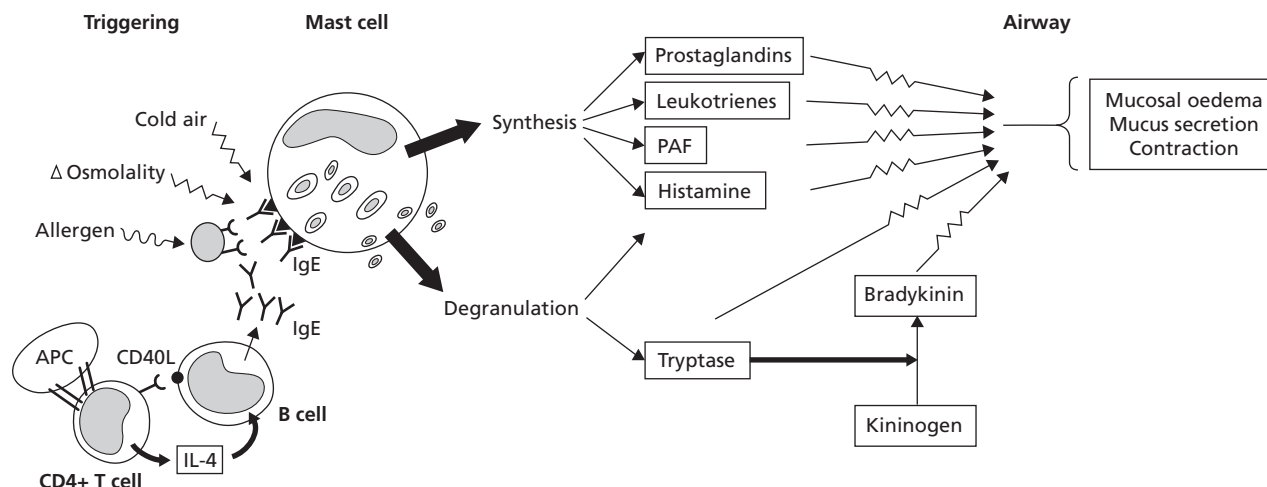
#### Late asthmatic response

Most asthmatic attacks in patients probably include elements of the mechanisms involved in the early asthmatic response but also involve major contributions from inflammatory cells (macrophages, neutrophils, eosinophils) and immune cells (lymphocytes), which have more complex, more prolonged and perhaps more damaging effects. The likely cellular events that follow the acute events described above when a sensitized individual is exposed to specific antigens are considered now. The discussion is divided into the cell recruitment phase and the effector mechanism phase, where products of inflammatory cells are likely to cause the histological features seen in severe asthma. However, while useful as a framework for understanding, the distinction is again somewhat artificial because in asthmatic patients acute and chronic inflammatory cells are often already present in airway tissues and because some damaging mechanisms are likely to have been initiated before cellular recruitment is complete.

#### Cell recruitment

Neutrophils are the first cells to arrive in the challenged

Fig. 33.4 Summary of the acute asthmatic response.





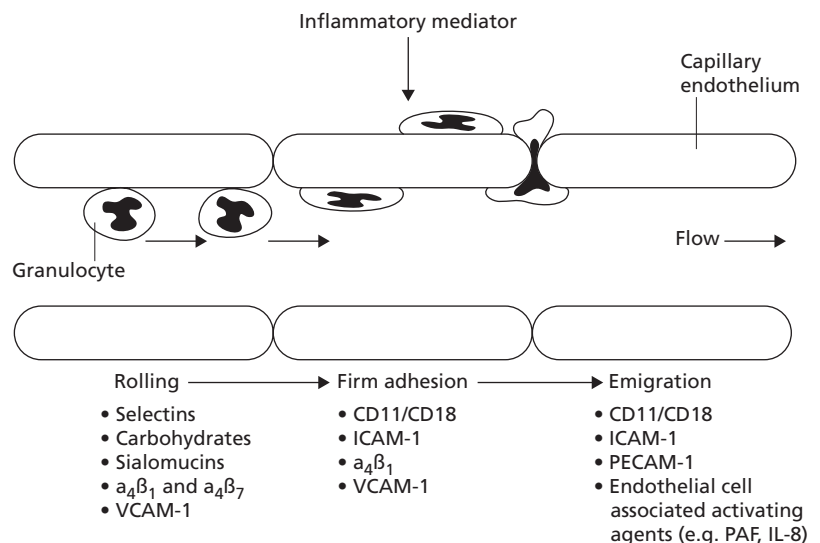
airways, followed by eosinophils and monocytes, which mature into inflammatory macrophages. The attraction of specific inflammatory cells is mediated by chemotactic factors. For the neutrophil, these would include the complement product C5a, LTB<sub>4</sub> and a number of chemotactic chemokines in the C-X-C group. IL-8 is perhaps the most relevant and powerful neutrophil chemokine in the lung. Eosinophils are attracted by a number of mechanisms, perhaps by the specifically eosinophilic chemoattractant peptide RANTES and a new member of the family the eosinophil-specific eotaxin [116–118]. Monocytes can be attracted by a number of chemokines in the C-C group. The selective emigration of neutrophils, eosinophils and monocytes is mediated initially by a trapping phase in the local microvessels followed by transmigration of the endothelial cell layer in the microvessels within the airway. This is a multistep process, the adhesion component occurring in at least two phases that utilize different components of the adhesion molecule repertoire (see Table 33.2). The early arrest phase of transient adhesion in microvessels requires adhesion molecules of the selectin family, whereas the tight adhesion that is a necessary prelude to capillary transmigration (Fig. 33.5) depends upon activation of molecules of the integrin family. Although current reports are a little confusing, it seems that under some circumstances eosinophils and monocytes may use components of the adhesion molecule repertoire (such as VCAM-1) that differ from those used by neutrophil granulocytes. This selective use of the adhesion molecule repertoire, together with the generation of chemokines with specificity for the different inflammatory cells, probably accounts for the selective accumulation of eosinophils in allergic responses and also for the differential timing of arrival of inflammatory cells at the inflamed site (neutrophils followed by monocytes and eosinophils). These selective mechanisms may also provide potential

targets for the development of new therapies in asthma and other allergic conditions.

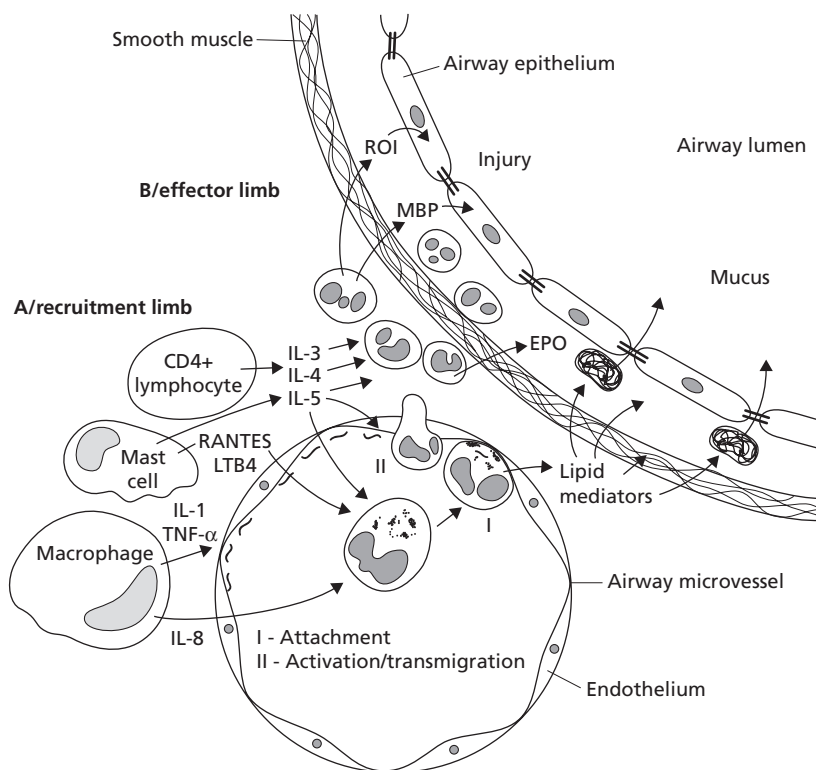
There is *in vivo* evidence that these early recruitment mechanisms are operating in human asthma and its models. During the late response to inhaled allergen, a number of poorly characterized chemotactic factors for neutrophils and eosinophils can be detected in circulating blood [50,119,120]. Bronchial biopsies taken after allergen challenge show increased numbers of neutrophils, eosinophils and T cells [121,122]. Immunocytochemistry shows increased expression of ICAM-1, which correlates with the accumulation of leucocytes, and other molecules (see Table 33.2) involved in leucocyte adhesion to vascular endothelium [123,124]. Experimental studies in non-human primates have shown that monoclonal antibodies directed against ICAM-1 and E-selectin are able to attenuate the allergen-induced late reaction. The increased expression of ICAM-1 and other adhesion molecules on the surface of activated endothelial cells is likely to be mediated by cytokines such as IL-1, TNF- $\alpha$  and IL-5, which are probably derived from macrophages and T lymphocytes in the asthmatic airway [125]. However, these cells take several hours to synthesize these agents, whereas mucosal mast cells store preformed TNF- $\alpha$ , IL-5, IL-6 and other cytokines and chemokines in their granules and which can be released rapidly by cross-linking of the IgE receptor. Thus mast cells may make a variety of important contributions to early pathogenetic events in asthma.

#### Effector mechanisms (Fig. 33.6)

Once recruited to the airways, extravasated neutrophils and eosinophils are able to secrete a large number of histotoxic granule contents (see Chapter 27), including elastase, collagenase, MBP and EPO, many of which have been implicated in endothelial injury but which also contribute



**Fig. 33.5** Stages of granulocyte adhesion and emigration in microvessels.



**Fig. 33.6** Inflammatory response and asthma effector mechanisms. ROI, reactive oxygen intermediate.

to vascular responses and mucous secretion. They can also release a wide range of highly histotoxic reactive oxygen intermediates, including superoxide anion, hydrogen peroxide and hydroxyl radicals, and synthesize a range of important leukotrienes and prostanoids that cause airway narrowing, mucosal oedema and increased mucous secretion.

#### *Vascular responses*

The inflammatory response stimulates increased blood flow in the local airway microvessels which, in concert with increased vascular permeability, causes mucosal oedema and extravasation of plasma proteins. Mucosal oedema probably plays a major role in the airway narrowing and increased airflow resistance that characterizes severe asthma. Plasma-derived mediators like bradykinin cause bronchoconstriction, mucosal oedema, increased mucous secretion and, by inhibiting mucociliary clearance, contribute to mucous plugging of the airways. In chronic severe asthma, angiogenesis is probably involved in the process of airway remodelling. A number of inflammatory cytokines, including IL-1, FGF and PDGF, and the chemokine IL-8 have been implicated in angiogenesis.

#### *Airway smooth muscle*

There may well be no inherent change in smooth muscle contractility in asthma [126], although clearly many

mediators cause bronchoconstriction both directly and indirectly via release of neuropeptides and by influencing local nerve axon responses. There is also evidence of increased smooth muscle thickness, which may be the result of both hypertrophy and hyperplasia. Like vascular remodelling these changes are probably brought about by the action of growth factor cytokines such as PDGF.

#### *Epithelial injury and shedding*

Epithelial changes range from epithelial stimulation and minor injury to epithelial shedding and even extensive areas of denudation [4,122]. Many inflammatory cell products, including reactive oxygen intermediates and granule enzymes, are capable of injuring the airway epithelium, but the highly cationic eosinophil products MBP and EPO are particularly implicated. The fact that a diverse range of agents, such as viruses, allergies, chemicals and toxic gases, may lead to airway hyperresponsiveness may in part be explained by their common property of causing epithelial damage. Depending on the degree of epithelial injury, there may be a variety of consequences of relevance to the pathogenesis of asthma.

1 Injured and stimulated epithelial cells may themselves secrete a variety of important mediators, cytokines and chemokines, for example GM-CSF, IL-1, IL-8, RANTES. In responding to macrophage-derived IL-1 and TNF- $\alpha$  by secreting a range of chemokines, it is believed that the

epithelium, a rich source of IL-8 for example, may exert important amplification effects in the evolution of the inflammatory response.

2 Significant denudation of the epithelium may itself result in a variety of important secondary effects:

- (a) loss of the epithelial barrier function may permit direct access and influence of allergens and other proinflammatory factors (e.g. pollutants) on tissue cells including mast cells;
- (b) loss of airway epithelial cells reduces the ability to degrade peptide and kinin mediators and to secrete

epithelial-derived relaxant factor, which may help to maintain airway dilatation;

(c) sensory nerve exposure may promote inflammation and bronchoconstriction by local nerve axon reflex mechanisms [127].

(d) epithelial denudation may provoke proliferation of myofibroblasts normally located beneath the epithelial membrane, and proliferation of these cells and their secretion of extracellular matrix protein including collagen may contribute to the thickened basement membrane described in chronic asthma [128].

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# ASTHMA: CLINICAL FEATURES

ANTHONY SEATON AND GRAHAM CROMPTON

## What is asthma?

The word 'asthma' is Greek, meaning 'breathless' or 'to breathe with open mouth'. Originally applied to shortness of breath of any cause, as in the description of the mode of death of metal miners ('from the disease the Greeks call asthma') by Agricola in 1556 [1], it has come to be applied particularly to episodic breathlessness due to bronchial disease. Sir John Floyer in his *Treatise of the Asthma* (1698) used the term in its general sense but confined himself largely to discussing the episodic type from which he himself suffered [2]. By the last century, as in another famous book by an asthma sufferer, Henry Hyde Salter's *On Asthma, its Pathology and Treatment* (1860), it was used specifically to describe this type of breathlessness [3]. Nevertheless, its application, as cardiac asthma, to left ventricular failure has only recently fallen into disuse.

The condition from which Floyer and Salter suffered is so distinctive that it may readily be diagnosed by non-medical people and its name is used in common parlance. It might therefore surprise the layman that there is so much debate about the definition of asthma, but such debate continues and is likely to do so unresolved. This is because, as far as can be seen, asthma results from the interaction of many genetic and environmental influences on the tone or reactivity of the airways, usually by causing inflammation; the response varies from individual to individual and from time to time. No single definition will ever cover all these variables in a way that is likely to be useful, particularly when one considers that asthmatic responses are not likely to be all-or-nothing phenomena but rather gradations of change on a continuum. As with other common diseases, the concept of what asthma is has been modified as knowledge of the disease increases. Originally it was acceptable to think of it in terms of a complex of symptoms and signs, then in terms of distinctive physiological and pathological features. Recently it has been popular to define it in terms of bronchial reactivity, although this leads to the uncomfortable recognition that some quite typically asthmatic subjects have normally

reactive airways between attacks. Of course, any definition in physiopathological terms requires arbitrary decisions about cut-off points between normality and asthma that make artificial distinctions between health and illness on that continuum.

It might therefore be appropriate to consider first why it is necessary to define asthma. From the point of view of the patient and the doctor, the name is unimportant; what matters is the management. Diagnosis leads to treatment and prognosis. For the former, it is necessary to demonstrate a response of the airflow obstruction to various drugs or to exclude exposure to a provoking agent, but for the latter it is desirable to fit the patient's disease into some broad category about which there is a body of medical knowledge on which attempts at prognosis may be based. Thus clinicians have tended to prefer definitions based on variability of symptoms and expiratory flow rates [4]. In contrast, pathologists, based on their experience particularly of fatal asthma, have inclined towards histopathological definitions, for example the presence of characteristic patterns in the sputum or of inflammation on bronchial biopsies or lavage [5,6]. Others, pursuing an interest in clinical pharmacology, have required tighter definitions based on physiological criteria; these definitions have often selected specific subgroups, for example in terms of exercise response [7] or the presence of evidence of cardiac stress in acute severe asthma [8]. Finally, epidemiologists have also needed to devise their own definitions for studies of asthma in populations; these range from positive answers to certain questions in a questionnaire to predefined responses to exercise or bronchial challenge [9,10].

Ultimately, it is conceivable that the propensity to develop asthma given appropriate environmental stimuli may be definable in terms of several chromosomal mutations. It is likely that there are separately inherited components of asthma, some genes leading to the development of atopy and others responsible for the many factors leading to bronchial inflammation and clinical asthma [11]. It has been suggested that the tendency for IgE



responses to occur is conferred by an 'atopy locus' on chromosome 11q [12], although there is dispute about this and other loci have been described [13,14]. However, studies of bronchial hyperresponsiveness in twins that have been adjusted for atopic status have suggested that environmental factors are at least as important as genetic [15,16]. Until we have more knowledge about the inheritance of atopy and asthma we will have to make do with more or less unsatisfactory definitions influenced by clinical, physiological and pathological factors that are inevitably imprecise. No harm will be done by this if physicians are aware of their reasons for using a particular definition or description of the disease, and the uncertainties surrounding it. A useful description of chronic asthma, based on the clinical, physiological and pathological findings, is

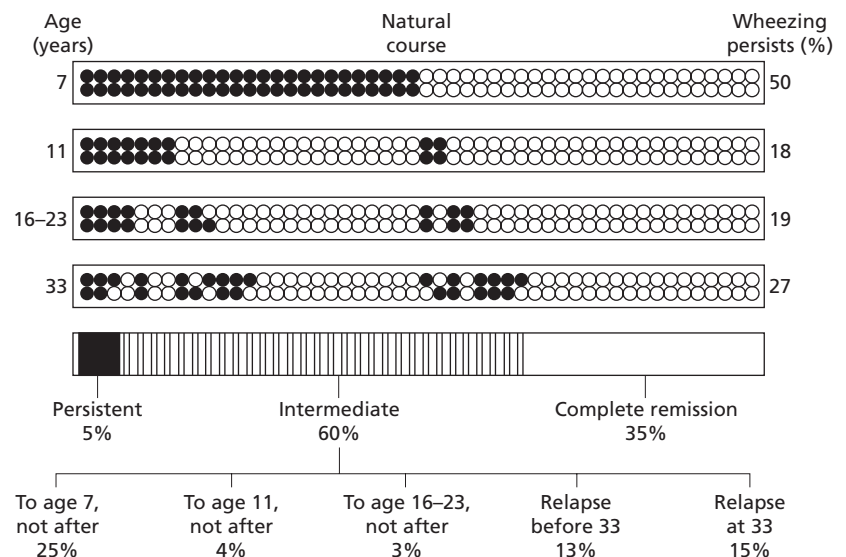
A common and chronic inflammatory condition of the airways. As a result of the airway inflammation the bronchi are hyperreactive and narrow readily in response to a wide range of stimuli. Whilst initially reversible, the inflammation may lead to irreversible obstruction to airflow.

This may then be qualified by a more quantitative definition in terms of, for example, sputum cytology, airway pathology, spontaneous change in flow rates, or responses to bronchodilators, steroids, exercise or bronchoconstrictors.

## Natural history

What happens to asthmatic children in adult life remains somewhat unpredictable [17]. It is a common observation that children with mild asthma tend to improve about the time of adolescence. Clinical and epidemiological studies indicate that 30–80% of asthmatics become asymptomatic

during puberty [18–22]. In the UK the prevalence of asthma or wheeze at the age of 7 has been assessed as 8.3% compared with 4.7% at the age of 11 and 3.5% at the age of 16 [23]. In a study of a 1958 birth cohort of over 18000 British children, Strachan and colleagues [24] showed a cumulative incidence of wheezy illness of 18% by age 7, rising to 43% by age 33. The prognosis in this cohort is shown in Fig. 34.1. Roughly one-quarter of those wheezing at age 7 were still wheezing at 33, and within this overall pattern there was a tendency for remission and later recurrence of symptoms in adult life. Furthermore, new wheezers added to the overall incidence throughout the study. Similarly, in a 25-year follow-up of 2500 primary school children in Scotland, Godden and colleagues [25,26] showed the incidence of new wheezy illness over this period to be 11% of those who had not wheezed in childhood and that these new incidences occurred steadily throughout the period. In a cohort study of Australian schoolchildren tested initially at the age of 8–10 years and then again at 12–14 years of age, the persistence of bronchial hyperresponsiveness at age 12–14 was found to be related to severity of disease at age 8–10, atopic status and parental asthma [27]. It has been suggested that improvement in asthma during adolescence may result from diminished clinical and immunological responsiveness directly related to hormonal changes [28], and that the effect of age on the prevalence of asthma in each sex may relate to differences in hormonal status, influencing airway size, inflammation and smooth muscle and vascular functions [29]. Factors found to predict persistence of asthma appear to be early age of onset of disease (younger than 3 years), infantile eczema (atopic status) and severe disease [30–32], as well as parental asthma [27]. When a cohort of children was assessed at the age of 20, about one-quarter were free from symptoms and had



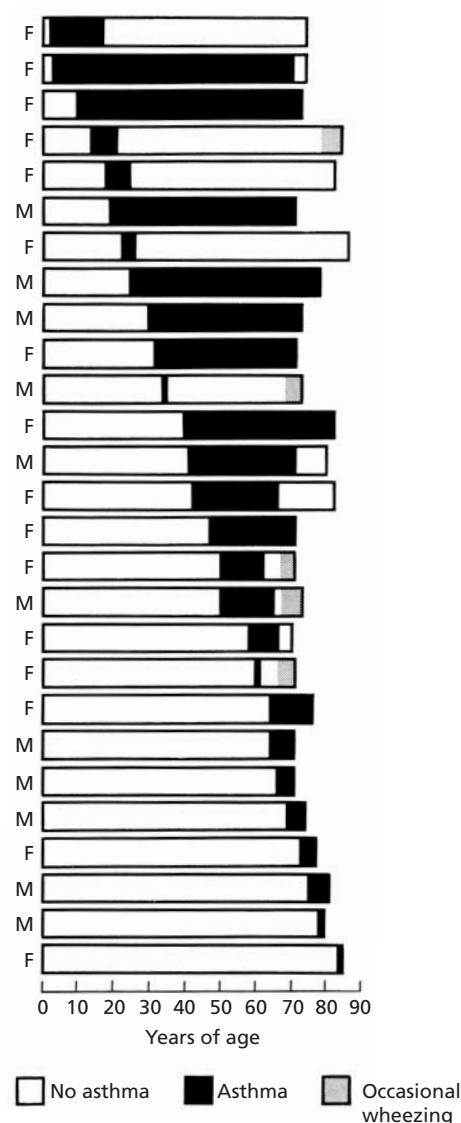
**Fig. 34.1** Prognosis of children who developed asthma or wheezy bronchitis by age 7, each symbol representing 1% of such children. Solid circles represent children reporting asthma or wheeze in the previous year at ages 7 and 11, since their 16th birthday at age 23, and in the previous year at age 33. (From Strachan *et al.* [24] with permission.)



normal pulmonary function tests, half had occasional mild wheezing and some 20% had persistent or frequent wheeze or subnormal pulmonary function tests [33,34]. At the age of 28, 30% of those who were free from symptoms at the age of 21 had relapsed and had recurrent wheeze [35]. This supports the clinical experience that patients who appear to develop asthma in adult life often remember chest symptoms during childhood.

There has been much speculation about the genetic and environmental determinants of childhood asthma. Some of the factors related to the development of atopic sensitization that have been discussed include exposure to allergens, infectious diseases, or tobacco smoke early in life. The dietary habits of the mother may also be important but the effects of outdoor air pollution are likely to be unimportant [36]. This and other potential risk factors for asthma are discussed below. One cross-sectional study of elderly people with a history of asthma, detected in a random survey of a town's population, attempted to trace back the natural history of the disease by clinical questioning [37]. Even allowing for problems with memory and diagnosis, this illustrated the liability of asthma both to start and to remit at any age (Fig. 34.2).

Prospective population-based studies of the natural history of asthma in adults are few and, like the studies in children, are limited by difficulties in defining the disease. Most of the patients whose asthma persists from childhood have allergy to various aeroallergens, although the genuine new-onset adult asthmatics have allergic symptoms less commonly unless they have developed occupational asthma (see below). The term 'intrinsic' asthma was introduced in 1940 to emphasize that this type is distinct from allergic 'extrinsic' asthma with respect to the absence of an obvious precipitating exogenous cause [38]. The debate about whether intrinsic asthma is a distinct immunopathological entity persists [39]. Of a group of 85 children consecutively referred to an allergy clinic in Copenhagen when aged 5–15, 70 were seen 10 years later [40]; 24 originally had intrinsic asthma, i.e. normal serum IgE and no evidence of allergy from history, skin tests, radioallergosorbent test (RAST) and, in some, specific bronchial provocation tests; the remaining 46 were labelled extrinsic asthmatics. At the 10-year follow-up, 60 (24 intrinsic and 46 extrinsic) had current symptoms and 54 were receiving maintenance therapy. In the patients with intrinsic asthma, outcome appeared to be predicted by a combination of initial frequency of symptoms, initial forced expiratory volume in 1s ( $FEV_1$ ), active smoking and age at onset of symptoms. In the extrinsic group, initial  $FEV_1$  was the strongest predictor for outcome and it was suggested that these differences pointed to different pathogenic mechanisms in the two types of asthma. However, a careful follow-up study of a cohort of wheezy children in Australia, to the age of 28, concluded that there is no difference in outcome between asthma and 'wheezy



**Fig. 34.2** History of asthma symptoms in 27 subjects found in a random sample of people aged 70 or more from a South Wales town. (From Burr *et al.* [37].)

bronchitis' in childhood [33,35]. In the view of the authors, asthma is best thought of as an inflammatory disease of the airways with multiple precipitating causes acting throughout life. In those most strongly predisposed genetically, atopy is a dominant factor and such individuals tend to present early in life. Those presenting in adult life are somewhat less frequently atopic, and factors such as smoking, poor diet, occupational exposures and infections appear to be more relevant to the aetiology than in childhood.

Several studies have investigated mortality from asthma. Interest in this subject was aroused by a sharp rise in mortality in the UK, New Zealand and other westernized countries (but not the USA) in the mid-1960s [41]. Among young people, death rates attributed to asthma

rose to about 2 per 100 000 population per annum, subsequently falling to the more usual levels of about half that (Fig. 34.3). In New Zealand there was a second rise in mortality in the 1970s to about 4 per 100 000 [43]. These changes stimulated a number of clinical and case-control investigations of possible causative factors; excess use of bronchodilators and inadequate use of corticosteroids have been suggested as likely ones [44–50]. The possible role of  $\beta$ -agonist bronchodilators and the increase in mortality, particularly in New Zealand, has caused most concern and has stimulated much debate. The New Zealand 'epidemic' was originally attributed to fenoterol [51]. However, the explanation is not straightforward; although the drug was also available in The Netherlands and the UK, the asthma mortality rates in these countries had returned to the levels observed before 1940 and remained there. Taken together, the time trends suggest a causal relationship between death from asthma and inhalation therapy with  $\beta$  agonists. However, others have rejected the view that the use of  $\beta$  agonists, one of the cornerstones of asthma treatment, is potentially dangerous [52], the argument being that  $\beta$  agonists merely served as a marker of patients with a poor prognosis. There are two main questions that remain unanswered with regard to  $\beta$  agonists: does regular inhaled treatment with these drugs make asthma worse or increase bronchial hyperreactivity either during therapy or after withdrawal and is this form of treatment dangerous when given to, or taken in excess by, the hypoxaemic asthmatic? Of course,  $\beta$ -agonist therapy cannot be an explanation of the increased prevalence of asthma, and whether it has had any role in the fluctuation in severity of patients with severe disease over

the years remains to be answered. There is evidence from experiments with animals that  $\beta$  agonists are much more toxic in the presence of hypoxaemia [53], and this has tended to be forgotten. It has been reported that similar findings resulted when human volunteers were studied in a hypoxaemic state [54]. In general the message from all studies is the slightly depressing one that death commonly occurs as a result of failure by patient or doctor to appreciate the severity of the condition or to take appropriate therapeutic action until too late. The pros and cons of  $\beta$ -agonist therapy are discussed in more detail in Chapter 35.

The actual risk of an asthmatic patient dying of the disease clearly depends on such factors as age, severity of disease, and availability and quality of medical care. Asthma deaths are rare in children, accounting for just over 1% of total deaths [55]. Thereafter, the risk increases exponentially with age (Fig. 34.4). Interpretation of geographical variations and time trends in mortality usually concentrates on deaths among children and adults up to age 35 where there is more confidence in the accuracy of diagnosis. However, only 10% of deaths occur in this age group and the rates for all countries where reliable data are available were similar in the 1990s at 1 per 100 000 or fewer [56].

## Pathology

### Gross pathology

The greatest amount of information on the pathology of the lungs in asthma originally came from necropsy studies of patients who had died from acute attacks [57–61]. However, some information has also been obtained from lungs of asthmatic patients dying of other causes while in remission and from the study of bronchial biopsies, bronchoalveolar lavage (BAL) fluid and sputum from asthmatics. Recently, developments in bronchoscopic techniques and methods to enable patients to produce sputum, together with electron microscopy, have allowed a much more detailed knowledge of pathological airway morphology to be obtained from living patients with mild, moderate and severe disease.

The lungs of asthmatic patients who have died of incidental disease may show the features seen in those who have died of asthma but in a less advanced form. There is usually some overdistension and plugging of airways. In contrast, patients with chronic asthma may die with lungs that look grossly quite normal, despite having had intractable symptoms in life [62]. The lungs of patients who have died of acute asthma are voluminous and do not collapse when the chest is opened at autopsy. When cut, thick and tenacious mucus is seen to be occluding almost all small- and medium-sized airways, but this can extend into the large bronchi. There may be small focal areas of

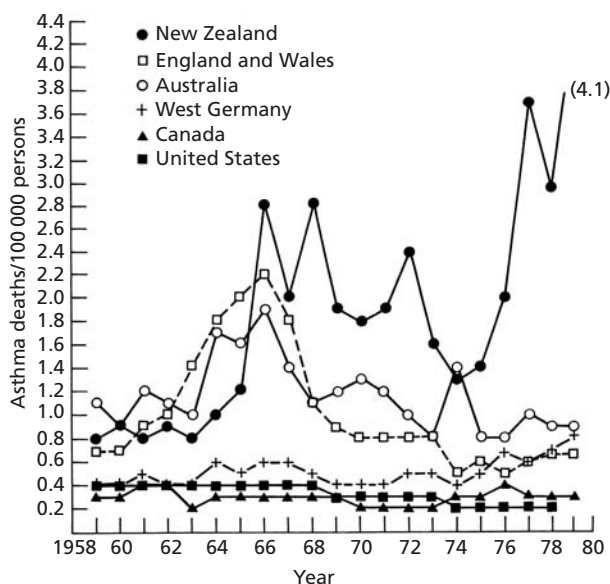
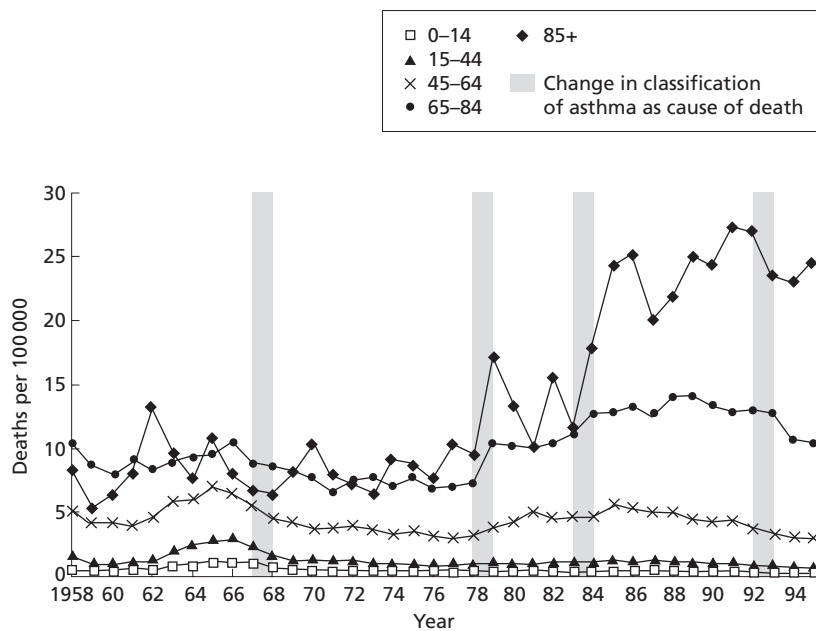


Fig. 34.3 Trends in mortality from asthma in 5–34 year olds in six countries, 1959–79. (From Jackson *et al.* [42].)



**Fig. 34.4** Age-specific asthma mortality rates, males and females combined, England and Wales 1958–95. (From Lung and Asthma Information Agency factsheet 97/3, with permission of Professor Ross Anderson.)

pulmonary collapse. Occasionally, when death has been sudden, widespread airway plugging is absent. Although the lungs are hyperinflated, there is usually no macroscopic evidence of emphysema.

### Bronchial biopsies

Much has been learned about the pathological processes in asthma by examination of bronchial biopsies and BAL fluid. These investigations are safe providing that they are performed by an experienced bronchoscopist and that published recommendations are followed [63,64]. The airway mucosa sampled by biopsy comprises surface epithelium and its supportive subepithelial tissue, often referred to as the lamina propria.

Data obtained by biopsy have shown beyond doubt that asthma is an inflammatory condition, and have provided the basis for the validation of less invasive techniques, such as airway lavage, bronchial brush biopsy and the examination of sputum, either produced spontaneously or induced. Pioneering studies of relatively large biopsy samples obtained using the rigid bronchoscope revealed the mucosal inflammation of asthma, contrasted the pathological appearances in asthma and chronic bronchitis and demonstrated the efficacy of inhaled corticosteroid therapy [65–68]. These studies also revealed the marked airway epithelial disruption in asthma, now accepted as a characteristic pathological feature of the disease even though described as early as 1962 [69]. With the advent of flexible fibreoptic bronchoscopy as a research tool there has been an explosion of interest in the pathological changes in the bronchial epithelium of the asthmatic patient [70]. Initial electron microscopic studies of biopsies

in mild chronic asthma reported the involvement and degranulation of mast cells [71], highlighted a controlling role for the lymphocyte in the inflammatory response, and demonstrated an association between loss of surface epithelium and airways hyperresponsiveness [72]. Most, if not all, of these pathological changes had previously been described in autopsy studies of patients dying from asthma [57,59–61]. These features of inflammation were shown to be present even in patients with newly diagnosed asthma or asthma of apparently recent onset [73].

Studies of bronchial biopsies together with clinical observations have led to the conclusion that early intervention with anti-inflammatory therapy is the most rational approach to treatment of asthma [74]. Homogeneous thickening of the basement membrane, also referred to as the lamina reticularis, is a constant pathological finding and has been shown to occur early in the disease process [72,75], in contrast to the lack of this change in chronic obstructive airways disease [76,77]. Basement membrane thickening in asthma is assumed to represent subepithelial fibrosis and is associated with close proximity of myofibroblasts [75,78]. Studies of bronchial biopsies from large numbers of patients have revealed activation of the CD4<sup>+</sup> subset of T lymphocytes and also eosinophils [79,80]. There appears to be a negative correlation between eosinophil activation and bronchial reactivity [80]. Observation of upregulation of gene expression for the proinflammatory cytokine interleukin (IL)-5, in association with the CD4<sup>+</sup> T lymphocyte, particularly in symptomatic patients [81], has led to the concept of a prevailing Th2 allergic inflammatory profile in asthma in which IL-4, IL-5 and IL-10 predominate [82,83]. Verification of these find-

ings has been achieved by using reverse transcriptase-polymerase chain reaction techniques. The profile of inflammatory cell and cytokine gene expression appears to be similar in different types of disease, such as atopic (extrinsic), non-atopic (intrinsic) and occupational asthma, although there is some debate about the role of IL-4 in intrinsic asthma [84–87].

Bronchial and nasal biopsies have been studied after exposure to allergens. The use of immunohistological and molecular (*in situ* hybridization) techniques has supported the involvement of CD4<sup>+</sup> T cells, mast cells and eosinophils, together with IL-4, IL-5 and IL-10 [82,88–90]. There is also great interest in the role of cell-surface adhesion molecules in the epithelial inflammatory events of asthma and allergy [91–93]. Myofibroblast numbers increase in response to allergen and transitional ultra-structural forms between fibroblasts and bronchial smooth muscle cells are found [94]. This suggests a possible mechanism to explain the increase in bronchial smooth muscle that is a characteristic feature of the airway wall remodelling found in severe asthma [95]. Exposure to toluene diisocyanate (TDI) in workers who develop occupational asthma resembles allergen exposure in many aspects, although in addition there is a marked recruitment of neutrophils [86,96,97].

Bronchial biopsies have been used to assess the effects of various treatments on the asthmatic bronchial epithelial inflammation. Inhaled corticosteroid therapy has been shown to improve these pathological changes [98–100] and the changes in bronchial biopsy appearances have been associated with symptomatic improvement. Similar improvements in symptoms and bronchial epithelial pathology have been reported in non-allergic asthma [101]. The anti-inflammatory properties of some other drugs have been assessed by bronchial biopsies, and oral theophylline has been shown to have some activity after 6 weeks of treatment compared with placebo in that it decreased cell numbers and the expression of IL-4 [102].

Bronchial biopsies sample mainly the proximal airways and it is somewhat surprising that so much inflammation and remodelling has been found in the large airways in asthma. There is some evidence that the changes in large airways reflect more peripheral pathology in the small airways, and perhaps also in the alveoli [103]. Since biopsies sample such a small fragment of epithelium, one would expect considerable variation between specimens, such that very large numbers of patients would have to be studied to obtain any meaningful data. However, it is reassuring that there seems to be larger intersubject than inter-biopsy site variation, and it has been estimated that study of groups numbering 15 patients should provide sufficient statistical power to detect most of the changes of interest in biopsies from inflamed airways [104].

The inflammatory cell that predominates within the

surface epithelium may be different to that in the tissue beneath it, and cells harvested from the bronchial lumen by BAL may not reflect the cell populations in any section of the bronchial mucosa. This may partly explain differences between biopsy and BAL findings. The correlations between cellular findings of lavage and biopsy specimens are poor and bronchial biopsy remains the gold standard [70]. Bronchial brush biopsies are being used to harvest cells from the bronchial mucosa and may in the future be of value in the assessment of the degree of pathological change in asthma and its response to treatment, if there proves to be a good correlation between these and bronchial biopsies.

### Sputum

Sputum is characteristically viscous. When held up to the light, pale green or white streaks can often be seen in the mucus and, when teased out, these can be shown to be bronchial casts (Fig. 34.5). Recently there has been considerable interest in the cell content and immunobiochemical characteristics of sputum from asthmatics [105]. Sputum is defined as expectorated lower respiratory tract secretions and is composed of fluid and cellular components, including macrophages, bronchial epithelial cells and inflammatory cells. As well as containing water and inorganic ions, it also contains non-dialysable components such as albumin, lysozyme, glycoproteins (including immunoglobulins, macroglobulin, complement and proteases), proteoglycan and lipids, perhaps in part derived from surfactant. Proteins and glycoproteins appear to occur in considerably higher concentration in asthmatic than in bronchitic sputum [106]. IgE is also increased, even in

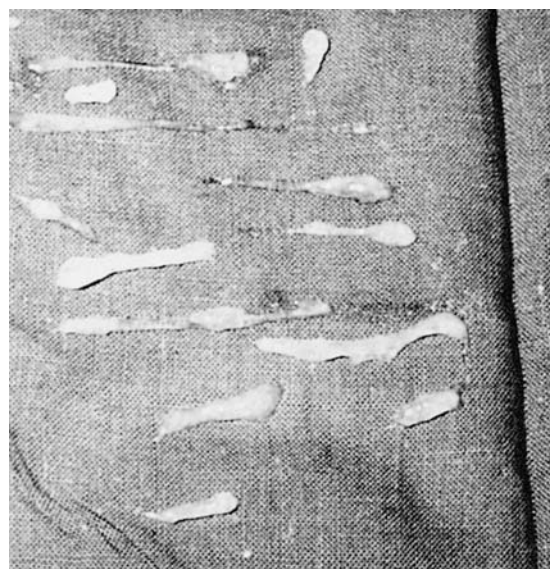


Fig. 34.5 Bronchial casts teased out from the sputum of a patient with asthma.

non-atopic asthma [107]. When expectorated, sputum is always mixed with saliva, composed mainly of fluid, squamous epithelial cells and oropharyngeal bacteria. Sputum contaminated with saliva may be examined for evidence of bronchial inflammation [108], although it is apparent that examination of sputum *selected* from the expectorate is preferable [109–111]. In asthmatic subjects, sputum may be induced by the inhalation of an aerosol of hypertonic saline after pretreatment with inhaled salbutamol [105,112].

#### *Sputum eosinophils*

Sputum eosinophilia is a hallmark of asthma and was shown to be associated with the disease almost 100 years ago. The eosinophil is probably the major effector cell in asthma [113]. Eosinophils arise from a bone marrow-derived progenitor cell and circulate via the bloodstream to the airways [114]. Under the influence of cellular adhesion molecules and cytokines the eosinophils migrate across the endothelium to the airway lumen. Sputum eosinophils in asthma are in an activated state, expressing cleaved eosinophil cationic protein (ECP) and CD11b [115]. Cell adhesion molecules ICAM-1 and HLA-DR are present in sputum eosinophils but not blood eosinophils, and these may allow migration across the endothelium and facilitate interaction with other immunocompetent cells such as T lymphocytes [116]. The eosinophil plays an important role in the pathogenesis of asthma, and sputum eosinophil counts reflect disease severity [112]. Eosinophils occur spontaneously and after allergen challenge in asthma [108,113–118]. Thus eosinophil counts and measurement of their products in sputum have a potentially important role in acting as objective markers of bronchial inflammation in asthma. Sputum eosinophils, and the biochemical markers ECP, albumin and fibrinogen, correlate with the diagnosis of asthma [108,112,117] but not with airway hyperresponsiveness in the absence of symptoms [119]. There is also correlation with disease activity and the magnitude of response following allergen challenge [112,114,120]. Patients with sputum eosinophilia tend to respond well to corticosteroid therapy [118,121,122].

#### *Sputum mast cells*

There is in the region of a 10-fold increase in the number of mast cells in spontaneously produced and induced sputum from asthmatic patients compared with normal subjects or patients with chronic bronchitis [112,117]. Mast cell counts are highest during exacerbations of asthma and increase after allergen challenge [120]. There is no correlation between sputum mast cell numbers and markers of disease severity such as FEV<sub>1</sub> and bronchial provocation tests, whereas in BAL and bronchial brushings mast

cells appear to correlate with airway responsiveness [123,124]. Mast cell mediators such as tryptase and histamine can be detected in induced sputum, although there are no major differences between normal and asthmatic subjects [108].

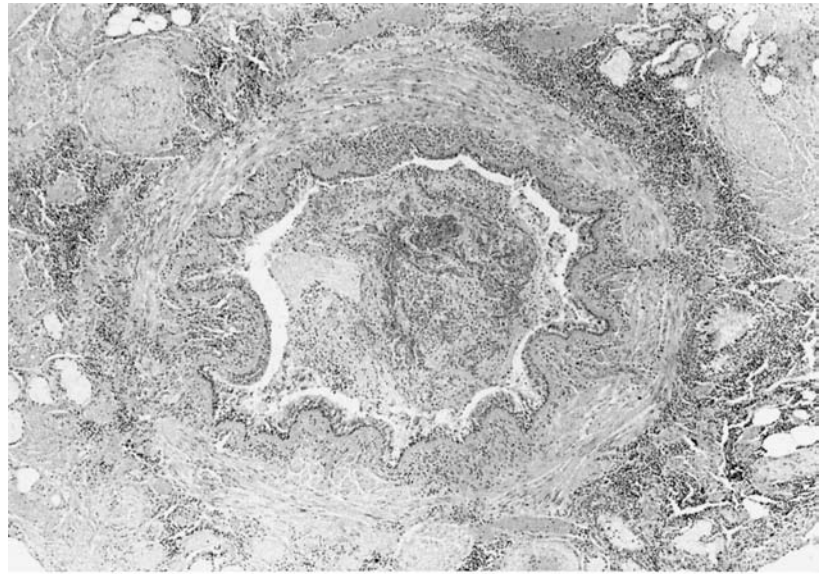
#### **Bronchoalveolar lavage**

BAL is a useful research technique but its role in the investigation and assessment of asthma has yet to be established. Together with other research techniques it has contributed to the understanding of disease mechanisms and treatment effects [125]. Interlobar variability of BAL findings has been assessed. Eosinophil and neutrophil counts are consistent between two lobes from the same individual, indicating that a single-site lavage yields fluid representative of the whole lung; however, there is poor agreement between soluble markers such as the neutrophil product myeloperoxidase and the eosinophil marker ECP [126]. In stable asthma there are increased numbers of eosinophils and mast cells in BAL fluid compared with normals [123], and the same pattern of BAL cell increases has been found in allergic and non-allergic asthma [124]. BAL eosinophils correlate with asthma symptoms, airflow obstruction and airway responsiveness [123,127]. Allergen challenge causes an increase in BAL eosinophils [128] and in eosinophil activation. This is accompanied by increased gene transcription for those cytokines that control eosinophilic function, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [127]. Treatment with prednisolone reduces BAL eosinophils and IL-5 gene transcription at the same time as symptoms are improved [129]. In general there is a correlation between the severity of airways responsiveness in asthma and the numbers of eosinophils, mast cells and their mediators in BAL [130]. In a comparison of induced sputum, bronchial washings and BAL in 16 patients, it was concluded that induced sputum is rich in neutrophils and eosinophils and poor in lymphocytes, suggesting an origin in the larger airways. It was also concluded that induced sputum adequately reflects the findings in fluid collected by BAL [131].

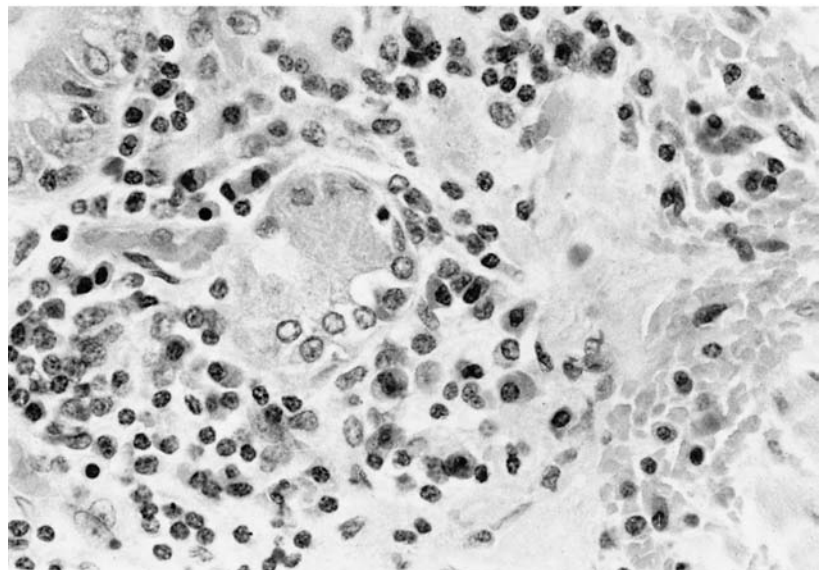
#### **Histological features**

Many of the microscopic features of the asthmatic airway are mirrored in the sputum. The airways of patients who have died from asthma characteristically show smooth muscle hypertrophy and thickening of the basement membrane (Fig. 34.6). The mucous glands are often considerably enlarged. The submucosa is oedematous, infiltrated with eosinophils and lymphocytes, and contains dilated capillaries with swollen endothelial cells. Mast cells may be found in the submucosa, especially in association with small vessels. Internal to the basement





(a)



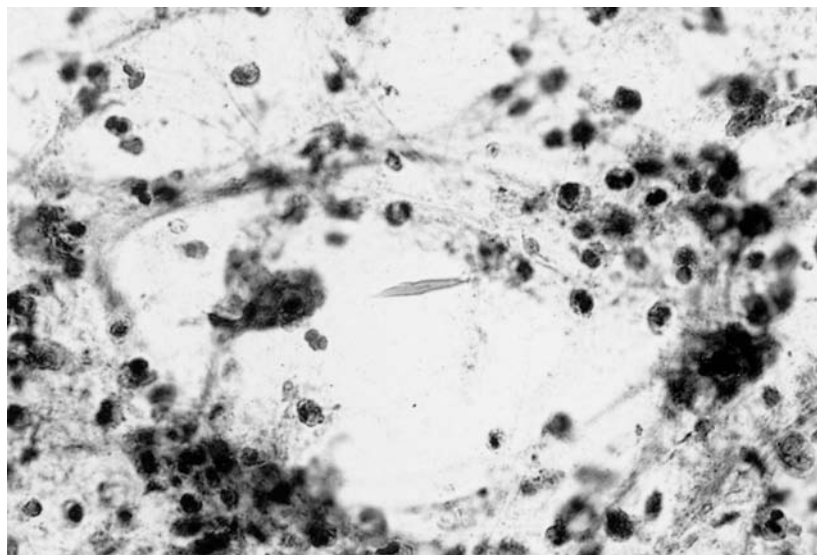
(b)

**Fig. 34.6** (a) Cross-section of bronchus from patient who died of acute severe asthma showing plugging of the lumen by mucus. Note also irregular loss of epithelium, thick basement membrane and hyperplastic smooth muscle. A conspicuous inflammatory cell infiltrate involves the full thickness of the wall (haematoxylin & eosin  $\times 35$ ). (b) Detail of the inflammatory infiltrate showing mixture of lymphocytes, plasma cells, macrophages and eosinophils (haematoxylin & eosin  $\times 335$ ). (Courtesy of Dr Peter Johnston, Department of Pathology, University of Aberdeen.)

membrane, the mucosa may have been almost totally destroyed. It is often very oedematous, the oedema being associated with a denudation of the internal surface cells leaving only basal cells. Remaining epithelium is often metaplastic, showing a stratified non-ciliated structure with prominent goblet cells. Eosinophils are a conspicuous feature of the inflammatory exudate. Within the airway lumen lies thick tenacious mucus that under the microscope is seen to contain strips of desquamated epithelial cells (Curschmann's spirals), eosinophils, isolated metaplastic epithelial cells or clumps of cells (Creola bodies) and crystalline material consisting largely of major basic protein derived from eosinophils (Charcot-Leyden crystals) [5,60,132–134]. These plugs may occur throughout airways of all sizes, sometimes reaching the smallest respiratory bronchioles, possibly by aspiration.

The consequences of these histological abnormalities may be found in the sputum of patients with symptomatic asthma, and are not confined to patients with severe disease (Fig. 34.7).

In contrast to the dramatic evidence of disease in patients dying of asthma, much less marked yet nevertheless similar changes are found in patients who have suffered from chronic asthma but have died from another cause [61]. There may be no plugging and little or no smooth muscle hypertrophy, and relatively few eosinophils in patients who have been treated with corticosteroids. Basement membrane thickening is the only characteristic feature, although mucosal and submucosal infiltration with lymphocytes and plasma cells, mucous gland hyperplasia and some peribronchiolar fibrosis may be seen.



**Fig. 34.7** Photomicrograph of asthmatic sputum showing strands of mucus containing eosinophils, some macrophages and one Charcot-Leyden crystal ( $\times 340$ ).

## Pathogenesis

An understanding of the pathogenesis of asthma requires answers to two questions: what predisposes an individual to show the characteristic pathophysiological airway changes, and how do the known provoking stimuli cause these changes? With respect to the first question, it is a matter of common observation that genetic factors must be important, particularly when the asthma is accompanied by the manifestations of atopy. This is discussed later. However, it is now clear that environmental factors may initiate the asthmatic process, rather than simply provoke attacks in someone already predisposed. The differences in prevalence of asthma in populations transferred to westernized from more primitive societies, between people living different lifestyles in the same country, and the secular changes in prevalence noted in developed countries over the past three decades all suggest an important environmental factor, as does the evidence that certain chemicals may act as initiators of asthma (which persists after exposure has ceased) in some workforces. Similarly, it is also a matter of common observation that adult asthma may be initiated by upper respiratory tract infections, sometimes for a short time but not infrequently permanently. Studies of bronchial reactivity and of responses to inhalation of irritant substances suggest that the liability of airways to constrict in response to such stimuli is distributed normally in the population, and is variable over time, indicating perhaps that all of us may be liable to develop some of the features of asthma in response to stimuli of appropriate severity.

The answers to the second question, namely the mechanisms whereby a stimulus provokes the airway reaction, lie in the study of the cellular, immunological and biochemical control of airway function. Any hypothesis

must explain why similar reactions occur in response to infection, allergic challenge, chemical challenge, exercise, sleep, emotion, ingestion of certain drugs and, indeed, for no obvious reason at all. It must also explain the presence of the characteristic histological and biochemical changes in the airways and their exudate, and must take account of the recognized patterns of response (and, in some cases, failure to respond) to therapy. Not surprisingly, understanding of the mechanisms of asthma remains incomplete; nevertheless, much research effort has been devoted towards this end and much interesting, if somewhat confusing, information has been obtained. In the following discussion, this evidence is considered under the headings of cellular mechanisms, mediators, neural mechanisms and bronchial smooth muscle function. There is evidence that all these factors, which interrelate with each other, play a part in producing the pathophysiological changes of asthma. Before embarking on this discussion, some relatively simple models of asthma are described.

## Simple models of asthmatic mechanisms

### Exercise and hyperventilation

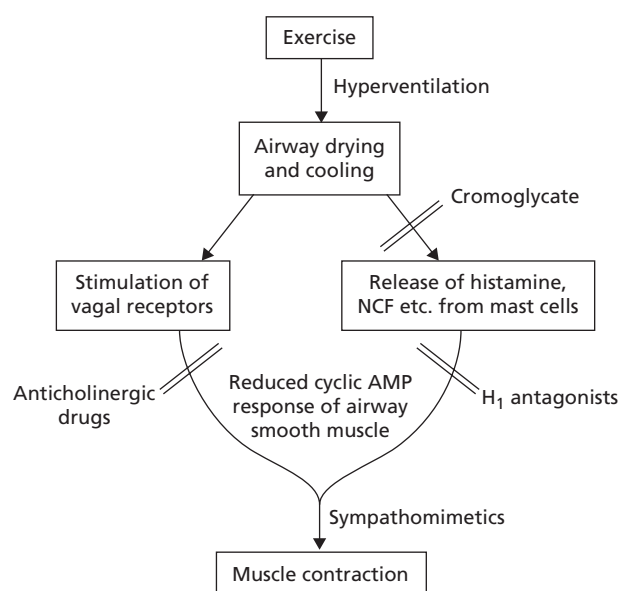
The simplest model of asthma, and one that has been much used in research, is the induction of airflow obstruction by exercise or breathing cold air [135,136]. In most but not all patients with clinical asthma, either of these manoeuvres causes an increase in airways resistance that lasts for some 30 min. This gave rise to the hypothesis that hyperventilation, with its associated drying and cooling of the airways, leads to the release of bronchoconstrictor substances or to a neural bronchoconstriction reflex, or to both [137,138]. Only rarely has exercise been shown to provoke



a delayed and more prolonged reaction [139,140], suggesting that in most cases if release of mediators occurs these are likely to be short-acting bronchial muscle constrictors rather than agents that lead to bronchial wall inflammation and oedema. This concept is supported by studies which have shown that once an attack has been provoked by exercise and the subject has recovered, further exercise does not provoke increasingly severe attacks [141]. On the contrary, subjects may be able to continue exercise and find that the asthma improves.

Thus exercise provocation provides an opportunity to study the mechanisms of the immediate component of the asthmatic reaction. Two approaches have been used: search for release of mediators and attempts to block the reaction with drugs. Studies of arterial total and plasma histamine have shown raised baseline levels (compared with controls) that increase during exercise [142–144]; however, similar rises have been described in exercising control subjects [143]. Rises in the levels of neutrophil chemotactic factor during exercise have also been observed [139,145]. Since asthmatic airways show increased sensitivity to histamine, it is likely that histamine release during exercise contributes to the production of airflow obstruction; this concept has been supported by demonstration of a protective effect of selective  $H_1$ -receptor antihistamine inhalation prior to exercise [146]. The exercise response can be blocked by inhaled  $\beta$ -sympathomimetic drugs and, in a proportion of cases, by sodium cromoglycate (cromoglycate) and high-dose inhaled antiparasymphathetic drugs [147–149]. The former observation is explicable on the basis of bronchodilatation, although it is interesting that studies of cyclic AMP levels show that subjects developing exercise-induced asthma do not show the marked rise seen in the non-asthmatic exercise response, indicating a reduced sympathetic response to exercise in such subjects [150–152]. Furthermore, the blocking effect of antiparasymphathetic drugs suggests that vagal reflex mechanisms may be involved in some cases.

Thus, what appears superficially to be a simple model of part of the asthmatic reaction can be seen to involve release of histamine and other mediators, reduced sympathetic response and sometimes parasympathetic reflexes. This leaves unexplained both the mechanisms whereby the response is triggered and also the increased susceptibility of airway muscle to histamine stimulation. Perhaps the clue to the latter lies in the failure of the cyclic AMP response, an area of research that has lately been neglected in favour of search for mediators. The mechanism of the trigger seems to be related to hyperventilation and associated drying and cooling of airways, although this is a feature of exercise common to asthmatics and non-asthmatics; the reason that one responds and the other does not may lie in differences in the reactions of mast cells or neural receptors in airway mucosa to these stimuli.



**Fig. 34.8** Mechanisms of exercise-induced asthma showing the three possible pathways: mediator release, vagal stimulation and reduced sympathetic drive in smooth muscle. The most effective preventive drugs are sympathomimetics, although  $H_1$  antagonists and anticholinergics are also moderately effective in adequate doses. Steroids have only a rather weak long-term preventive effect. (NCF, neutrophil chemotactic factor.)

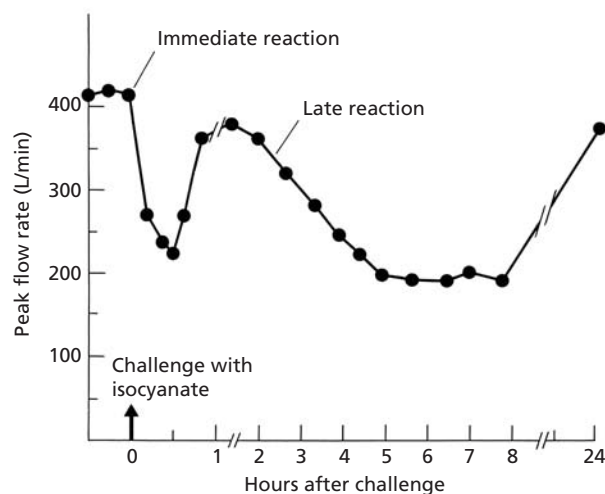
Here, again, the reduced cyclic AMP response may be an important clue. A suggested scheme for the mechanisms of exercise-induced asthma is shown in Fig. 34.8.

### Antigen challenge

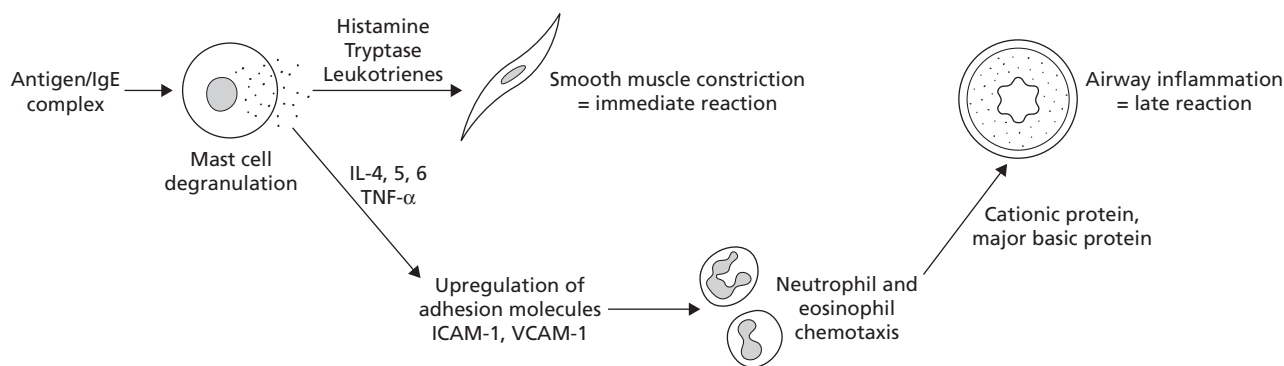
Another model of the asthmatic reaction that has been much studied is the response to inhalation of antigen. This differs from the response to exercise in one important particular: it commonly comprises an immediate and a delayed reaction (Fig. 34.9). The immediate reaction is similar to that occurring after exercise and is blocked by sympathomimetics and cromoglycate but not by corticosteroids. The delayed reaction usually starts during recovery from the immediate (which is shown by the fact that flow rates rarely rise to baseline levels between the two), is prolonged up to 24 or 48 h, and may be followed by a period of increased bronchial reactivity or even by recurrent asthma attacks for several days [153]. It is usually blocked by corticosteroids and cromoglycate but not by sympathomimetics [154–156]. An identical dual reaction may occur in response to inhalation of low molecular weight chemicals such as isocyanates or colophony that are known to cause workplace asthma, probably by combining as haptens with plasma proteins.

This dual reaction and its modification by drugs are clearly suggestive of immediate bronchial muscle constriction followed by a progressive bronchial wall

inflammation and mucosal swelling. Moreover, the persistence of the late reaction and the fact that it is only partly responsive to sympathomimetic drugs suggest that it is a more realistic model of the situation in most patients with attacks of asthma. It is reasonable to hypothesize that the initial antigenic stimulus results in the release of both short-acting and long-acting mediators, which initiate both reactions; it is known that the combination of antigen molecules with pairs of IgE antibody molecules on the surface of mast cells leads to release of such substances [157]. Studies of blood and urine levels of histamine and its metabolites and of neutrophil chemotactic activity after bronchial challenge with antigen have shown an initial rise, consistent with the hypothesis [158,159]. Furthermore, bronchial lavage studies during the late reaction have shown evidence of an influx of eosinophils and ECP



**Fig. 34.9** Response of peak flow rate to challenge with toluene diisocyanate vapour from varnish showing immediate and late reactions.



**Fig. 34.10** Mechanisms of response to inhaled antigen. Mast cell degranulation provoked by surface binding of IgE–allergen complex releases both short-term mediators, which cause immediate smooth muscle constriction, and also interleukins and

at that time, indirect evidence for the release of eosinophil chemotactic factor during the earlier part of the reaction [160]. The cellular and humoral mechanisms of the late response are discussed further in Chapter 33.

Thus, as far as the evidence goes at present, antigen challenge may be regarded as a means of releasing short-acting and delayed-acting mediators, almost certainly from mast cells, which produce immediate bronchoconstriction and later bronchial wall, predominantly eosinophilic, inflammation. In most subjects, the basic requirement is atopic sensitization, with the ability to react to antigen with an IgE antibody response. These reactions are illustrated in Fig. 34.10.

### Challenge with mediators

In concept, the simplest model of asthma results from the identification of mediators of the reaction and their use in a challenge test. Histamine is the one most studied; its inhalation provokes an immediate increase in airflow obstruction that can be blocked by prior administration of inhaled  $H_1$ -receptor but not  $H_2$ -receptor antagonists [161,162]. The response to inhaled histamine varies in the population, most people showing very little reaction, some showing a moderate reaction and a few being very sensitive [163,164]. There is no clear distinction between reactors and non-reactors, rather a gradation. Moreover, some people show reactivity at one time and much less or none at others [165]. The test may therefore be used as an index of bronchial reactivity but does not in itself shed much light on the mechanisms of asthma.

Methacholine, a parasympathomimetic agent, affects airflow similarly to histamine and is also used as a non-specific indicator of bronchial reactivity [166]. Similar effects have been demonstrated by inhaled prostaglandin ( $PG$ ) $D_2$  and  $PGF_{2\alpha}$  and leukotriene ( $LT$ ) $C_4$  and  $LTD_4$ , which are more potent than histamine on the asthmatic

tumour necrosis factor  $\alpha$ , which upregulate adhesion molecules. These in turn cause chemotaxis of neutrophils and eosinophils, leading to airway inflammation and the later more prolonged reaction.

airway [167–171]. The leukotrienes exert a rather slower and more prolonged effect than does histamine.

All these studies indicate that such chemicals are able to provoke airflow obstruction much more readily in people with hyperreactive airways than in those without. They thus suggest that at least part of the mechanism of asthma is related to reactivity of airways rather than excessive release of mediators. However, it is possible that prolonged exposure to these or other mediators may in some way sensitize the airways. This subject remains an area of active research.

### Immunological mechanisms

While it is clear that what would be regarded as classical immunological reactions are not responsible for all the manifestations of asthma, there is little doubt that they are among the important factors in the genesis of the disease in atopic individuals. Such people have the inherited ability to produce IgE antibody in response to allergenic stimulation (see p. 939). The reaginic antibody described as the important factor in allergy by Prausnitz and Kustner in 1921 [172] was characterized as IgE in 1966 [173]. It is a glycoprotein of molecular mass 190 kDa, with two heavy ( $\epsilon$ ) chains bound by disulphide bridges to two light ( $\kappa$ ) chains. It is synthesized and secreted by B lymphocytes and plasma cells in response to specific antigen challenge, the response being under the control of T helper and suppressor lymphocytes [174]. In common with other immunoglobulins, IgE has two functional components, an Fc (crystallizable) part responsible for eliciting the biological response and two identical Fab (antigen-binding) parts responsible for attachment to the allergen.

The simplest concept of allergic asthma is that an antigenic response to allergen provocation results in the binding of an antigen with multiple binding sites to the Fab part of the IgE molecule. At least two of these IgE molecules bound to a common antigenic particle then link to Fc-binding sites on a basophil or mast cell, leading to a sequence of events in the cell resulting in the release of mediators [174]. It is now known that this is only part of the story and that other cells, including macrophages, eosinophils, lymphocytes and platelets, also have IgE Fc receptors and may well play a part in the pathogenesis of the disease. Much is known of the changes occurring in the mast cell membrane in response to antigen–antibody binding [175]. The bridging of two Fc receptors by the IgE–antigen complex leads to two parallel biochemical events, the influx of calcium into the cell and the conversion of ATP to cyclic AMP. Cyclic AMP, in the presence of an appropriate calcium concentration, activates protein kinases that phosphorylate the specific enzymes concerned with histamine release. The conversion of ATP to cyclic AMP is promoted by augmentation of the activity of adenylate cyclase by the bridging event, this enzyme in

turn cleaving the ATP molecule. The influx of calcium is governed by the methylation, again in response to the bridging event, of phosphatidylethanolamine to phosphatidylcholine. This phospholipid migrates to the cell surface and the consequent change in the structure of the cell membrane allows the influx of calcium. The same biochemical reactions probably result in the release of other preformed mediators, including the low molecular weight eosinophil chemotactic factor [176].

Antigen–antibody binding to the surface of mast cells or basophils can also lead to the release of mediators derived from arachidonic acid [177]. This substance is stored in the phospholipids of the cell membrane and is released by activation of phospholipase during influx of calcium following the bridging event described above. Platelet-activating factor (PAF) may also be derived by similar mechanisms from basophils and other cells [178–180].

The basophil and mast cell are not the only cells involved in the release of mediators of asthmatic inflammation [181,182]. Macrophages, eosinophils, lymphocytes and platelets also have receptors for the Fc portion of IgE. Macrophages have been shown to release reactive oxygen intermediates, lysosomal enzymes and derivatives of arachidonic acid in response to surface binding of multiple IgE molecules bound to antigen. Eosinophils are attracted by the binding of IgE–antigen complexes to mast cells and this may lead to release of the major basic protein, which is very toxic to airway epithelium [183,184]. T-lymphocyte IgE receptors may play a role in the control of IgE production by B lymphocytes via a process of negative or positive feedback [181,185]. Platelet receptors may facilitate the secretion of serotonin.

Thus the events related to the immunological induction of asthma may be summarized as follows. In an individual with a predisposition to react to antigen challenge by production of IgE from B lymphocytes, such challenge leads to the formation of IgE–antigen complexes that bind to the surface of basophils, mast cells and macrophages in particular. Release of preformed mediators, such as histamine and eosinophil chemotactic factor, leads to bronchoconstriction and an influx of eosinophils. Release of other inflammatory mediators leads to progressive oedema and infiltration of the bronchial wall, while toxic substances such as major basic protein and PAF cause epithelial cellular disruption. Enzymes released from macrophages may be responsible for the characteristic separation of the epithelium from the basement membrane.

### Immunopathogenic mechanisms

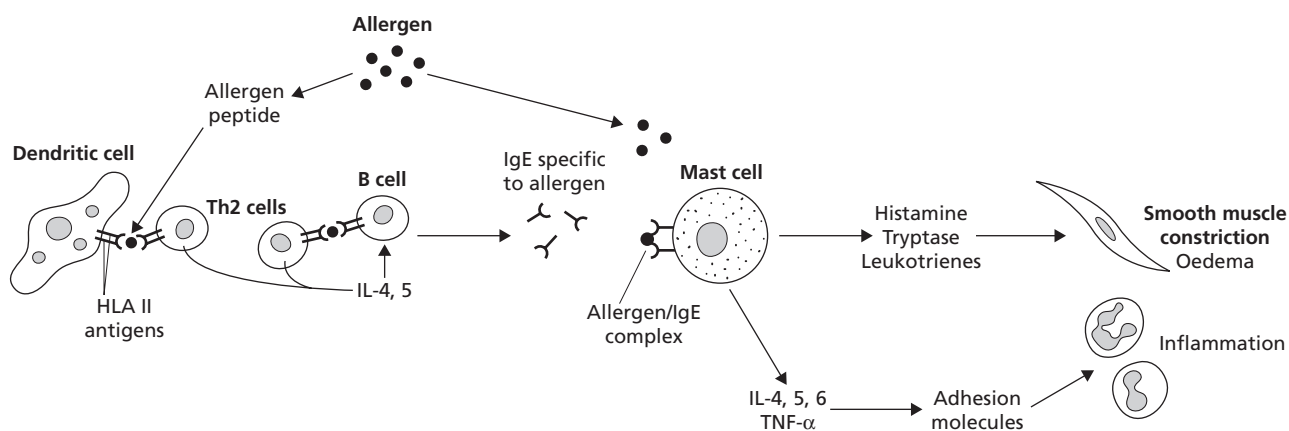
It is, of course, of some interest to speculate why the human organism should have evolved such a sophisticated mechanism of self-injury; the answer must lie in a biological advantage obtained by those with the ability to produce IgE in these amounts [186,187]. One simple and

perhaps partial explanation is that this may be related to the role of IgE in defence against parasitic organisms, by facilitating the binding of such organisms to cells such as eosinophils and macrophages able to secrete substances toxic to the invaders. More interestingly, it has been suggested that the reason may be found in the need for the fetus to protect itself from attack by the mother *in utero* [188]. This concept relates to the fact that the propensity to mount an IgE-mediated allergic reaction depends upon a predominant differentiation of T-helper lymphocytes into the Th2 subtype responsible for production of cytokines, especially IL-4, which stimulate B lymphocytes to produce IgE. It is argued that undifferentiated helper T cells may produce clones of predominantly Th1 or Th2 type. The former secrete, *inter alia*, interferon (IFN)- $\gamma$ , important in defence against many infecting organisms, including viruses and intracellular bacteria, but which is also very toxic to the conceptus; the latter produce IL-4 and IL-5. These cytokines may counter the effect of IFN- $\gamma$ , and it appears that the natural state of the fetus is skewed towards production of Th2 cells. This bias persists in infant life, but in the majority is displaced by a predominantly Th1 clone as the baby develops. At least one stimulus to this may be infections acquired in childhood, which promote the development of Th1 clones. Thus it has been argued that early childhood infections, perhaps particularly the intestinal infections associated with relatively poor living conditions, may switch newborn children from an atopic to a non-atopic potential. This concept fits well with evolutionary theory and provides an explanation not only for the persistence of atopy but also possibly for the increase in asthma and allergic diseases.

The interrelationships of Th1 and Th2 cells and their

cytokines are complex and far from fully understood. It is thought that the initial stage of differentiation involves the dendritic cell, which is derived from CD34 lymphocytes and which is present in asthmatic airway walls [189]. Cytokines, including tumour necrosis factor  $\alpha$  and IL-4, cause dendritic cells to express receptors for antigen; after binding with this, they migrate to local lymph nodes where they present their major histocompatibility complex (MHC) class II antigens to naive T lymphocytes, leading to Th2 differentiation. In contrast, infections leading to secretion of IL-12 from dendritic cells can influence naive T cells to differentiate into Th1 cells. In atopic disease, allergen is processed and presented by the dendritic cells to T lymphocytes, which then differentiate into the Th2 phenotype; this secretes IL-4 that further aids in the maturation of the Th2 cell and in switching B lymphocytes from production of IgM and IgG to IgE. In contrast, IFN- $\gamma$  from Th1 cells, driven by IL-12, downregulates Th2 differentiation and IgE production. The Th1 phenotype is associated with cell-mediated cytotoxicity and delayed-type hypersensitivity, and it is likely that early induction of high levels of IFN- $\gamma$  may reinforce T-cell differentiation in the Th1 direction, leading to unresponsiveness to allergens.

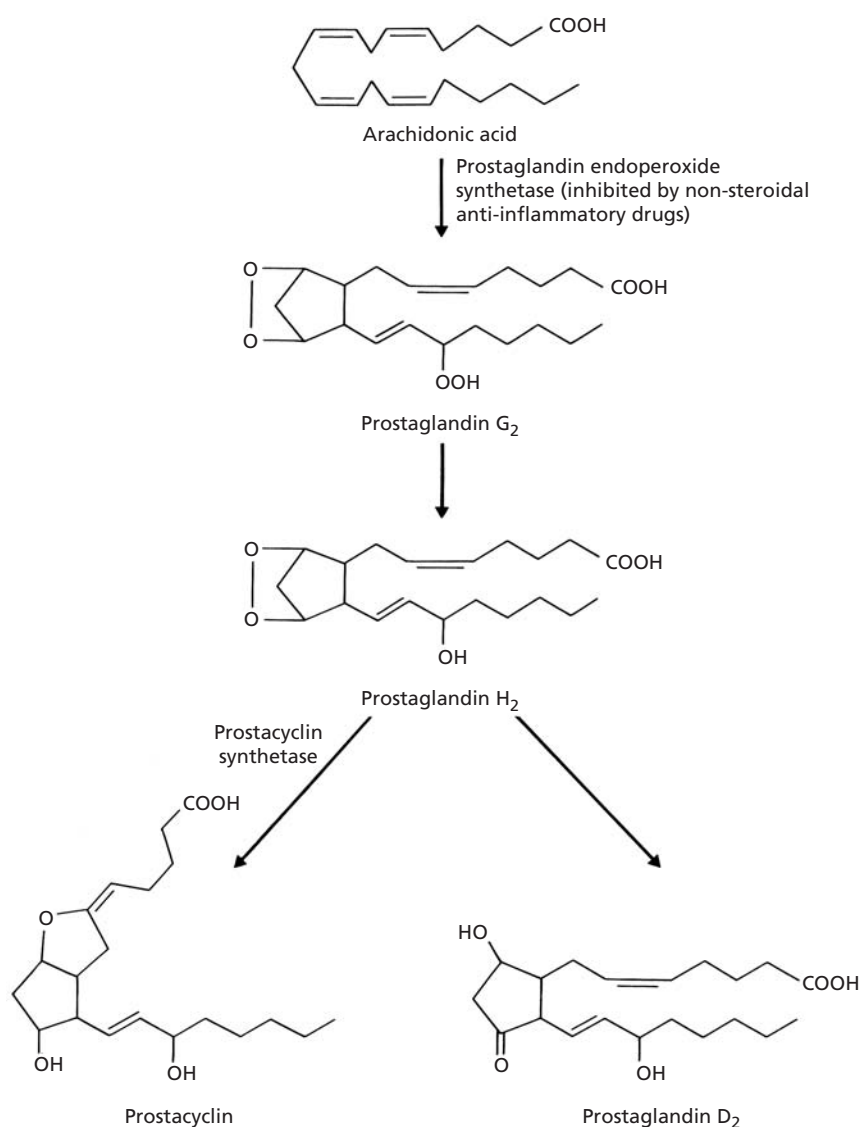
Whatever the precise relationships between T lymphocytes and their cytokines, it is apparent that there are opportunities for understanding the reasons why one person develops asthma and another does not; even more importantly, this may lead to explaining the reasons for the rise in atopic diseases as societies become wealthier and more sophisticated. This is discussed below. A simplified summary of the proposed cellular and humoral mechanisms in the allergic asthmatic reaction is shown in Fig. 34.11.



**Fig. 34.11** A summary of the main proposed cellular and humoral mechanisms in the allergic asthmatic reaction. Allergen fragments are presented to T lymphocytes by the major histocompatibility complex (MHC) class II antigens on dendritic cells. They are then presented to B cells, which under the

influence of interleukins from T cells produce allergen-specific IgE. This then binds to allergen on the surface of mast cells, leading to release of mediators and the pathological features of the asthmatic airway.





**Fig. 34.13** Biosynthesis of some of the prostaglandins.

capacity to produce different metabolites. LTD<sub>4</sub>, LTE<sub>4</sub> and LTC<sub>4</sub> (which together were originally described as slow-reacting substance of anaphylaxis, SRS-A) are most potent in terms of bronchial smooth muscle constriction and LTB<sub>4</sub> in terms of causing neutrophil chemotaxis and release of lysosomal enzymes [199]. Leukotrienes have been shown to be released from allergen-challenged human lung and to be present in sputum and blood from patients with asthma [200–202].

#### Platelet-activating factor

PAF (1-O-alkyl-2-acetyl-*n*-glyceryl-3-phosphorylcholine also known as PAF-acether or AGEPC) is a lipid substance derived from phospholipids in a large number of cells, including basophils, neutrophils, mast cells, eosinophils, macrophages and platelets [203]. Its actions include aggre-

gation of platelets, induction of lysosomal enzyme and oxygen free radical release from neutrophils and macrophages, and bronchoconstriction and pulmonary oedema. These latter effects may well be secondary to the release of other lipid mediators from cells stimulated by PAF. It is of interest also that it is able to produce both immediate and delayed local reactions when injected into the skin [204].

#### Kinins

Kinins are polypeptides generated in plasma from kininogen precursors with molecular masses of about 200 and 500 kDa. The enzymes responsible are called kallikreins, which in turn are derived from prekallikreins by the action of activated Hageman factor. While this process may take place wholly within the plasma, there is evidence that



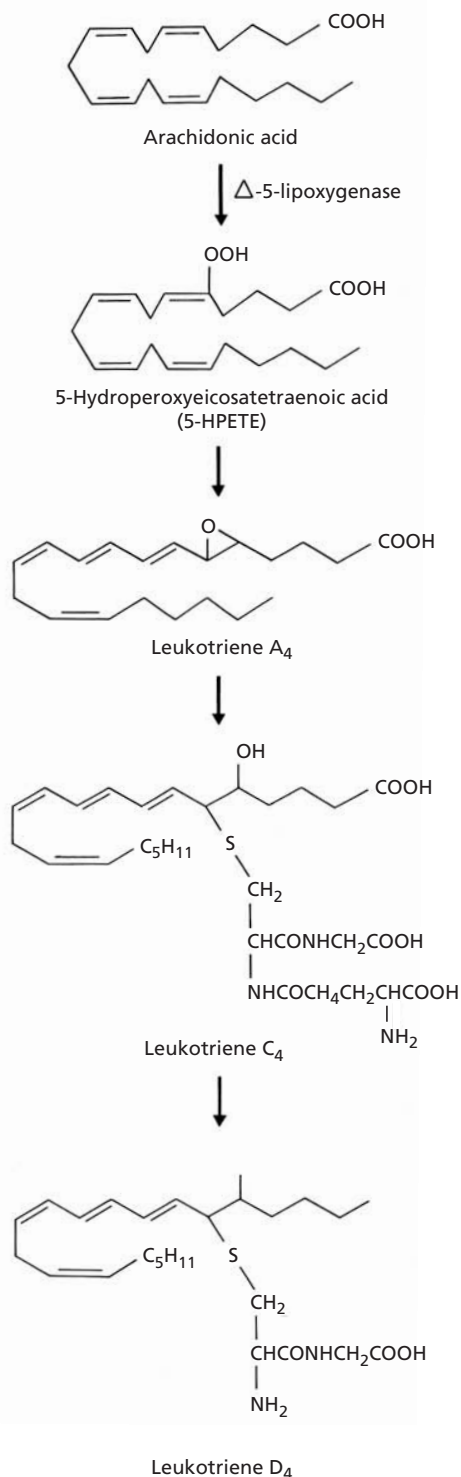


Fig. 34.14 Biosynthesis of some of the leukotrienes.

mast cells may produce a kallikrein-like substance [205]. The best-known kinin is bradykinin, a nonapeptide to which asthmatic airways are hypersensitive and which has been found in the skin reactions of atopic subjects [206]. It has no action on normal airways, and it has been

suggested that it may act via a local axon reflex, its release in airways stimulating exposed non-myelinated afferent nerve endings and causing release of sensory neuropeptides [207,208]. These in turn may cause bronchoconstriction, mucosal oedema and hypersecretion of mucus.

### Neural mechanisms

The allergic or immunological model of asthma discussed above provides the best-understood key to the mechanisms of the disease. However, it is plain that allergic sensitization is of little or no importance in a great number of people with asthma. Moreover, studies of mediators have so far been unable to demonstrate convincing qualitative differences between people with asthma and those without, except that patients with asthma tend to show increased susceptibility to their actions. Thus it is necessary to search elsewhere for an understanding of the disease. Two observations in particular have led to an interest being taken in neural mechanisms: first, patients with asthma usually show non-specific bronchoconstrictor responses to a wide variety of non-immunological stimuli such as infection or inhalation of irritants; and, second, psychological stress may lead to exacerbations of the disease. Even more importantly, from a practical point of view, the first-line drugs used in asthma are most frequently those that act upon autonomic nervous control of the bronchi.

Three components of the autonomic nervous system play a part in control of the airways and their secretions [209]: the parasympathetic system via the vagus; the sympathetic system via its hormonal control of cyclic AMP levels; and the peptidergic or non-adrenergic non-cholinergic (NANC) system.

### Parasympathetic control

The vagus nerve includes afferent fibres from sensory receptors in the bronchial epithelium. It is thought, largely on the basis of studies on animals, that stimulation of these receptors by irritants can initiate a reflex impulse along vagal efferents that causes release of acetylcholine and bronchoconstriction [210,211]. Bronchial glands are also under parasympathetic control, and vagal stimulation can also lead to secretion of mucus [212]. The vagal efferent nerves end in ganglia close to bronchial smooth muscle in the posterior walls of the larger airways. The postsynaptic fibres are short and connect with muscle and glands. Vesicles containing norepinephrine (noradrenaline) have been found in the parasympathetic ganglia, suggesting that the sympathetic system may have a modulatory effect on the parasympathetic [213].

In terms of relevance to asthma, parasympathomimetic drugs induce bronchial constriction in patients in much the same way as histamine [214]. Antiparasympathetic



drugs cause bronchodilatation in normal subjects and in patients with asthma [215,216]. In high doses they usually block the bronchoconstrictor response to exercise [149]. Finally, vagal receptors may be stimulated by a number of inflammatory mediators, including bradykinin and histamine [217–219], and this may explain in part the effects of respiratory infections in provoking asthmatic symptoms [220].

### Sympathetic control

The lung receives sympathetic innervation mainly via the stellate ganglion [221]. The postsynaptic nerves supply bronchial vessels but not smooth muscle. Nevertheless, bronchial tone is influenced to a major degree by the sympathetic system,  $\beta$ -receptor agonists causing bronchial relaxation that is antagonized by  $\beta$  blockers. Other studies have demonstrated  $\beta$  receptors on smooth muscle, mast cells and bronchial glands that are presumably stimulated by circulating catecholamines [222,223].

The  $\beta$  receptors exist on the surface of cell membranes, though they should not be regarded as unchanging structures because their numbers may vary from time to time in response to external stimuli. The receptor receives a hormone that has a steric configuration complementary to its own, the binding of hormone to receptor initiating a chain of events that leads to the cell producing its effect. The first step is conversion, in the cell membrane, of guanine nucleotide regulatory protein into its active state, when it combines with the hormone–receptor complex. This leads to activation of adenylate cyclase that catalyses the conversion of ATP to cyclic AMP, the so-called second messenger, which in turn activates the particular cell's specific protein kinases. Cyclic AMP is metabolized by phosphodiesterase to AMP. The actions of the protein kinases depend on the cell; in smooth muscle they phosphorylate myosin light chain kinase and reduce actin–myosin coupling in order to produce relaxation. The release of preformed mediators from mast cells also appears to be under the control of cyclic AMP, reduced levels being involved in the process of degranulation. The relevance of  $\beta$ -receptor mechanisms to clinical asthma is clear from the effects of sympathetic agonist and antagonist drugs. However, study of these mechanisms has pointed to something more fundamental to the understanding of the disease [221]. It has been known for many years that asthmatic subjects may show diminished responsiveness to adrenergic stimulation, in terms of a rise in blood sugar, free fatty acids and levels of cyclic AMP in blood and urine. Much evidence has now accumulated to support the hypothesis that subjects with asthma have a relative reduction of  $\beta$  receptors and a reciprocal increase in excitatory  $\alpha$  receptors. Such differences may be related to genetic factors or may be acquired as a result of allergic, infective or possibly autoimmune factors.

### Peptidergic control

The NANC nervous system was originally described in the gut. Fibres of this system run with the vagus and supply postganglionic fibres to bronchial muscle, glands and vessels [224–226]. Two neuroendocrine peptides in particular have been demonstrated in human sensory airway nerves, substance P and neurokinin A. Activation of these nerves by such stimuli as mechanical or chemical irritation may lead to a form of neurogenic inflammation, with bronchoconstriction, extravasation of protein-rich fluid and vasodilatation in the airways. There is also evidence that release of these transmitter substances may influence the attraction of inflammatory cells to the site. Both substance P and neurokinin A administered by inhalation cause bronchoconstriction; this effect is reduced by prior inhalation of cromoglicate and amplified if the action of neutral endopeptidase, the enzyme responsible for their natural breakdown, is blocked. It seems reasonable to propose that neural mechanisms such as these play an important part in the initiation of non-immunological asthma, such as occurs after viral infection or exposure to irritant substances, the so-called reactive airways dysfunction syndrome.

### Bronchial muscle

The contractile mechanism of bronchial smooth muscle is due to the ability of the proteins actin and myosin to interact and to slide over one another [227,228]. In outline, myosin is composed of a pair of filamentous heavy chains coiled around each other, ending in a globular structure to which are attached two pairs of light chains. The globular head is attached by a cross-bridging mechanism to actin, which is also a filamentous protein consisting of two intertwined polymers. These in turn are wrapped round two intertwined molecules of tropomyosin. Contraction takes place by detachment of the globular part of the myosin from the actin and reattachment further along the structure, the energy for the reaction being derived from breakdown of ATP by activated myosin ATPase. The sequence of events leading to activation of myosin ATPase is as follows [228,230]. A fundamental requirement appears to be an approximately 10-fold increase in intracellular calcium ion concentration. Normally the concentration of calcium in smooth muscle cells is about 10 000 times less than that in extracellular fluid, the differential being maintained by the cell membrane and an active energy-dependent removal mechanism whereby it is exchanged for sodium. However, the cell membrane may allow calcium to enter when channels are opened, either via the actions of drugs or hormones on receptors or by changes in the transmembrane potential difference. Influxing calcium combines with the protein calmodulin and this combination activates myosin light chain kinase. The acti-

vated enzyme then phosphorylates one of the pairs of myosin light chains on the globular part of the molecule, leading in turn to activation of myosin ATPase and contraction. Another calcium-dependent pathway has also been described in the activation of myosin ATPase; an enzyme present in the cell membrane called protein kinase C alters the sensitivities of actin and myosin to calcium. The protein kinase C is in turn activated by calcium flux across the membrane.

Thus calcium is thought to play a central role in the contraction of smooth muscle. Yet calcium channel blocking drugs have proved of little therapeutic value in asthma, in contrast to  $\beta$ -sympathomimetic drugs that act to increase levels of cyclic AMP in the smooth muscle cell. The part played by cyclic AMP is not clear, although rises in its concentration have a wide range of effects including activation of various protein kinases (that may inhibit calcium transfer and activation of protein kinase C) and by increasing the inward flow of sodium in exchange for calcium. The lack of efficacy of calcium-blocking drugs may be explained partly by their inability to block the receptor-dependent channels. Despite the well-recognized bronchial hyperreactivity of asthmatic airways, no clear picture has yet emerged of the biochemical correlates of this process. Although it is tempting to believe that a fundamental abnormality may be present in the regulation of intracellular calcium metabolism, the evidence seems to indicate that bronchial reactivity *in vivo* does not relate to altered mechanical properties and responses of the excised muscle *in vitro* [231]. However, there is some evidence that asthmatic airway smooth muscle does have altered mechanical properties [232].

## Genetic factors

The frequent clinical observation that asthma runs in families has been supported by many more formal investigations [233–237]. There is a greater concordance for asthma in monozygotic than dizygotic twin pairs. The risk of having an asthmatic child is greater if both parents have the disease than if one does, and greater if one has it than if neither does. However, study of the genetics of asthma is made particularly complex by the absence of agreement on definition of the phenotype, which could for example include atopy, bronchial hyperresponsiveness and any number of consequences due to genetic polymorphisms involving individual cytokines and cell receptors [238]. Recent studies, in which atopy has been defined in terms of one or more positive skin tests, positive specific IgE or raised total IgE levels, have produced somewhat contradictory results. The original findings suggestive of autosomal dominant inheritance based on a gene on chromosome 11q13 have been supported by work that has shown an association between atopy and an amino acid substitution in the  $\beta$  subunit of the receptor for IgE, the

gene for which is also located on chromosome 11q13 [239–241]. This receptor is responsible for the changes in calcium flux leading to mediator release. However, studies of other family groups have failed to replicate these findings and it seems very likely that different genetic polymorphisms in different populations can produce what to the clinician appears to be the same phenotype [238]. Other linkages have been demonstrated between chromosome 14, the T-cell receptor and specific IgE reactions to major allergens [242], and between chromosome 5q and a cluster of cytokines including IL-3, IL-4 and IL-5 [243]. The complexity of the multiple mechanisms and network of cells, cytokines and chemokines involved in asthma, the differences in the clinical manifestations of the disease and the now very obvious increasing prevalence of atopic diseases, and thus the dominance of environmental factors in their expression, make one wonder whether the current emphasis on genetic research is likely to pay the rich dividends anticipated by some of the pharmaceutical companies investing in it. While it will surely lead to new and possibly better drugs, it may be that a greater research emphasis on factors influencing the expression of whatever genes are involved in determining atopy and bronchial reactivity may produce greater dividends in terms of prevention.

## Why has asthma increased?

One of the greatest enigmas in the study of asthma arises from the repeated observation that the disease has become more common in prosperous societies. This has been demonstrated in repeated cross-sectional studies in the same place, in studies of populations that have migrated from poorer to richer societies, and in studies of people of similar racial background living traditional or more sophisticated lifestyles. The increase in asthma appears to be paralleled by increases in atopy and the other allergic diseases, hay fever and eczema. These observations provide an important challenge in understanding and reversing the environmental factors that lie behind them.

Early attempts to attribute these changes to an increasingly toxic environment, whether due to maternal smoking, increases in exposure to mites and other allergens or to air pollution, are likely to provide at best a very partial explanation [244]. The changes in prevalence of atopy seem to be occurring very early in infancy, and possible or recorded changes in these toxic factors are unlikely to be large enough to have produced the observed effects. For example in the UK, smoking prevalence in women of child-bearing age has decreased over the relevant period, pet ownership has not increased and urban particulate air pollution has decreased substantially. If the increase in asthma was due to a large increase in exposure to mites, an unlikely event given the high exposures in bedclothes almost universal 30 years ago [245], it is strange that hay

fever has increased despite no change in grass pollen levels [246]. Thus it seems much more likely that the increase in prevalence is primarily a consequence of an increase in population susceptibility (Fig. 34.15).

Two hypothetical but plausible means by which population susceptibility could have increased suggest themselves. First, the diet of the population could have altered in such a way as to decrease resistance to allergens [244,247]. Secondly, falling rates of infection in infants could have removed a stimulus towards development of the anti-infection Th1 phenotype, leaving a population with an increased proportion of the atopic Th2 phenotype [248,249]. There is evidence that newborn babies destined to become atopic already show decreased concentrations of IFN- $\gamma$ , a cytokine associated with the Th1 phenotype, and evidence of *in utero* sensitization to allergen in their cord blood [250], suggesting that the key determinant of atopic and therefore likely asthmatic status in childhood may occur before birth. Other evidence, from studies of populations, has suggested that early childhood infections may protect against later atopy, though not asthma. Children in Guinea-Bissau who had severe measles were less likely to become atopic, while the same was true of children in Japan who were tuberculin positive and of Italian military recruits who had serological evidence of past hepatitis A infection [251–253]. In contrast, except for measles which had a weak effect, the common childhood infections in Aberdeen schoolchildren did not protect from (but rather in general appeared to increase the risk of) later asthma [254]. All these studies have pointed to an intriguing effect of family size on risk of atopy, in that children in larger families were relatively protected, an observation not wholly explained by infection but which also may point to some subtle intrauterine effect.

It is becoming apparent that the change in asthma prevalence is associated with a rising standard of living rather than with westernization *per se*. Thus children in the

same country, be it Ethiopia or Saudi Arabia, neither of which can be regarded as westernized, show a much greater prevalence of asthma and allergic symptoms among the wealthier urban than among the poorer rural children [255,256], whereas urban–rural differences do not exist in countries that are relatively uniformly wealthy. Some factor associated with increased prosperity, be it a different diet, reduced opportunity for childhood infection, increased use of immunization or a combination, must be responsible. The authors favour a dietary hypothesis, since increasing prosperity is accompanied by the consumption of less fruit and vegetables and a different pattern of fat intake. A lowered consumption of vitamins C and E, coupled with changes from  $\omega$ -3 to  $\omega$ -6 fatty acids in the diet of the pregnant woman, could theoretically influence T-lymphocyte differentiation in the unborn child and tip the balance towards a predominantly Th2 phenotype persisting at birth when the child first meets inhaled allergens [247,257] (Fig. 34.16). At this stage a lowered antioxidant level in the child could further reduce its resistance to substances capable of causing bronchial inflammation. As childhood progresses, it is conceivable that immunization and freedom from, say, intestinal infections reinforce rather than switch the Th2 phenotype, so that by the age of 12, the stage at which most of the epidemiological studies have been done, atopic symptoms have become commonplace. It must be stressed that this hypothesis remains unproven but forms a useful template for further research and may point the way to future prevention.

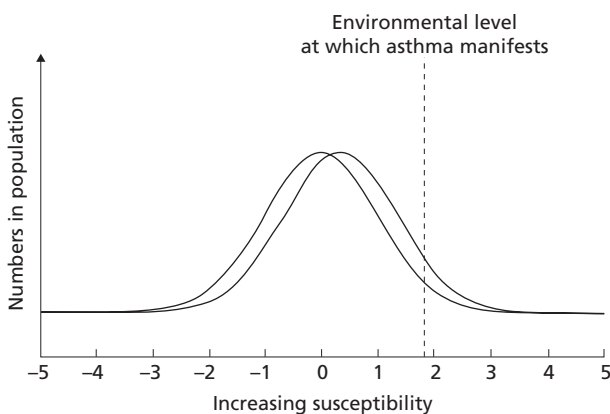
## Clinical features

### Taking the history

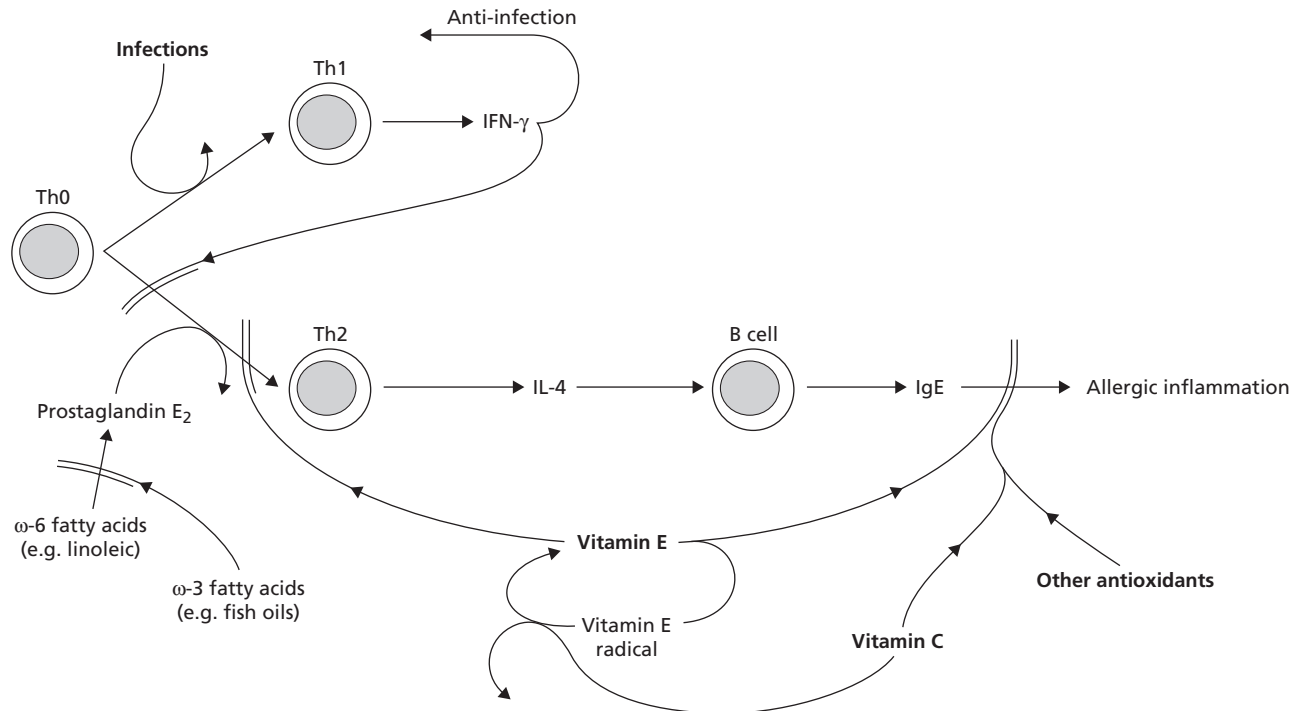
The diagnosis of asthma is usually made as a result of careful history-taking, supported by a few tests or by a trial of therapy. In most cases a properly taken history gives the diagnosis. The history should discover the presenting symptoms, their periodicity and evolution and factors related to their variability. In particular, factors provoking attacks should be sought. An assessment of the patient's level of disablement should be made, not forgetting that disturbed nights lead to impaired performance in the day. The history should also discover any associated features, such as other atopic disease and drug sensitivity.

### Presentation

Asthma may present at any age, including the extremes of life. The most common presenting symptom is breathlessness usually associated with chest tightness, often coming on in attacks, although in older people it is frequently a chronic symptom. Wheeze is often not the primary complaint and is a term usually put into their mouths by their



**Fig. 34.15** Distribution of susceptibility to asthma in a population showing how a small overall shift can substantially increase the prevalence of overt disease.



**Fig. 34.16** Possible factors influencing susceptibility to asthma. The undifferentiated T lymphocyte may become either the antimicrobial Th1 cell, producing interferon  $\gamma$  under the stimulus of certain infections, or the Th2 cell, producing interleukin 4 and leading to allergic inflammation through the production of IgE

by B cells. Antioxidants might protect directly against allergic inflammation and vitamins E and C may together downregulate Th2 differentiation. The balance of fatty acids in the diet may also affect T-cell differentiation.

doctors, patients often preferring to refer to tightness in the chest. A large minority of patients present with cough, which may be the only symptom, especially in children. When cough is troublesome, bilateral aches or pains in the chest are common. In some patients cough is productive of small amounts of sticky sputum, although it is rare for profuse or frothy sputum to be produced. Sputum is usually described as being white or clear; sometimes more solid or greenish streaks are noticed in it.

Of particular importance in making the diagnosis of asthma is the periodicity of symptoms. In children and young adults the usual complaint is of episodes of cough, wheeze and breathlessness. These characteristically occur shortly after exertion and at night. Persistent dry cough may be the only symptom. Exercise-induced symptoms occur after several minutes of usually unaccustomed exertion, increase in severity over a minute or two and wane over about half an hour, though mild attacks may last only a few minutes. The patient may or may not notice wheeze. Nocturnal symptoms typically disturb sleep in the small hours of the morning. Many patients feel the need to get up and out of bed to go to a window for air. Others make themselves a cup of tea after being awakened by symptoms, an almost pathognomonic symptom. Attacks also vary greatly in severity, from a mild episode of cough lasting a few minutes to a night repeatedly disturbed by

frightening breathlessness, wheeze, chest tightness and cough. In general, the frequency and severity of nocturnal episodes may be taken to be a useful guide to the current severity of asthma. If a patient is seen during the day and is clinically reasonably well but describes distressing nocturnal symptoms, more weight should be put on the history than on the immediate apparent good health when assessing the severity of asthma and the planning of its treatment. Moreover, the time at which the attacks occur is also a guide to severity. Most patients with mild to moderate untreated asthma wake in the morning at their normal time with a tight chest and some wheeze, or a dry cough. Measurement of peak flow rates, which are characteristically lower in the mornings in asthma, has led to this being described as the 'morning dip'. As asthma, and presumably airways hyperreactivity, becomes more severe, symptoms occur earlier and disturb sleep, until in some cases the patient barely sleeps at all or is woken repeatedly through the night by breathlessness, wheeze and cough. Nocturnal asthmatic symptoms are discussed further in the next section, but it should be pointed out that they are a feature of asthma of all types at all ages and not simply related to house-dust mite hypersensitivity.

Particular attention should be paid to factors provoking attacks. Exercise has been mentioned; almost as frequently, patients comment on attacks following 'colds'.

Care should be taken to distinguish genuine viral infections, with fever and malaise, from rhinitis. While the latter is common in asthmatics and frequently accompanies attacks, the former commonly provoke them. Often a bad upper respiratory tract infection leads to cough and wheeziness that persist, sometimes for weeks, and do not respond to the antibiotic therapy which is often unnecessarily given in repeated courses. Such patients do not have persistent bronchial infection despite their cough and sputum. Their sputum, if apparently purulent initially, rapidly becomes mucoid and sticky and they usually have troublesome nocturnal symptoms. Sputum may occasionally appear to be purulent in asthmatics; this green colour is due to peroxidase, which is released from eosinophils as well as neutrophils. Symptoms are due to bronchial hyperreactivity following the infection and respond to anti-inflammatory therapy but not antibiotics. Other common factors that may provoke asthma are exposure to allergens, cold air, chemicals in the workplace, drugs and emotional upsets. These are discussed in subsequent sections.

In terms of making a diagnosis from the history, the most difficult presentation is in middle-aged and elderly people. While most such patients present with typical symptoms, some present with progressively increasing cough and dyspnoea, without the characteristic day-to-day variability. Nevertheless, they usually admit to nocturnal symptoms and these are frequently assumed to be manifestations of cardiac disease. One important feature of the history should always be sought, namely the relationship of the start of symptoms to cigarette smoking. Anyone who starts wheezy breathlessness and cough some weeks or months after stopping smoking is likely to have asthma. It is a commonplace observation that such patients complain that their chest has never been right since they stopped, although a careful history reveals that the symptoms usually started some time after cessation. If symptoms were present when the patient stopped smoking, a diagnosis of smoking-induced chronic obstructive airways disease is more likely. In terms of management this distinction is less important than it appears, since all such patients developing airflow obstruction are treated similarly initially in order to assess their response and many initially categorized as having smoking-induced disease nevertheless respond at least partially to such treatment. This is discussed further below.

### Provoking factors

#### Allergy

The possible mechanisms whereby allergy provokes asthma have been discussed. Over 90% of childhood asthmatics are atopic, though this proportion falls among

adults to some 50% [258–260]. In most atopic subjects allergy is only one of many factors, including exercise, infection and emotional upsets, that provokes attacks. Nevertheless it is always desirable to consider possible allergic factors and to try to eliminate important ones wherever possible.

The chest physician confronted by an asthmatic patient is faced with a daunting task in investigating allergic factors. The most important guide to the relevance of these comes from the history. Allergens may be encountered in the general, the domestic and the occupational environment, and timing of the symptoms may give an important clue. Seasonal variation suggests allergy to pollens or spores in the air. Symptoms in the working week and improvement when away from work throw suspicion on occupational factors. Associated rhinitis or conjunctivitis is a useful pointer to an allergen; house dust, animals and pollen rarely cause attacks of asthma without some nasal manifestations. Allergy to food or food additives is usually very difficult to detect from the history, although many such patients find that certain foods or drinks make their symptoms worse. The following sections discuss the main allergens with the exception of those encountered in an occupational setting, which are dealt with separately.

#### House dust and mites

Most atopic asthmatics report symptoms on exposure to house dust, usually when making beds and when dusting. Exposure while in bed may cause perennial rhinitis and nocturnal attacks of asthma, although this is by no means the only cause of asthma during the night. The major allergen in house dust was shown in the 1960s to be due to mites [261–263], though an occasional patient shows sensitivity to house dust alone and not to the mites in it. At least in temperate climates, *Dermatophagoides pteronyssinus* (Fig. 34.17) is the most prevalent of the mites found in house dust; others such as *Euroglyphus maynei*, *Chyletus* spp., *Glycyphagus* spp. and *Tyrophagus* spp. may also be found in small numbers [245]. *Dermatophagoides farinae* is rare in the European house habitat and is a more common organism in the USA; it should be noted that different species become dominant in different environments such as holiday caravans or stored grain. *D. pteronyssinus* lives mainly on skin scales and the fungi that feed on them [264]; it prefers a dark, warm and humid environment, around 25°C and 80% relative humidity, being in temperature and fluid equilibrium with its environment. These conditions are ideally provided by a bed. It breeds rapidly, the female producing up to 300 eggs in its short life. It is easily found in the small collections of dust round buttons and piping on mattresses and in blankets, pillows and other bedclothes, as well as in dust accumulated in curtains, carpets and other household sources. The highest

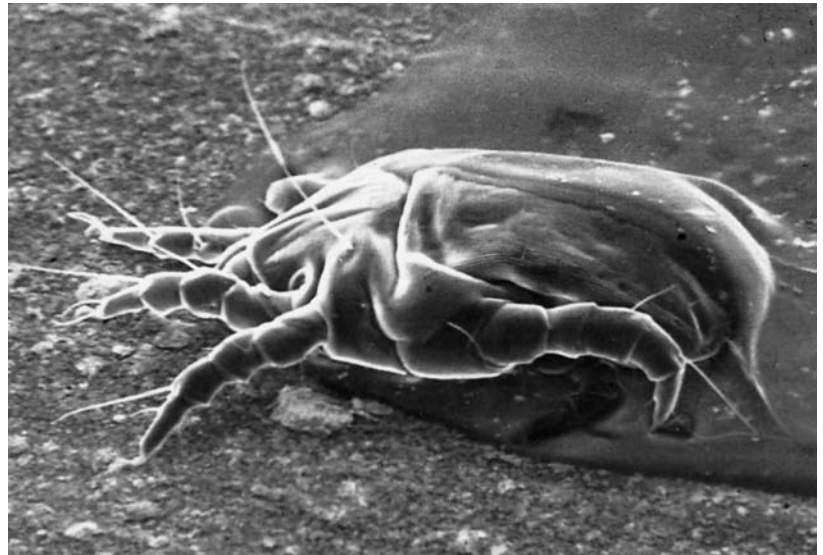


Fig. 34.17 Scanning electron micrograph of *Dermatophagoides pteronyssinus*.

concentrations, up to 13 000/g of dust in one study, are found in mattresses [245], although large numbers (up to 100 000/m<sup>2</sup>) may be present in a carpet. Interestingly, hospital mattresses are usually free of mites, indicating that regular disturbance of the colony by changing beds and exposing the mattresses to light makes the microenvironment unsuitable for their survival [245,265]. Conversely, low standards of domestic hygiene encourage house-dust mite colonies to thrive. The main allergen from mites seems to be excreted in the 20 or so faecal pellets each mite produces daily [266]. The faecal pellets are some 10–40 µm in diameter and thus easily become briefly airborne and inhaled into the nose and conducting airways [267,268]. Once inhaled and deposited onto a moist mucous membrane, the soluble allergens leach out of the faecal pellet. The main allergens have been characterized and are known as *Der pI*, II, III and IV indicating the order in which they were found [269]. Monoclonal antibodies to these allergens allow their quantification in air, dust and other media. *Der pI* is a cysteine protease with a molecular mass of about 25 kDa, while *Der pIII* is a trypsin with a molecular mass of about 30 kDa; these are the two allergens to which almost all mite-sensitive subjects react. *Der pII* is probably unimportant as an allergen and *Der pIV*, an amylase with a molecular mass of about 60 kDa, sensitizes a minority of subjects. The fact that these allergens, derived as they are from the gut of mites, are enzymes is interesting in terms of their ability to obtain access to sub-mucosal lymphocytes in the respiratory tract.

Other allergens in house dust include animal dander and feathers. Hair itself is not allergenic. The presence of an animal in the house ensures that it makes some contribution to the dust's antigenicity, though the main threat is usually posed by more direct contact between patient and pet (see below). Feather allergy seems to be related to a

mixture of proteins from keratin, although apparent allergy to feathers in pillows or downies may rather be related to their mite content.

#### Pollens

Plant pollen grains are major causes of seasonal rhinitis (hay fever) and in such patients commonly provoke asthmatic symptoms as well. Allergy to pollens causes a distinctive illness in that the rhinitis is usually associated also with itchy conjunctivitis and lacrimation, and the symptoms have a distinctly seasonal pattern. Pollination of plants occurs at the same season each year but the amount of pollen that becomes airborne depends on the plant's natural method of pollination (via wind, water or insects) and the climatic conditions [270,271]. Pollen allergens therefore differ considerably between different regions of the world and from time to time in the same region. In Europe, the most frequent allergens are grass pollens and these cause symptoms from about April to August; pollination is promoted by wind and sunshine and occurs earlier in more southern latitudes. Counts of grass pollen may rise as high as 1000/m<sup>3</sup> on a hot summer's day. Symptoms typically start in the mid-morning and may persist through the next night.

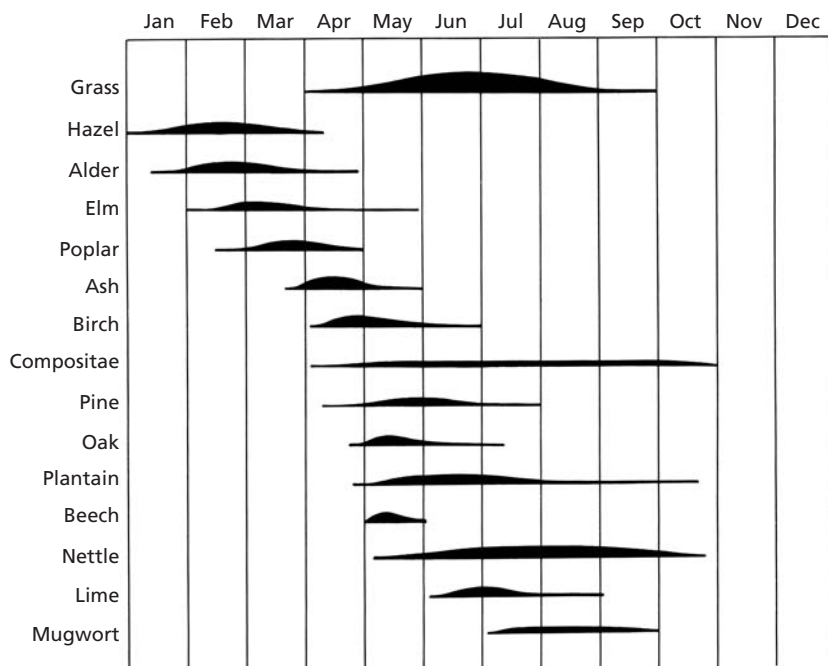
Grass pollens are 30–50 µm in diameter and soluble antigens with molecular masses of 30–40 kDa are found on their surface. Osmotic rupture of the grain may cause release of starch granules bearing these antigens; this has been proposed as a mechanism whereby heavy rain during a thunderstorm may be responsible for epidemic outbreaks of asthma [272,273]. There is considerable cross-reactivity between pollens from different species of grass [274]. Certain weeds, generally of the family Compositae, may also be important sources of allergen. As with mites,

the major allergens are denoted by letters and numbers indicating the source species and the order in which they were characterized. In North America in particular, especially in agricultural areas of the central and eastern regions, ragweed (*Ambrosia* sp.) is a major source of allergen [275–277]. It pollinates in August and September. Mid and late summer allergic symptoms may be due to nettle or mugwort pollen, while symptoms in the spring may be due to pollen from trees such as alder, elm, ash, birch, beech or oak, all of which pollinate between February and May in temperate climates. The seasons of some of the important pollen allergens in the UK are shown in Fig. 34.18.

Seasonal asthma always suggests an airborne biological allergen. However, it should be clear that this depends on the local flora and a knowledge of this is essential for making a diagnosis. Pollens may travel hundreds of miles in the air, although high concentrations are obviously only likely to occur close to a source. The introduction of new species of plant into a region may be followed by important epidemics of respiratory symptoms, as occurred in Kuwait when decorative trees of the species *Prosopis* were planted in previously desert areas [278]. The widespread cultivation of oilseed rape in the European Community has given rise to fears that it may be an important new cause of epidemic asthma; however, since it produces large grains and is primarily pollinated by insects, this seems not to be the case [279,280]. Nevertheless, it does occasionally sensitize people working with it in agricultural laboratories and therefore has allergenic potential with respect to heavily exposed atopic individuals.

### Fungal spores

Like plant pollens, fungal spores may also become airborne and cause sensitization. Fungal spores are usually smaller than pollen, being about 5–20µm in diameter [270,271]. Each species has its distinctive shape, varying from roughly spherical to torpedo-like. They usually appear to cause asthmatic symptoms without rhinitis. Although the total numbers of spores in the air may be exceedingly large, because of their smaller size the antigenic load is usually much less than that from grass pollen and this probably explains why fungal allergy is generally less of a problem than pollen allergy. Nevertheless, some patients do become sensitized and also develop seasonal symptoms in relation to the sporing season of the organism [281,282] (Fig. 34.19). Most fungi are either parasites or saprophytes of plants or live on dead organic matter. Their classification and nomenclature are discussed in Chapter 21. Different fungi predominate in different macroclimates and microclimates, according to the availability of suitable substrates. In Britain and other temperate climates, *Cladosporium* spp., basidiomycetes (including smuts and rusts), ascospores, *Sporobolomyces* spp., *Alternaria* spp., *Fusarium* spp. and *Penicillium* spp. are the most common spores in the air generally. However, local factors such as fields of cereals, compost heaps or rotting wood may cause very high local concentrations of other organisms. *Aspergillus fumigatus* may sensitize people working with compost, farmers may develop asthma in relation to large numbers of spores liberated at harvest time, and people living in damp mouldy houses or exposed to dry rot may develop asthma related to organ-



**Fig. 34.18** A guide to the pollen season of common British plants. This varies somewhat according to latitude and weather.



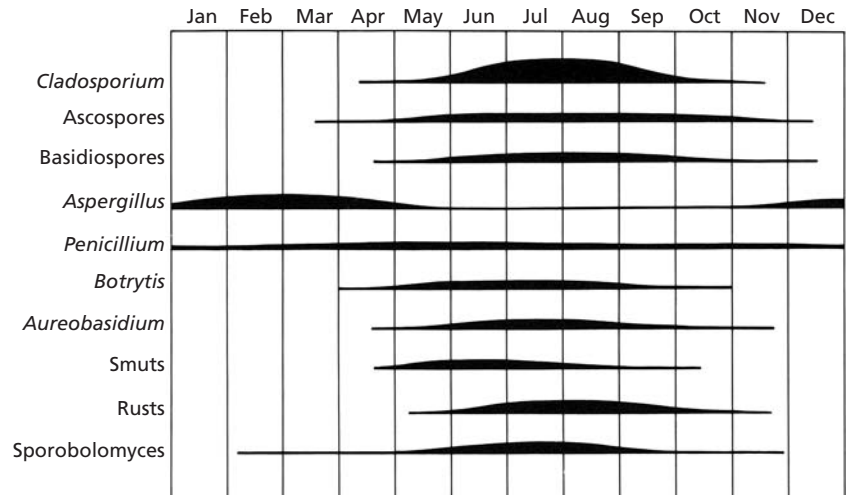


Fig. 34.19 A guide to the spore season of common British fungi. This varies according to the weather and local availability of substrates.

isms such as *Aspergillus niger*, *Merulius lacrimans* or *Penicillium* spp. It is of interest that *Aspergillus* spp. are not among the most frequent fungi in the air spora and yet they are probably the most troublesome species of fungus in terms of sensitization and disease; this is discussed separately in the section on bronchopulmonary aspergillosis. It has been postulated that the presence of activated epithelial cells and the exposure of basement membrane that occurs in asthma, together with oxidant stress, may facilitate the colonization of the asthmatic lung by *A. fumigatus* [283]. The incidence of positive skin reactions to *A. fumigatus* in unselected atopic asthmatics ranges from 10 to 20% [258]. A prerequisite for the development of aspergillar hypersensitivity is repeated exposure to the *Aspergillus* antigen [284]. Two distinct antigens, *Asp fl* (an 18-kDa protein) and a 48-kDa protein, have been identified as important causes of IgE antibody responses [285].

In clinical terms, fungal allergy (apart from aspergillosis) is probably not a frequent cause of troublesome symptoms [286]. However, there is increasing evidence that damp housing, which predisposes to the growth of moulds, is associated with a higher prevalence of asthma [287–290], although it is often difficult to separate this from the effects of the house-dust mite which also thrives in some damp houses [290]. Suspicion should be aroused in seasonal asthma without rhinitis [282] and when symptoms point to some specific site of asthma provocation, such as the house or workplace. The use of fungi in biotechnology is another area where sensitization may occur [291]. Fungal-induced asthmatic reactions in general have been well reviewed [292].

#### Animals

Up to 25% of atopic asthmatics show skin sensitivity to an animal [293]. Sensitization usually arises as a result of regular contact, and therefore is normally to a household

pet or farm animals. Cats, dogs, horses and guinea-pigs are those most commonly encountered, though rabbits, white mice and even rats and ferrets are kept as house pets. Occupational sensitization to laboratory animals is a widespread problem. Birds, such as budgerigars, occasionally provoke asthma, although allergic alveolitis is a more common problem. All asthmatic patients should be asked about pets and animal contact. If sensitization is of clinical significance, the patient is likely to have noticed rhinitis and conjunctivitis as well as wheeze on contact with the animal. The sensitization is to animal proteins on particles derived from urine or saliva. In occupational cases, animal allergy may be the only cause of the asthma, which often remits when exposure ceases; occasionally this may be the case with domestic exposure. Allergy to the major cat allergen, *Fel dI*, is much more of a problem than allergies to other domestic pets. Cat-owning asthmatics with proven allergy to their pets rarely (and understandably) take medical advice about removal of the animal from their households [294], and there is evidence to suggest that asthmatics with cats require higher doses of inhaled corticosteroid therapy to control their symptoms than patients with dogs and other pets [295]. It has been suggested that in some countries, such as Sweden, cat allergy is the most important problem in childhood asthma [296].

Occasionally arthropods other than mites may cause asthma, and in some parts of the world cockroaches rather than mites are the main domestic allergen. Research workers studying locusts have been reported to develop symptoms, as have people exposed to various flies and to cockroaches [297–300]. Epidemic asthma has been reported in the Sudan due to a midge [301].

#### Food, drink and drugs

Atopic asthmatics may occasionally notice that their

symptoms are provoked by certain foods or drinks and it is worth asking all asthmatic patients whether they have noticed such an association. In the authors' experience it occurs in less than 10% of patients. The foods most frequently suspected are milk, eggs, fish, cereals, nuts and chocolates, but very many others have been described [302,303]. Meats containing antibiotics fed to animals or tenderized with enzymes are recognized as occasional causes. It is thought that sensitization occurs as a result of pinocytosis of antigenic protein molecules by intestinal mucosal cells (perhaps in the Peyer's patches) and induction of an IgE antibody response [304]. Subsequent entry of antigen into the bloodstream provokes an IgE-mediated reaction. Some of these patients notice gastrointestinal symptoms as well as wheeze; indeed such symptoms alone are a more frequent consequence of food allergy than is asthma. Anaphylaxis is a serious consequence of food allergy and appears to be occurring more frequently than before; peanuts, widely used in a large number of prepared foods, are most commonly to blame. Such patients need to exclude the offending substance absolutely from their diet and to be instructed in use of emergency epinephrine (adrenaline) injections.

Food may also provoke asthma via mechanisms that may not be related to IgE-mediated allergy. Preservatives such as benzoates, sodium nitrite and sodium metabisulphite, synthetic antioxidants, dyes such as tartrazine, and flavourings may be found in many foods and may provoke asthma. Red wines contain a number of congeners that give them their distinctive flavours but which also may provoke attacks of asthma, perhaps by a direct effect on mast cells causing liberation of mediators [305,306]. In general, however, alcohol itself is a mild bronchodilator [307,308]. It has been postulated that asthma associated with chewing betel-nut is chemically mediated by cholinergic stimulation [309].

An observation of some interest was that regional variations in asthma mortality in England and Wales correlated with dietary intake of sodium [310]. It has also been shown that bronchial reactivity to histamine is related to 24-h urinary sodium excretion [311], and it is possible that changes in dietary salt intake could alter the activity of the bronchial smooth muscle cellular sodium pump, which may be relevant to bronchial reactivity [312]. However, in a study of Montreal schoolchildren no association was found between asthma or exercise-induced bronchospasm and dietary salt intake, although bronchial responsiveness to methacholine did appear to increase with greater salt intake [313]. Absence of a relationship with peak flows and and peak flow variability has been reported [314], as has presence of a relationship to bronchial reactivity in some populations and not in others [315]. Yet other studies have linked increasing dietary salt intake with worsening asthma symptoms and increased bronchodilator use [316–318]. These discrepancies suggest

that the effect of salt intake is unlikely to be an important determinant of asthma [315], and it may be that it is a marker of an otherwise unsatisfactory diet [319].

Recently it has been suggested that omissions from, or changes in, the pattern of diet rather than allergenic additions may have played some part in the increase in allergic diseases in developed countries (see p. 940) [244]. Although diet may be responsible for some of the differences in the prevalence rates of asthma between countries, the extent of the effect is not known [56]. Breast-feeding is often cited as a protective factor, although the evidence is contradictory. A regular fish diet appears to reduce the risk of airway hyperresponsiveness in Australian children [257] and there are theoretical reasons why fish oils might alter the course of asthma via metabolites produced from arachidonic acid. Recently it has been postulated that dietary polyunsaturated fats, notably  $\omega$ -6 fatty acids such as linoleic acid, may influence the development of allergic sensitization by increasing the formation of PGE<sub>2</sub>, promoting Th2 lymphocyte responses and IgE generation [247]. Also dietary changes leading to a decrease in the intake of antioxidants such as vitamins C, E and  $\beta$ -carotene have been suggested as a possible cause of alterations in population susceptibility to atopic disorders [244], and some evidence now supports the concept that a diet high in fats and low in vitamins C and E is an important risk factor for adult-onset asthma and bronchial hyperreactivity [320,321]. Vitamin E may also be immunomodulatory and able to influence T-helper cell development in the direction of Th1, while vitamin C acts to reduce oxidized vitamin E radical and thus regenerate the active vitamin. It now seems likely that diet will prove to play a role in the development of susceptibility to allergens, although the magnitude of this effect has yet to be determined.

Drugs are an important but occasional cause of asthmatic attacks. Aspirin and other non-steroidal anti-inflammatory drugs are the most frequent offenders, followed closely by  $\beta$  blockers. The drugs and mechanisms are discussed in more detail in Chapter 55. It should be noted that aspirin sensitivity occurs particularly in non-atopic adult asthmatics, the combination of asthma, anti-inflammatory drug sensitivity and nasal polyposis constituting a well-defined syndrome. Tartrazine, a well-recognized chemical cause of asthma, may also be present in many drugs as well as in foods [322].

### *Infection*

Viral infections are one of the most common and important triggers of asthma exacerbations, especially in atopic infants [323]. There is some evidence that viral infections in childhood may predispose to the development of asthma and bronchial hyperreactivity in later life [324–326]. Both respiratory syncytial virus infection and croup may be followed by persistent wheezing and hyper-

reactivity, and it has been suggested that such infections may also precede sensitization to common allergens in children of atopic parents [327–330]. The other view is that genetic predisposition is required to allow this to happen, and only transient damage occurs in previously normal individuals [331]. Asthma and acute viral infections are among the commonest of respiratory afflictions. There is a strong association between viral respiratory infections and both the onset and exacerbation of asthma, and the nature of the association is an important area for future research. Recent information suggests that this link may not be wholly accidental but may reflect specific interactions of viral proteins with the host immune system [332].

From the point of view of the chest physician, viral infections in adults are frequently followed by protracted cough and wheeze indistinguishable from asthma [333,334]. The viruses usually responsible are influenza, rhinovirus and respiratory syncytial virus, together with the bacterium *Mycoplasma pneumoniae*. Asthmatic patients with these infections usually suffer attacks of wheeze lasting several weeks. Even non-asthmatic subjects can be shown to have a prolonged period of hyperreactivity, probably related to the mucosal epithelial damage and irritation of vagal receptors [220,335,336]. In contrast, infection with pyogenic bacteria rarely causes acute exacerbations of asthma, though such infections may occasionally be superimposed on a previous viral infection.

### *Air pollution*

Certain air pollutants, notably sulphur dioxide (SO<sub>2</sub>), ozone and nitrogen dioxide (NO<sub>2</sub>), are able to cause bronchoconstriction when inhaled at high concentrations, although the concentrations that cause this effect are rarely reached in outdoor air in the West nowadays. Nevertheless, epidemiological studies have shown an association between episodes of pollution, primarily with particles and ozone, and exacerbations of asthma [337]. Some reports from the UK indicate that currently encountered levels of air pollution may have measurable but small effects on hospital admissions for asthma and on the lung function of adult asthmatics [338,339]. Studies in the USA and Canada have also shown positive correlations between asthma admissions and ozone, SO<sub>2</sub> and sulphates [340,341], and fluctuations in the concentrations of SO<sub>2</sub> and ozone have been associated with patterns of attendance at casualty departments for acute wheezy episodes [342]. In children a small but statistically significant adverse effect on lung function has been linked with air-borne respirable particulate matter, measured as PM<sub>10</sub> (particles <10µm in diameter), but not with levels of ozone or NO<sub>2</sub> [343,344].

Although these studies point towards an interaction of

air pollution and asthma, the results are not entirely consistent, particularly when linking an individual pollutant to asthma. The main problems with these studies have been difficulty in differentiating asthma and other chronic airway disease and in controlling for confounding variables, including geographical variations in weather, other pollutant levels, occupation, lifestyle, smoking habits, infections, allergens, socioeconomic status and healthcare facilities [345]. Air pollution in general has lessened in the UK at a time when asthma and atopic disorders have increased, and there is the well-known paradox that heavily polluted countries have in general more chronic obstructive pulmonary disease (COPD) and less asthma than do less polluted countries. It is highly unlikely therefore that air pollution is responsible for the increased prevalence of childhood asthma, episodic wheezing and hay fever seen over the last two decades [346]. Functional responses of asthmatics to ozone, NO<sub>2</sub> and SO<sub>2</sub> have been extensively evaluated in controlled exposure studies [346,347] and these studies have shown that asthmatics are abnormally sensitive to SO<sub>2</sub> but not to NO<sub>2</sub> or ozone. However, the possibility of some synergistic effects of combinations of ozone, NO<sub>2</sub> and SO<sub>2</sub> cannot be excluded.

Controlled human exposure studies suggest that air pollutants can potentiate inhaled responses to aeroallergens [348–351]. The mechanisms contributing to the potentiation of responses to aeroallergens following exposure to outdoor and indoor air pollutants is not well understood, but could be the result of pollutants causing shedding of the bronchial basal epithelial cells [345], allowing access of antigen to submucosal lymphocytes and possibly exaggerating the immune response by increasing IgE synthesis [352].

There is thus good evidence that air pollution can influence asthma morbidity and mortality in those who have the disease. However, the evidence does not support the view that air pollution could account for the increasing prevalence of asthma, nor does it support the view that chronic exposure to raised levels of ambient air pollutants can trigger asthma in normal healthy individuals [345].

### *Smoking*

The interrelations of smoking, asthma and atopy are ill understood. Smokers appear to be at greater risk of developing asthma and have a higher prevalence of hyperreactivity [353,354] but the role of smoking as an independent cause of asthma has been questioned [355]. In a long-term follow-up study of a childhood cohort, atopy and smoking were two important predictors of adult-onset wheezy illness [356]. It seems likely that smoking is an important risk factor for reversible airflow obstruction in adults, although the very fact that a patient is a smoker inclines doctors towards a diagnosis of COPD rather than asthma, causing unnecessary confusion to epidemiologists.

The role of environmental tobacco smoke as a cause of asthma remains uncertain. Asthma has been associated with tobacco smoke more strongly in young children [357–359] than in school-aged children in whom the evidence is confusing [360–365]. On the other hand, there are many reports of a significantly increased risk of wheeze in school-aged children. While wheeze is often used as a surrogate measure of asthma, different definitions of wheeze have been used in various studies, making comparisons between studies difficult. Another difficulty with these studies is the confounding effect of other factors associated with social class, and it seems to the authors that in general a relatively poor environment in the West, associated with parental smoking, poor housing and a bad diet, combine to increase the risks of wheezy illness in adolescents and adults.

To add further complexity, it has often been observed by clinicians that asthmatic symptoms commence more frequently than would be expected in individuals who have recently stopped smoking; in some of these, symptoms improve if they restart. There may be an immunosuppressant effect of smoke (which could also explain the relative resistance of smokers to the development of allergic alveolitis) and this is an area that requires further research.

### *Psychological factors*

Most patients with asthma acknowledge that exacerbations may be provoked by psychological events, such as shock, bereavement or excitement. However, such factors are rarely the dominant cause of the disease [366,367]. Suggestion (and its extreme form, hypnosis) may have important effects in modifying asthmatic reactions to provoking factors in either direction [368,369], and good doctors make use of this in their management of such patients. In one study hypnosis abolished skin sensitivity, even though the presence of antibody in serum was still demonstrable by the Prausnitz–Kustner reaction [370].

The psychogenic effects on airways reactivity are presumably mediated by the autonomic nervous system, and the effects of suggestion in provoking bronchospasm may be blocked by atropine [371]. Hyperventilation induced by anxiety or laughter may also be responsible for asthmatic reactions.

The severe asthmatic attack may be very frightening, and such patients are understandably anxious. It is important to recognize this and to reassure the patient, while treating the asthma rather than the anxiety with drugs. The parents of an asthmatic child frequently and understandably become anxious and tend to be overprotective towards the child. This also should be recognized by the doctor, and managed by proper care of the child and reassurance of the parents. It is likely that such psychosocial factors in a family contribute to the severity of the asthma,

and they should always be sought for and dealt with as far as possible. Occasionally, psychological illness, family disputes or marital problems may be major factors in the aetiology of intractable asthma and expert psychiatric help may be necessary.

### *Gastro-oesophageal reflux*

It is now well recognized that episodes of gastro-oesophageal reflux may provoke wheeze as well as the more familiar symptoms of heartburn [372,373]. Not all asthmatics respond in this way to reflux, but in those that do a lowered intraoesophageal pH seems to initiate a fall in FEV<sub>1</sub> over about 90 min [374,375]. Acidic drinks, such as colas and fruit juices, and iced water produce similar effects. In some cases where reflux symptoms are troublesome, fundal plication or treatment with an H<sub>2</sub> blocker has also resulted in amelioration of the asthmatic symptoms [376,377]. Gastro-oesophageal reflux is common and enquiry about it should be routine in history-taking in the asthmatic. While it plays no part in the generation of the common nocturnal symptoms in most patients [378], reflux should always be considered as a possible provocative factor in the 'difficult to control' asthmatic [379]. If an asthmatic patient has prominent reflux symptoms, a trial of treatment with an H<sub>2</sub> blocker or a proton pump inhibitor is justified.

### *Exercise*

Almost all young, active asthmatic subjects may provoke attacks by exercise, although their responsiveness to this form of challenge varies according to other factors such as associated allergen challenge and baseline bronchial reactivity and the ambient temperature. The typical exercise required to provoke an attack is several minutes of running, though a quick sprint for a bus on a cold winter morning may be sufficient. The bronchoconstriction usually starts at or towards the end of the exercise and lasts 20–30 min. The mechanisms have been discussed above.

### *Weather*

Almost all asthmatic patients notice effects of the weather on their symptoms and learn which individual patterns suite them best or least. Aside from the effects of air pollution and seasonal airborne pollen and spores, extremes of temperature seem most likely to provoke attacks in the susceptible. Notable epidemics of asthma have been described on many occasions in association with thunderstorms [380–382], although the causes of these are not understood and not all such storms are associated with epidemics. It has been suggested that in some cases they may be due to release by the associated rainfall of large

numbers of fungal spores or allergenic grass pollen particles, and epidemics are most likely to occur if the storm follows a period of high pollen counts [272,383].

### *Occupational factors*

Work-related factors are important provokers of asthma, and asthma is now the most common type of work-related respiratory disease in industrialized countries [384,385]. Occupational asthma can be defined as variable airways narrowing causally related to exposure in the working environment to airborne dusts, gases, vapours or fumes [386]. Most authorities now recognize that typical asthma may occur following exposure to high concentrations of irritant gases or fumes [387], the so-called reactive airways dysfunction syndrome discussed further in Chapter 36. This section concerns itself with asthma following exposure to a sensitizer. Symptoms usually commence within 2 years of starting the job, although this period is sometimes much longer, and may be associated with a particular place or process. Typically, the symptoms initially occur towards the end of the working day and in the evening, and are relieved at weekends and on holiday. As the condition progresses, so the symptoms become more persistent and may last over weekends and even for several weeks after work has ceased [385,388]. Indeed, there is no doubt that exposure to allergens, particularly those of low molecular weight, in the workplace can act as a trigger of persistent asthma that continues despite complete cessation of exposure; unless the patient ceases exposure relatively quickly after symptoms commence, this is the usual outcome [387,389,390]. Thus, if the patient presents for diagnosis when the condition has become well established, typical patterns of work-related peak flow rate changes may be absent. There are a number of factors that influence prognosis. Further occupational exposure in sensitized subjects leads to persistence and sometimes progressive deterioration of asthma, irrespective of any reduction of exposure to the specific sensitizer. Other determinants of an unfavourable prognosis are long duration of exposure before the development of asthma, long duration of symptoms before diagnosis, poor baseline pulmonary function, dual responses after specific challenge tests and the persistence of markers of airway inflammation in BAL and bronchial biopsies [388]. The diagnosis of occupational asthma is discussed in a later section.

Occupational asthma is considered for medicolegal purposes to be asthma provoked by some agent in the work process that was not present before the individual was so exposed. The agent (identified or not) should be specific to the workplace as well as causally related to the disease [386,389,391]. A previous history of asthma does not exclude a diagnosis of occupational asthma, but in such individuals the diagnosis is much more difficult to estab-

lish. People with pre-existing asthma are of course liable to develop exacerbations if they choose jobs in which allergen exposure is a problem. Atopic individuals are also at greater risk of developing asthma in jobs where they are exposed to one of the classical high molecular weight allergens, such as animal dander, grain dust or other organic debris. In general, however, this is not true of exposures to low molecular weight chemicals, where atopics appear to be at relatively little greater risk [392], with some exceptions such as platinum complex salts. Nor are non-atopics immune from asthma even when exposed to classical allergens, so prevention of the condition by screening out atopics is not usually a very effective means of control. More than one immunological mechanism must be involved in occupational asthma. The mechanisms of asthma due to small molecular weight substances are not known, and it is unlikely that classical IgE-mediated allergic processes are responsible in all cases. There is evidence to confirm that T-lymphocyte activation and local accumulation of activated eosinophils in the bronchial wall occurs in asthma of diverse aetiology [392]. It should be noted in passing that bronchoconstriction in response to workplace exposures may not always imply the potential of persisting hypersensitivity. For example, it may be a transient phenomenon provoked by irritant exposures, such as to smoke, chlorine, SO<sub>2</sub> or citric acid, or by exposure to the anticholinesterase organophosphate insecticides [393].

### *Causes of occupational asthma*

The list of proven causes of asthma in the workplace is long and inevitably increasing. For a detailed review, the reader is referred to the article by Chan-Yeung and Malo [394]. However, it is more important always to bear in mind the possibility of occupational factors, which may not have been recognized previously, and to make appropriate investigations than to remember a long list of known causes. The list may be simplified by subdivision into categories that may prompt a question in the history, i.e. exposure to animals or animal products, plants or their derivatives, and enzymes, drugs and chemicals. The best known of these are listed in Tables 34.1–34.3.

**Table 34.1** Causes of occupational asthma of animal origin.

Agent	Occupation
Cats, dogs, horses	Veterinarians
Rats, mice, guinea-pigs	Laboratory workers
Grain mites	Farmers
Locusts	Research workers
Moths, silkworms, flies	Breeding
Pigeons, chickens	Breeding, farming
Oyster, prawn, crab, salmon	Food production

**Table 34.2** Causes of occupational asthma of vegetable and bacteriological origin.

Agent	Occupation
Grains and flour	Farmers, millers, bakers
Hardwood dusts	Millers, joiners, carpenters
Castor, coffee beans	Processing
Gum acacia	Pharmaceuticals
Tragacanth	Sweet manufacture
Colophony	Soldering
Enzymes	
Alcalase	Detergent production
Trypsin	
Papain	Pharmaceuticals, food technology
Amylase	
Ispaghula	Laxative manufacture

**Table 34.3** Causes of occupational asthma of chemical origin.

Agent	Occupation
Isocyanates	Paints, varnishes, plastics
Epoxy resin hardeners	Adhesives, varnishes
Ethanolamines	Aluminium soldering
Formaldehyde, glutaraldehyde	Hospital workers
Azodicarbonamide	Plastics
Platinum	Refining
Nickel	Plating
Chromium	Leather tanning
Cobalt	Hard-metal work
Vanadium	Boiler cleaning
Persulphates, henna	Hair colouring
Reactive dyes	Manufacture, dyeing
Pharmaceuticals	Pharmaceutical industry
Penicillins	
Tetracyclines	
Cephalosporins	
Piperazine	
Psyllium	
Chloramine T	
Ceftazidime	

Important animal causes include small laboratory mammals, where urinary protein is usually the principal allergen [395–397], insects such as locusts [297], fruit flies [398] and honey-bee dust [399], grain mites [400], fowl mites [401], moths (including silkworms) and flies [299,402], birds such as pigeons and chickens [401,403], and molluscs such as oyster, prawn and crab [404,405]. Sensitization occurs as a result of exposure to airborne particles such as urine droplets, mite faeces or small fragments of insect parts. Prawn workers may be exposed because of the water jets used to blow the meat from the exoskeleton. Farmers and veterinarians may become sensitized to any number of animals that they handle, as may laboratory workers.

The best-known vegetable causes are wood dusts, espe-

cially from hardwoods such as western red cedar [389] and grain dusts [406–408]. The largest numbers of subjects sensitized to wood have been reported from sawmills, although joiners and carpenters not infrequently develop symptoms [409]. They can usually prevent attacks by avoiding the particular wood. It is probable that the active agent in hardwood dust is a small molecular weight chemical, plicatic acid, which can combine with serum albumin to form a sensitizing hapten [410]. In common with other types of asthma provoked by small molecules, atopic individuals do not seem to be at increased risk of western red cedar sensitization. Less is known of the immunological mechanisms of asthma caused by other wood dusts, although in view of their common characteristic of hardness it is likely that they act similarly. Grain dust contains a complex mixture of allergens and has been known to cause respiratory problems among bakers and millers since the eighteenth century. Flour itself may be allergenic, and not uncommonly sensitization to enzymes used in the process, notably  $\alpha$ -amylase, occurs [411,412]. Occasionally the grain may be contaminated by fungi and mites. The grain mites *Tyrophagus* and *Acarus* spp. have been shown to be an important cause of asthma in farmers in Scotland handling stored grain [413]. Other vegetable causes of asthma include castor and coffee beans [414,415], in workers manufacturing their products, and gums from acacia and tragacanth used previously in printing and currently in pharmaceuticals and sweet manufacture [416,417].

Colophony (or rosin), the residue that remains when oil of turpentine has been distilled from pine resin, is known to be an important cause of asthma [418,419]. It is used as a component of multicore solders and has widespread industrial application in the manufacture of circuitry in electronics. The principal component of the fume liberated when it is heated is a small molecular weight chemical, abietic acid. The mechanism whereby this provokes asthma is not known, although there is no evidence that it causes IgE-mediated sensitization. Asthma caused by colophony is commonplace in the electronic industry and again affects atopics and non-atopics, even though atopy may be a weak predisposing factor [420,421]. Occupational asthma caused by enzymes was first described in workers making so-called biological washing powders, where proteolytic enzymes derived from *Bacillus subtilis* were introduced into the product [422–424]. This problem has now been controlled by careful attention to industrial hygiene in the process [425]. Sporadic cases may be seen of workers sensitized to other enzymes such as trypsin, papain and amylase in plastic, pharmaceutical laboratory and food technology work [426–428]. Asthma caused by drugs administered to patients is discussed in Chapter 55. Pharmaceutical products or chemical compounds involved in their synthesis may also sensitize workers. Among these are penicillins, tetracyclines, cephalo-

sporins, piperazine, chloramine disinfectants and psyllium [429–435].

In recent years, the substances that have attracted most attention as causes of occupational asthma have been low molecular weight chemicals. Isocyanates, especially TDI but also the diphenyl methane, hexamethylene and naphthylamine compounds and prepolymers [436–444], are particularly important because of the large numbers of workers exposed in the production of polyurethanes and synthetic rubbers and in the use of foundry binding materials, varnishes and other surface coatings. Isocyanates are irritant substances and in high concentration can cause non-specific bronchial reactivity, although sensitized subjects react to extremely low concentrations. They are reactive chemicals but the method by which they cause sensitization is not known; there is no strong evidence that they cause their effect via hapten formation and an IgE-mediated reaction, though occasional subjects show a positive RAST to TDI-albumin complexes [445]. Isocyanates may occasionally also cause hypersensitivity pneumonitis (see Chapter 37).

Epoxy resins are polymers that are converted into solids by the addition of acid anhydrides or other chemicals as curing agents. Mixing of the two components in their use as adhesives, surface coatings or plastics may cause liberation of anhydride fumes that can produce asthmatic sensitization, as can heating materials containing them, as in meat-wrappers' asthma [446–448]. There are several such chemicals in use: phthalic, trimellitic, hexahydrophthalic, maleic and tetrachlorophthalic anhydrides. Trimellitic anhydride may also cause alveolitis, an influenza-like syndrome and haemolytic anaemia and haemoptysis [447,449]. These reactive chemicals do act as haptens, and both IgE and IgG antibodies have been described in exposed subjects [450,451]. Aliphatic amines are also potent causes of occupational asthma, described in shellac and lacquer handlers and also in aircraft fitters [452–454]. These compounds include ethylenediamine, dimethylethanolamine, triethylenetetramine and aminoethylethanolamine.

Several metals or their salts may cause bronchial (and skin) sensitization: complex salts of platinum in refining [455,456], nickel in polishing and plating [457], chromium in plating, printing and tanning leather [458,459], cobalt in coolants used in making and machining tungsten carbide (hard metal) and diamond polishing [460,461] and vanadium in cleaning residues from boilers which have burned oil containing the metal [462]. Exposure to cobalt in hard-metal work may also lead to an alveolitis and pulmonary fibrosis, so-called hard metal disease [463]. Asthma in aluminium refinery workers is probably due to fumes of fluoride rather than to the metal itself [464].

Many other chemicals have been described as occasional causes of asthma and no doubt many others will be in the future. Worthily of note are formaldehyde and

glutaraldehyde in hospital workers [465,466], azodicarbonamide (a blowing agent in plastic manufacture) [467], paraphenylenediamine in fur dyeing [468], various dyes in hairdressing [469] and aminoethylethanolamine in aluminium soldering [470]. Reactive dyes in the textile industry, when handled in powder form, are another cause that has on occasion proved fatal [471]. More recently, a large variety of causes have been reported including latex especially in rubber gloves used in hospitals [472], fungicides [473,474], and polyethylene shrink wrapping [475]. Latex allergy is becoming an important and increasing problem in hospitals, causing both allergic dermatitis and asthma. It is caused by liberation of particles of protein from the gloves, which are now generally made of cheaper, less well-washed latex.

Some studies have shown that asthma related to chemical and vegetable agents occurs more commonly in cigarette smokers. It has been speculated that this may be due to the effect of smoke on bronchial epithelium, improving access of the sensitizer to submucosal lymphocytes and mast cells [476,477].

Several mechanisms, including immunological, pharmacological and genetic, have been suggested as causes of occupational asthma, acting in concert with airway and neurogenic inflammation [392]. It is likely that more than one mechanism is operative, and it is certain that many more causes or 'inducers' of this problem will be identified in the future. The medicolegal and compensation aspects of occupational asthma have been well reviewed [478].

### Clinical course

The only certain things about the course of asthma are its variability and its unpredictability. However, some general points about the natural history can be made and are useful in discussing prognosis with patients and their relatives at the time of diagnosis. The course of asthma is usually one of periods of normality punctuated by attacks of cough, wheeze and breathlessness. Factors provoking attacks have been discussed above; however, attacks often occur without obvious provocation. They may be brief, as after exertion, or last several weeks, as after a viral illness. Between attacks, patients are usually free of symptoms though symptoms may be provoked by exercise or exposure to allergens. During symptomatic periods, patients are usually more sensitive to such stimuli than when well. In atopic asthmatics, exacerbations provoked by allergens are commonly accompanied by rhinitis, while perennial rhinitis of non-allergic but uncertain aetiology commonly accompanies non-atopic asthma. During periods of poor symptom control the characteristic features are variation of symptoms and expiratory flow rates within the 24-h cycle, usually being worst in the small hours and first thing in the morning and least troublesome in the early



afternoon [479,480]. Appropriate changes in the timing of this cycle occur in shift workers [481]. There has been much discussion of the cause of diurnal variation and, particularly, nocturnal deterioration in asthma. Suggestions that it might be related to feather pillows or mites in the bed do not explain its occurrence as frequently in non-atopic as in atopic patients. Circadian corticosteroid variation does not explain its occurrence in those on regular medication with these drugs. On balance, it seems likely to be related to increased vagal tone and reduced NANC tone acting on a hyperreactive airway at night [482,483]. It has been shown that bronchial inflammation is increased at night [484] and this is likely to contribute to airway narrowing and hyperreactivity [485].

When asthma starts in childhood, there is a reasonable probability that it will remit (sometimes temporarily) at about the time of adolescence and it usually improves at that age [486–488]. In a Finnish study, 108 asthmatic children were followed up to 20–24 years of age [489]; one-quarter were symptom-free, while another quarter had symptoms at least once a week, half had increased airway responsiveness but only 18% had a below-normal FEV<sub>1</sub>. Risk factors for persistence of asthma appear to be severe childhood asthma starting at an early age associated with atopic eczema. Asthma starting in adult life remits less frequently, except when it occurs simply as a prolonged response to a viral infection. The disease may start at any age, from infancy to extreme old age [37], and may announce itself with an acute severe attack, with increasing wheeze and breathlessness, or with persistent cough. When it presents in middle age or later in this insidious manner, especially if cough is a prominent symptom, it is very liable to be misdiagnosed as chronic bronchitis by the unwary physician. A patient developing asthma for the first time in adult life frequently gives a family history of the disease and atopy is a major risk factor [356], although personal allergic factors are much less important than in childhood, unless the asthma is occupational in origin. It is common clinical experience that older more severe asthmatic patients frequently develop a substantial degree of fixed airway obstruction, and the rate of decline in lung function tends to be accelerated in these patients [490,491].

Acute severe attacks, previously called status asthmaticus, occur spasmodically and unpredictably. They are usually provoked by one of the factors mentioned above. Some patients suffer such episodes frequently but some never (this condition is discussed in the next section). A relatively small proportion of patients develop progressive chronic disease that becomes largely irreversible, even to large doses of corticosteroids. This syndrome, chronic severe asthma, is also discussed below.

### Acute severe asthma

Acute severe attacks represent progression of airways nar-

rowing to the point where the patient is distressed at rest and may have signs of cardiac stress. Episodes may be of extremely sudden onset, as in an anaphylactic reaction, but more commonly build up over several hours or days. Often they are initiated by a viral infection and preceded by a period of a few hours or days during which asthmatic symptoms are increasingly troublesome, especially at night.

The symptoms are of increasing breathlessness, wheeze, cough and chest tightness, culminating in difficulty in talking or inability to do anything other than concentrating on breathing, usually in an upright position but sometimes crouching on hands and knees. Anxiety to the stage of panic is a usual and understandable feature. The patient sits up in bed or chair [492], wheezing is audible without the stethoscope, unless the patient is desperately sick, and the chest is visibly overinflated. Sweating may be profuse in severe attacks, and more often than not patients are pale and sweaty. If cyanosis is present this indicates life-threatening severe acute asthma. Considerable effort is clearly being expended on inspiration, the hyperinflated thoracic cage working at a great mechanical disadvantage, even though all accessory respiratory muscles are being used in an attempt to improve breathing. Cough is usually not prominent, as it is almost impossible for the ill patient to generate sufficient expiratory flow; if it is a feature, it is rarely productive of sputum. Indeed, production of sputum can be taken as an encouraging sign of recovery or indicative of an episode that at this time is not life-threatening. Tachycardia is always present, unless the episode has caused profound hypoxaemia. A paradoxical pulse (pulsus paradoxicus) is frequently detected; the extent of the fall in systolic pressure on inspiration may be as much as 50–60 mmHg and if present is a good indicator of the severity of the condition [493–495]. However it is not always present in patients with severe acute asthma and therefore its absence may be misleading [496]. Because of this, it has been withdrawn from the most recent British Thoracic Society guidelines on the management of asthma [497].

Assessment of the severity of the attack prior to treatment includes judging the degree of breathlessness by the patient's ability to talk (e.g. complete sentences in one breath) and measurement of heart rate and pulsus paradoxicus, peak flow rate and arterial blood gases [493,498]. Of these, the ability to talk, pulse rate and arterial blood gases provide the best indicators of severity and prognosis. The degree of breathlessness can be categorized conveniently according to the scheme of Sherwood Jones, which ranges from 'able to carry out housework or job with moderate difficulty (Grade 1A)' to 'immobilized and exhausted (Grade 4)' [498]. Blood gases, as discussed later, show hypoxaemia and hypocapnia initially, hypercapnia only occurring in the preterminal stages of an attack [499].

Even before the introduction of corticosteroids, the majority of attacks resolved spontaneously after several very frightening and stressful days. Nowadays, the use of aerosol and intravenous bronchodilators usually brings some symptomatic relief within minutes, while resolution of the attack can be expected to start some 6–12 h after the commencement of high-dose corticosteroids. A few patients prove resistant to this treatment and require several days or even weeks of steroids before the attack resolves, while some patients have attacks of such suddenness (or present for treatment at such a late stage) that assisted ventilation is necessary immediately. These matters are discussed in Chapter 35. A proportion of patients die of cardiorespiratory arrest in the course of such attacks, and management of asthma patients should foresee and plan to prevent this possibility.

### Chronic severe asthma

Some patients with long-standing asthma develop increasingly severe airflow obstruction progressively over several years. While this may occasionally occur in young people, it is more frequently seen in the middle-aged and elderly [500,501]. Sometimes it is due to bronchopulmonary aspergillosis but usually there is no clinically obvious cause. The characteristic feature is failure to respond, more than partially, to high doses of prednisolone [502], although sometimes change to an alternative corticosteroid in high dose (e.g. intravenous methylprednisolone or intramuscular triamcinolone acetate) may produce some improvement [503]. Bronchodilator responsiveness in these patients is usually preserved. The frequency with which this condition develops in asthma patients is not high but, because of the therapeutic problems it presents, it is disproportionately represented in specialist respiratory medicine clinics.

The pathology of the disease does not apparently differ from that of more steroid-responsive asthma [62]. Occasional such patients show unexpectedly dramatic improvement, sometimes lasting months, following a severe febrile illness; this was recognized by the generations of physicians before the advent of steroids, who occasionally treated such patients with fever therapy induced by injections of milk or vaccines. Understanding this syndrome, which is probably due to corticosteroid resistance [504–506], is an urgent priority of asthma research in order that appropriate therapy may be found. For the present, chronic severe asthma causes untold misery to large numbers of older asthmatics, misery compounded usually by the side-effects of high-dose corticosteroids. Glucocorticosteroid responsiveness in asthma can be defined as an increase in FEV<sub>1</sub> or mean peak expiratory flow (PEF), of 30% or greater during a 14-day course of prednisolone 40 mg daily, and glucocorticosteroid resistance as a less than 15% improvement in FEV<sub>1</sub> or mean

PEF, with the same 2-week treatment with prednisolone [507]. Glucocorticosteroid resistance is not caused by altered pharmacokinetics and the defect in asthmatics is not organ-specific [507,508]. Comparison of cells from normal individuals and from patients with corticosteroid-sensitive asthma has shown peripheral blood mononuclear cells and T lymphocytes to have different *in vitro* characteristics, especially with regard to their response to corticosteroids [504,505,509,510]. All aspects of corticosteroid-resistant asthma have been comprehensively reviewed [506].

### Bronchopulmonary aspergillosis

Skin sensitivity to *A. fumigatus* is commonly present in atopic individuals and occurs also in a proportion of otherwise 'non-atopic' patients with chronic asthma. The frequency with which this occurs varies between 16 and 38% in different studies which, being based on clinic populations, may be assumed to be biased towards the more severe end of the asthmatic spectrum [511–513]. In some of these patients, bronchial hypersensitivity to the fungus is also present, while in a small proportion attacks of asthma provoked by the organism are accompanied by a systemic illness with fever and malaise associated with radiographic evidence of peripheral patchy infiltrates or collapse of a lobe, segment or even a whole lung [514–516]. Sputum can be shown to contain hyphae of *A. fumigatus*, which therefore may be presumed to be growing in the airways. Characteristically, the sputum contains typical bronchial casts, with eosinophils, Curschmann's spirals, desquamated epithelial cells and hyphae (Fig. 34.20). The serum contains both IgE and IgG antibodies to *A. fumigatus*, and the total IgE is usually markedly raised. Both immediate and delayed skin sensitivity to intradermal injection of antigen are present [517–519]. Blood eosinophilia ( $1-3 \times 10^9/L$ ) is a common finding. The full-blown picture is known as allergic bronchopulmonary aspergillosis (one of the causes of pulmonary eosinophilia; see Chapter 38). Attacks are recurrent and tend to occur at first predominantly in the winter months. Untreated, an episode may last many weeks before resolving; recurrent attacks characteristically cause a proximal form of bronchiectasis, with evidence of distal pulmonary fibrotic changes [520,521]. Occasionally, especially in patients treated with long-term corticosteroids, typical radiographic exacerbations may occur without clinical symptoms [522–524]. Usually, however, attacks are noticed by the patient; they may present with chest pain and fever, as well as worsening of asthmatic symptoms, so appropriate therapeutic action can be taken. In patients with frequent attacks, progressive disease may occur leading to extensive, mainly upper zone, bronchiectasis and fibrosis. Radiological features are described in the following section. A diagnosis of allergic bronchopulmonary aspergillosis



**Fig. 34.20** Asthmatic sputum smear showing hyphae of *Aspergillus fumigatus* and a Charcot-Leyden crystal at bottom right (Papanicolaou  $\times 350$ ).

should be suspected in any patient with asthma who has an abnormal chest radiograph and a high peripheral blood eosinophil count. The diagnostic criteria include:

- 1 asthma (in most cases);
- 2 peripheral blood eosinophilia of greater than  $0.5 \times 10^9/L$ ;
- 3 presence or history of chest radiograph abnormalities;
- 4 positive skin-prick test to an extract of *A. fumigatus*;
- 5 serum precipitating antibodies to *A. fumigatus*;
- 6 raised total serum IgE;
- 7 fungal hyphae of *A. fumigatus* on microscopic examination of sputum.

Patients may sometimes present with typical attacks without having previously had asthma; in these cases diagnosis is often delayed [525,526]. Bronchoscopy is sometimes necessary to make a diagnosis and is of great value therapeutically. This often reveals thick tenacious plugs, which should be removed to restore an airway and to allow cytological examination to reveal the diagnosis. Occasionally, lobes or segments are excised surgically in the mistaken belief that bronchial occlusion has been caused by tumour. The histological features in the lung infiltrates are infiltration with eosinophils, areas of collapse, typical asthmatic bronchial inflammatory changes with intraluminal hyphae and sometimes intramural granulomas [527]. The more florid features of bronchocentric granulomatosis may sometimes be present [528].

The spectrum of response of the lungs to *A. fumigatus* is wide (see Chapter 21). Typical allergic bronchopulmonary aspergillosis may occasionally occur in people with aspergilloma and vice versa, and aspergillomas may occur as a sequel to treated invasive or allergic aspergillosis [529,530]. Very occasionally, allergic bronchopulmonary aspergillosis may develop features of invasive disease [531].

The immediate cause of the clinical manifestations of allergic bronchopulmonary aspergillosis appears to be the development of both immediate and delayed hypersensitivity to *A. fumigatus*, with an important cell-mediated component [532,533]. *A. fumigatus* spores are inhaled into the lungs since they are present in the air spora, predominantly in winter, the natural habitat of the organism being dead leaves, compost heaps and other decaying organic matter [534]. Since *A. fumigatus* is not by any means the most profuse fungal organism in the air, its special propensity to cause pulmonary problems requires explanation. This is probably related partly to its small spore size, which allows inhalation to alveolar level, and partly to its optimal temperature requirement of  $37^\circ\text{C}$ . In addition, its spores have developed sophisticated antiphagocytic defences that allow it to survive macrophage attack [535–537], and colonization may be facilitated by the pathological changes in the asthmatic's bronchial wall that expose the basement membrane [283]. A syndrome similar to allergic bronchopulmonary aspergillosis has been described occasionally in response to other fungal spores, both other species of *Aspergillus* and unrelated organisms such as *Curvularia* spp. and *Dreschlera* spp. It would be surprising if others were not to be described in the future, as the fungal air spora varies according to local climate and vegetation. For further discussion of these matters, see Chapter 21. The natural history of the condition is for recurrent episodes of pulmonary infiltration associated almost always with symptoms of exacerbation of asthma to occur over many years [538]. Between attacks, which tend to occur in autumn or winter when spores are most prevalent in the air, the patient is usually well. If attacks are treated promptly with oral corticosteroids, the condition does not usually result in progressive lung or airway damage, though early unrecognized or untreated

episodes often leave some localized bronchiectatic change [538]. The management of allergic bronchopulmonary aspergillosis is discussed in Chapter 35.

### Other complications of asthma

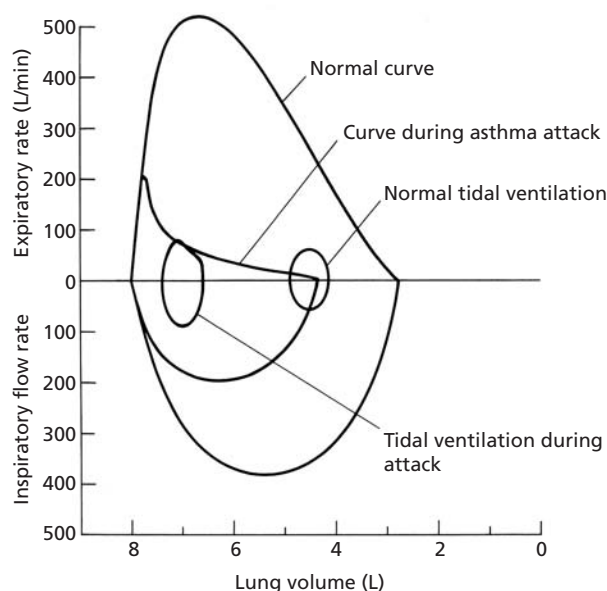
The most common complications of asthma relate to the long-term use of corticosteroid drugs. Facial changes, skin dystrophy, bruising, osteoporosis and vertebral collapse, and adrenal suppression are all commonplace and distressing features in chronic asthmatics. In children, growth retardation may be blamed on the drugs, but was a feature of chronic childhood asthma prior to their introduction [539]. In general the literature on the effects of inhaled corticosteroids on growth is reassuring, although long-term oral corticosteroid therapy, even in low doses equivalent to prednisolone 2.5–5 mg daily, significantly stunts short-term and intermediate-term growth and can reduce final height [540]. Treatment with inhaled budesonide in doses up to 400 µg daily seems not to affect growth adversely in children with asthma [541]. Higher doses can be seen to have an effect on short-term lower leg growth as assessed by knemometry; while no firm conclusions can be made about the long-term effects of inhaled corticosteroids, studies addressing this question suggest that children with asthma treated with these drugs usually attain a normal final height [542]. The question of the possibility of individually increased sensitivity to a growth-retarding effect of inhaled corticosteroids needs further study. Structural chest cage deformities caused by uncontrolled severe chronic asthma [543], such as pigeon chest and kyphosis, are now rarely seen in countries in which modern drug therapy can be afforded.

Other complications are relatively uncommon, except for respiratory infections. These are often difficult to differentiate from acute asthmatic exacerbations, especially as purulent sputum may be mimicked by sputum containing large numbers of eosinophils. Pulmonary infiltration on chest radiographs in adult asthmatics is very suggestive of allergic bronchopulmonary aspergillosis, although other eosinophilic pneumonias or segmental collapse due to plugging may be responsible. The latter is not uncommon in children [544]. Very rarely, lung collapse unrelated to aspergillosis may occur [545]. Cough fractures of ribs may occur, especially in osteoporotic bones, and acute attacks may rarely be complicated by pneumothorax or mediastinal and subcutaneous emphysema [546,547]. Even patients with long-standing chronic severe asthma occasionally develop pulmonary hypertension and cor pulmonale, and chronic hypercapnia is also a most unusual feature. When these complications do occur, the patient usually has cigarette-induced COPD as well; nevertheless, occasional non-smoking chronic asthmatics do ultimately develop cor pulmonale and, in contrast to the clinical findings, right ventricular hypertrophy at

necropsy is a not uncommon finding in chronic asthma [548].

### Physical findings and functional effects

The characteristic clinical findings in a patient with asthma are wheezes (sometimes, harking back to Laënnec, called rhonchi). They are usually polyphonic, indicating their origin from many airways of different calibre. A wheeze is generated by vibration in the wall of an airway on the point of closure, in the same way as a reed in a woodwind instrument generates a note [549]. The airway narrowing is due to smooth muscle constriction, mucosal oedema and mucous plugging. From this central principle of asthma derive all the physiological abnormalities, which may be considered in terms of primary alterations in pulmonary mechanics and secondary changes in gas exchange and cardiac function. However, the cardinal feature of asthma is its variability, and the main role of lung function testing is in demonstrating change in expiratory flow rates in response to bronchodilators or various forms of challenge. It should also be noted that lung function is often completely normal when the patient is in clinical remission, or even during the day at a time when nocturnal symptoms are troublesome. During the asthma attack there is widespread narrowing of airways and this has the effect of reducing airflow rates. Measurements of this by FEV<sub>1</sub>, PEF or flow rates at different lung volumes derived from the flow–volume curve therefore show reduction in proportion to the severity of the attack [550]. Inspiratory flow rates are also reduced, though not to the same extent as those on expiration. In partial compensation for the airway narrowing the patient breathes at a higher lung volume, which increases the (negative) pressure within the thorax acting to distend the airways. This, and the widespread closure and partial closure of small airways, results in increased residual volume and increased work of breathing. These changes are illustrated in Fig. 34.21, which shows a progressive increase in residual volume. As the attack becomes progressively more severe, tidal breathing moves up towards total lung capacity and the tidal expiratory flow rate approaches the maximal expiratory flow rate. At this point, the thoracic system is working on a part of the pressure–volume relationship that is relatively inefficient, large negative pressures being required to generate adequate tidal volumes. This inefficiency is due to the increased elastic recoil pressures in the lungs and thoracic cage, together with the shorter initial length of the intercostal and diaphragmatic muscles at high lung volumes. At the same time, the reduced vital capacity and the low flow rates available mean that adequate ventilation can be maintained only by increasing the frequency of breathing. Thus the patient in an acute attack expends a considerable amount of energy in maintaining rapid inspiratory efforts at high lung



**Fig. 34.21** Flow-volume curves in remission and during an asthma attack. Note that during the attack residual volume is increased and tidal breathing takes place at a high lung volume. Also during the attack, tidal expiratory flows approach maximal values.

volumes. Indeed, there is evidence that total lung capacity actually increases during an acute attack of asthma, thereby putting the patient's respiratory muscles at an even greater mechanical disadvantage [551–553]. These physiological features are easily seen in the patient with acute severe asthma, who sits upright fighting to breathe in, and are the reason for the increasing fatigue that occurs terminally in this condition.

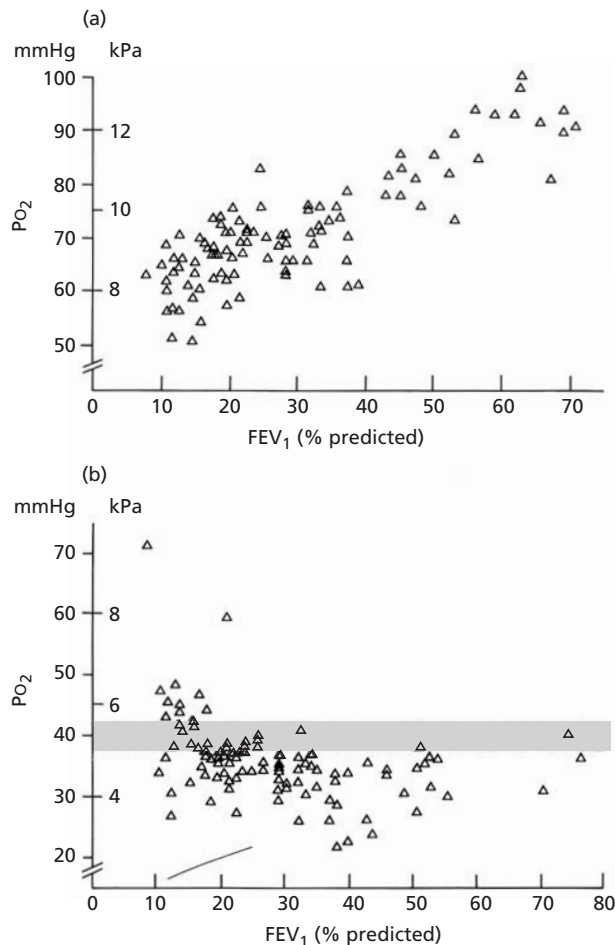
At one time there was much discussion about the site of airway narrowing in asthma, as determined by physiological tests [554,555]. There is little purpose in such studies, and the validity of so-called tests of small airways resistance is dubious in subjects with the patchy changes one might anticipate in asthma. There is little doubt that airways at all levels, from the larynx to the bronchioles, may be narrowed in an attack; glottic and major bronchial narrowing have been seen at bronchoscopy and demonstrated physiologically [556,557], and widespread plugging of small airways seen pathologically is universal in fatal attacks, unless death has occurred within minutes of the onset of the attack. It would be expected that different patterns of obstruction would occur in different attacks. Irregular distribution of airway narrowing through the lungs has been demonstrated by studies using inert gas washout and by ventilation scanning using radioactive isotopes [558–560].

### Changes in gas exchange

The irregular distribution of ventilation of lung units men-

tioned above is matched by local reduction in perfusion, resulting in patchy but similarly distributed areas of reduced activity on ventilation-perfusion scans [560]. The mechanisms of this are likely to be reflex, due to local hypoxia, together with increased local alveolar pressure from the elastic recoil of overdistended parts of the lung acting on capillaries in alveolar walls. Thus a compensatory mechanism exists that permits excessive physiological shunting and thus hypoxaemia in the stable, less severe, asthmatic. The infrequency with which segmental or subsegmental collapse occurs despite widespread hypoventilation is suspected to be due to collateral ventilation between acini, maintaining an air supply to alveoli distal to blocked bronchi. The asthmatic in remission and in the early stages of an attack may therefore have evidence of gross unevenness of ventilation, with only slight increase in alveolar-arterial oxygen gradient and mild hypoxaemia. Similarly, the diffusing capacity for carbon monoxide is rarely reduced in asthma (a useful point in differentiating the chronic asthmatic from the patient with emphysema) and indeed during remissions is often raised [561,562]. The reason for this high  $DL_{CO}$  is not clear; it is not wholly due to a raised alveolar volume and may be related to increased pulmonary capillary blood volume, perhaps as a consequence of distension of the capillary bed by the increased negative transpulmonary pressure [563]. Small reductions in  $DL_{CO}$  may be found in chronic bronchopulmonary aspergillosis [520,538], after administration of bronchodilator drugs (perhaps due to increased mismatch of ventilation and perfusion when both airways and vessels respond to the drug) [563] and when the steady-state rather than the single-breath method is used [564].

However, there is in general a direct relationship in asthma between  $FEV_1$  and  $P_{aO_2}$ . The lower the  $FEV_1$ , as a patient deteriorates, the lower the  $P_{aO_2}$ , and in acute severe asthma the patient is often markedly hypoxaemic [499,565] (Fig. 34.22). This presumably relates to the inability of reflex changes in perfusion to match exactly the increasingly severe and diffuse reductions in ventilation as the attack progresses. In contrast to the case in patients with smoking-induced chronic airways disease, the asthmatic patient is able to respond to this acute episode by hyperventilation. Because of the shape of the oxygen-haemoglobin dissociation curve, this has minimal effect on hypoxaemia, only allowing a rise roughly in proportion to the reduction in  $P_{CO_2}$  in the alveoli. In contrast, however, hyperventilation of those units of lung still accessible to inspired air allows removal of sufficient carbon dioxide to maintain normal pressures of this gas in the arterial blood; indeed, during most of a severe asthmatic attack the  $P_{aCO_2}$  is below normal, and a rise to normal levels together with increasing hypoxaemia is an ominous sign. The arterial pH usually simply reflects the ventilation and, except in prolonged attacks,



**Fig. 34.22** Effects of increasing airflow obstruction on (a)  $P_{aO_2}$  and (b)  $P_{aCO_2}$ . Progressive decline in  $P_{aO_2}$  is accompanied by a fall in  $P_{aCO_2}$  until severe airflow obstruction, when a rise to, or above, normal levels may occur. (From McFadden & Lyons [565].)

metabolic compensation for respiratory alkalosis is unusual [566].

### Cardiac function

Cardiac function is not normally altered in asthma except in an acute attack and, as mentioned above, right-sided heart disease of sufficient severity to present clinical problems is rare even in patients with chronic severe asthma. Indeed, when such a patient does have evidence of cor pulmonale, other diagnoses such as smoking-induced COPD or recurrent pulmonary embolism should be considered.

In the acute severe attack, tachycardia and pulsus paradoxus are evidence of cardiac stress, and the ECG may show P pulmonale and inverted anterior chest T waves [493]. Few studies of the pulmonary circulation in such circumstances have (understandably) been carried out,

although there is little doubt that pulmonary arterial pressure would normally be raised both in response to hypoxaemia and as a consequence of the high intra-alveolar pressures [567]. These pressures are due to the high recoil pressure of the lungs when breathing towards the top of the pressure-volume curve and are, of course, transmitted directly to the pulmonary capillary bed in the alveolar walls. In very severe attacks requiring assisted ventilation, it is noteworthy that the high ventilator pressures required to inflate these already overinflated lungs commonly provoke a marked decrease in venous return that can result in cardiac arrest [45]. In patients with respiratory acidosis and high inflation pressures, attempts to normalize blood gases quickly are abandoned and 'controlled hypoventilation' is employed, providing an adequate  $P_{aO_2}$  can be maintained [568].

Perhaps also related to cardiac stress is the occasional occurrence of myocardial infarction during an acute severe attack [569]. Such episodes are usually painless and rarely fatal, being identified from ECG changes. Plasma free fatty acids are raised, presumably reflecting greatly increased sympathetic activity [570]; this, together with impaired coronary circulation, may be the explanation of infarction. It is reasonable to suppose that the lack of pain in such episodes may be related to raised levels of endogenous opioids, the stress of the attack being not dissimilar to that occurring during severe prolonged exercise in which painless infarction and raised  $\beta$ -endorphin levels may occur [571].

### Variability in function

The greatest value of lung function testing in asthma is derived from measuring variability in flow rates. Fortunately this requires only the simplest of equipment, a peak flow meter or spirometer; the portability of the former makes it invaluable. Three types of testing are within the scope of every physician: measuring response to bronchodilators, examining the effect of exercise, and measuring variability over a period of days or weeks, with or without a course of steroids. A fourth type, assessing the effect of challenge testing, is usually carried out by specialists.

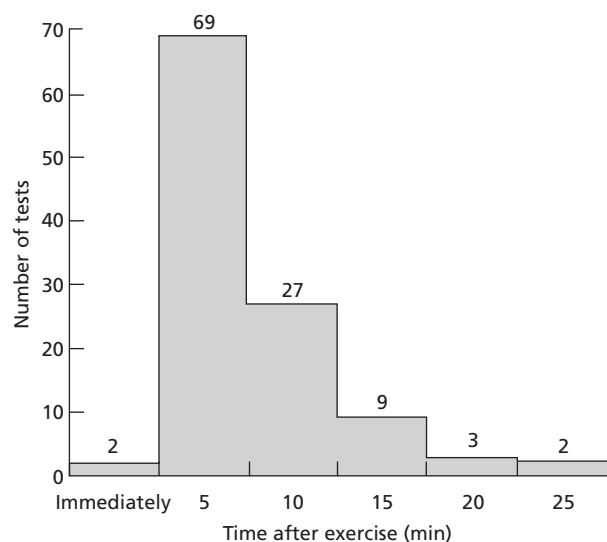
Many asthmatic patients when first presenting to their general practitioner do so during an attack. Measurement of  $FEV_1$  or PEF, followed by two puffs of a fast-acting inhaled bronchodilator, a wait of a few minutes and repeat measurement help to confirm the diagnosis in most cases and give an immediate indication of the patient's likely responsiveness to further treatment. It has the added bonus of encouraging patients to believe that they have found a physician who understands their condition. However, there are a few snags to this simple test. It should be borne in mind that responsiveness to bronchodilator varies according to the degree of airflow



obstruction at the time of administration, and little or none would be expected in someone with no obstruction or in someone with very severe obstruction. In the latter case, poor access of the bronchodilator to the airways may be a partial explanation, though intravenous bronchodilator may not be much better and it is therefore probable that in this situation airway oedema and plugging are making the major contribution to the obstruction [572,573].

Exercise testing can also be carried out with ease in clinic or surgery, and finds its application in confirming a suspected diagnosis in a (usually younger) patient who is not obstructed at the time of presentation. The simplest procedure is to measure PEF or  $FEV_1$  and then to ask the patient to jog at a steady pace for about 8 min. While laboratory treadmill or bicycle are perfectly satisfactory means of ensuring appropriate exercise is taken and are necessary for scientific study of the effect of different forms of exercise [574] and therapy, lack of a laboratory should not be a deterrent to the physician; a hospital corridor, the adjacent street or a nearby staircase are adequate substitutes [575]. The response to exercise, as discussed previously, varies from time to time depending on the pre-existing bronchial reactivity. A patient with typical asthma shows a period of bronchodilatation in the early stages of exercise but by the end of 8 min usually has started to bronchoconstrict. The expiratory flow rates usually continue to decline for a few minutes after exercise has ceased, then gradually recover to normal over an hour or less depending on the severity of the initial fall [576] (Fig. 34.23). The recovery can be speeded up by administration of a bronchodilator.

Another method of confirming the diagnosis of asthma is to record measurements of PEF several times daily over



**Fig. 34.23** Time of maximal fall in peak flow rate after exercise in 112 tests on asthmatic patients. (From Hartley [152].)

a period of days or weeks. This is also of inestimable value both in the investigation of suspected provocative factors, such as occupational or environmental sensitizers, and in investigating patients in whom the history of episodic breathlessness is equivocal. For the latter purpose, it is usually sufficient to ask the patient to record PEF morning, midday and at bedtime, together with recordings during any attacks (especially if any occur at night). In patients with normal flow rates when first seen, this allows assessment of the amount and severity of variability, while in those with a persistently reduced PEF it allows a baseline to be measured for comparison with similar readings during a period of treatment. In many patients with relatively severe airways obstruction, there is doubt about whether asthma or cigarette-induced disease is the dominant condition, and monitoring of PEF during a 2-week course of high-dose prednisolone usually resolves this matter. In investigating possible occupational factors, it is desirable to ask the patient to record PEF more frequently, up to every 2 h during work [577]. Unfortunately, such records are very time-consuming to analyse, and a compromise number of recordings (four or five times daily) is usually adequate. This should be combined with a diary kept by the patient, noting work activities, times away from work and symptoms. The use of lung function in challenge testing is discussed in the section on diagnosis. Again, simple and repeatable tests such as  $FEV_1$  and PEF are ideal for this purpose.

## Radiological features

In most patients with asthma, either in remission or during an attack, the chest radiograph looks normal. Slight overinflation, with depressed diaphragm, laterally spread ribs and enlarged retrosternal airspace, may be seen in some patients during an attack and in some with chronic severe asthma [578,579]. In contrast to emphysema, the diaphragm normally retains its upwardly convex curvature and the pulmonary vessels do not show the same degree of attenuation. The most usual abnormality seen on the asthmatic radiograph is thickening of bronchial walls, as tramline shadows and rings close to the hilum [580]. This is a non-specific finding that is seen also in chronic bronchitis.

The most important function of a chest radiograph in asthma is the exclusion of other abnormalities. In acute attacks pneumothorax may (rarely) occur and may be difficult to detect clinically. There may be evidence of mediastinal and subcutaneous emphysema, usually in the absence of pneumothorax. If consolidation is present, it is likely to be due to pneumonia but the possibility of allergic bronchopulmonary aspergillosis should always be considered.

Episodes of allergic bronchopulmonary aspergillosis are characterized by recurrent fleeting pulmonary

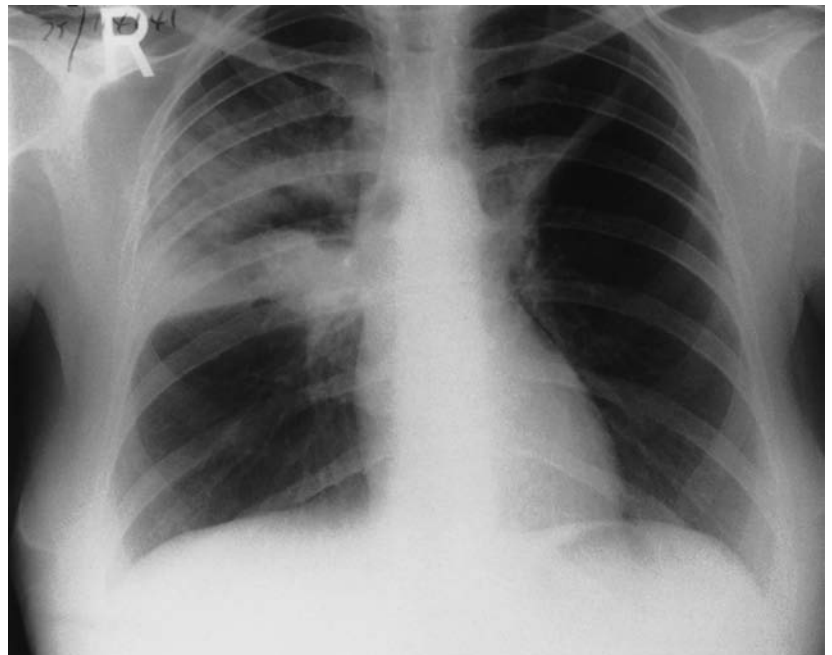


shadows [538], although lobar or segmental collapse, nodular or band shadows may occur (Figs 34.24 & 34.25). If untreated they resolve only slowly over several weeks, but with corticosteroid treatment they may be expected to clear within days. In some patients they recur at the same site; equally, recurrences occur apparently at random sites

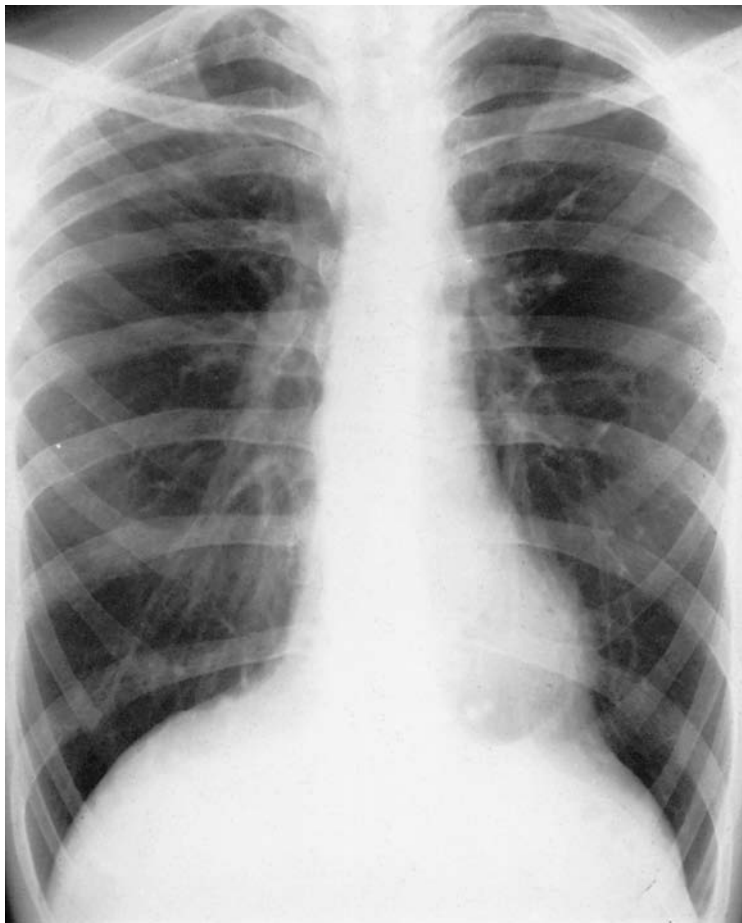
in the lungs. Recurrent episodes may, but do not always, lead to chronic lung damage [538]. This shows radiologically as tubular (tramline), 'gloved-finger' and ring shadows, lobar or segmental fibrosis and lung shrinkage (Fig. 34.26) and the end-result in severe cases may resemble the appearances in cystic fibrosis. CT or



**Fig. 34.24** Radiograph of patient with acute episode of allergic aspergillosis showing segmental consolidation in left upper lobe. This resolved after a 2-week course of corticosteroid.



**Fig. 34.25** Acute allergic aspergillosis showing segmental consolidation in both upper lobes.



**Fig. 34.26** Chronic allergic aspergillosis showing shrunken upper lobes with linear and ring shadows.



**Fig. 34.27** CT of a patient who had had repeated attacks of allergic aspergillosis, the first of which had resulted in bronchiectasis in the right lower lobe.

bronchography shows bronchiectasis [538] (Fig. 34.27), commonly though not always confined to more proximal bronchi, giving a characteristic appearance of normal-looking bronchi distal to the ectatic lesions.

## Diagnosis and investigation

In most cases the diagnosis of asthma is made readily from the history. An account of episodic wheezy breathlessness, interspersed with periods of normality, is sufficient evidence on which to suspect asthma. In children and younger adults almost nothing else can cause such symptoms. However, a few conditions do need to be considered in the differential diagnosis at different ages, as all can mimic asthma when the disease presents in a less typical manner. Further evidence in support of asthma comes from a history of marked diurnal variability, attacks in the small hours of the night, and provocation by strong smells, exercise, changes in ambient temperature and allergens.

In infants, acute respiratory infections and asthma are hard to differentiate, and this problem persists in early childhood. When it presents with predominantly respiratory symptoms, cystic fibrosis may also be misdiagnosed as asthma. In older children and adults, bronchiectasis may be associated with wheezy breathlessness and airflow obstruction mimicking asthma, although these patients usually have productive cough as their predominant problem. In adults there can be great difficulty in dif-

ferentiating asthma from COPD due to smoking. The two conditions coexist in many patients, and it is often impossible to be sure whether an asthmatic component is present without a formal trial of treatment.

Two other conditions must be considered in older patients presenting with wheeze, namely carcinoma of the larynx and proximal bronchial or tracheal tumours not visible on the chest radiograph. Both present with persistent symptoms rather than with attacks of breathlessness, although in this age group asthma also frequently presents in a similar manner. Both may cause wheezy breathlessness on exertion and at night. Clues may come from other symptoms, such as voice changes, haemoptysis or weight loss, but the diagnosis of main airway partial obstruction should follow the physical examination, when a fixed monophonic inspiratory wheeze or stridor is heard. Confirmation is obtained by laryngoscopy or bronchoscopy. Extrathoracic airflow obstruction causes disproportionate inspiratory obstruction (hence stridor) and this may be demonstrated in the laboratory on flow-volume loops. However, this investigation is usually less readily available and less specific than laryngoscopy/bronchoscopy.

Confirmation of the diagnosis of asthma is usually achieved by serial PEF monitoring, which in the majority of cases shows a diurnal variation of more than 15%, and the response to therapy. In most cases no other investigations are necessary. General support for the diagnosis is usually obtained by showing a response in ventilatory function (FEV<sub>1</sub> or PEF) to an aerosol bronchodilator or, in younger subjects, the demonstration of a fall in FEV<sub>1</sub> or PEF following exercise. A raised eosinophil count (above 5% of the total white cell count) is common in untreated asthma [581]. Sputum eosinophilia is a useful indication of an asthmatic type of airways reaction, though it does not invariably predict a response to corticosteroids [582,583]. The demonstration of all the histopathological features of the asthmatic exudate by examining stained sections of sputum fixed in alcohol or formalin is probably a more reliable indication of asthma than a sputum eosinophil count [5]. This technique is also useful for the demonstration of hyphae of *A. fumigatus*.

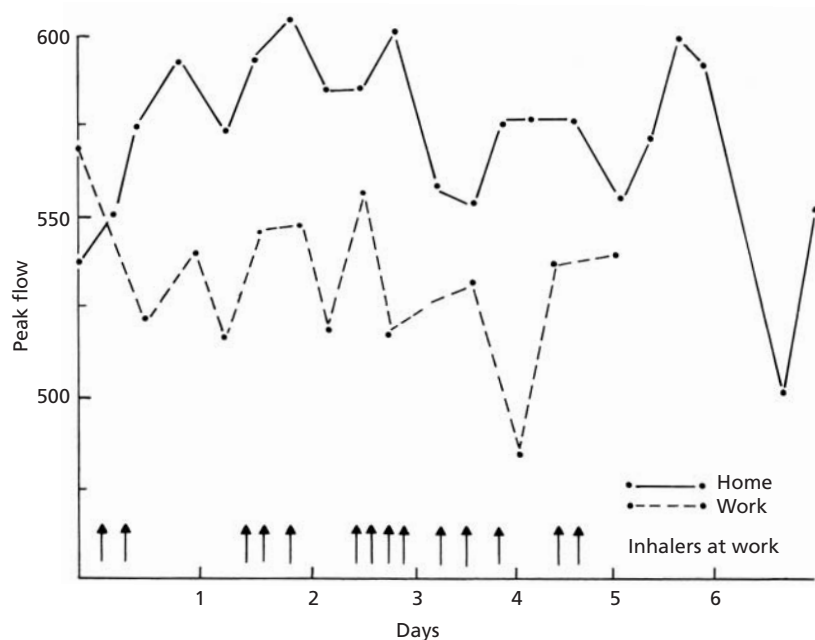
Skin-prick tests may be useful in identifying suspected provocative allergens. The tests should be chosen from the history and should include a control solution, the most common allergens (house dust, *D. pteronyssinus* and grass pollen or whatever airborne allergens are most common in the locality), together with any allergens that are suspected of causing the patient's reaction in the home or work environment. There is no point in routinely performing a large battery of skin tests. In general, RAST for specific IgE levels correlates closely with the results of skin-prick testing [584]; as it is more expensive and cannot be performed in the clinic immediately, most physicians manage without it in the investigation of most of their

patients. In the past, not all commercially available methods of allergy testing have been entirely reliable and care must be taken before using results of these tests in the decision about whether 'hyposensitizing' vaccines should be recommended [585]. The sensible physician relies on a good history and skin testing for the detection of suspected allergens, backed by selective use of RAST, reserving challenge testing for the few occasions when it is thought necessary.

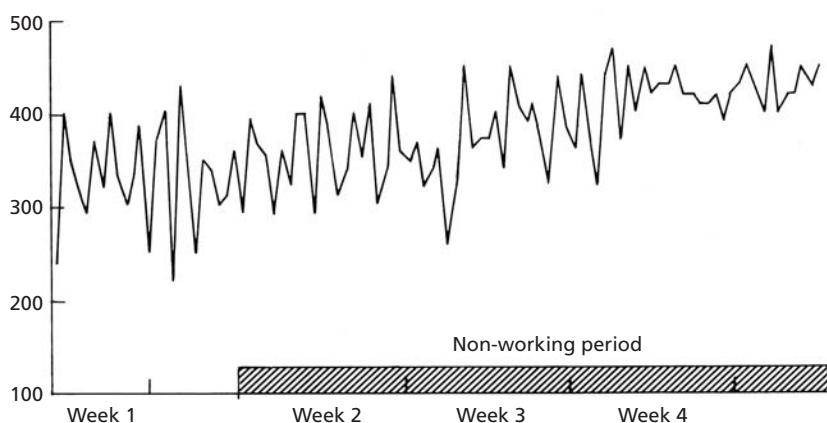
The skin-prick test is performed by putting a drop of allergen on the skin, usually the front surface of the forearm, and lifting the skin lightly through the drop with the point of an intradermal needle. Blood should not be drawn. The test should be read about 15–20 min later. A wheal is a positive result and should be compared in size to that obtained with the control solution, as some subjects react simply to the prick. Intradermal injection of allergen can be used for showing delayed reactions. It requires a larger dose of antigen and there is a higher risk of provoking an anaphylactic reaction; this method of testing is best confined to specialized investigations of aspergillosis or allergic alveolitis and should not be used in outpatient clinics. It should be noted that a positive skin test does not prove that the subject has bronchial hypersensitivity to the allergen in question, but simply adds support to the clinical suspicion. Conversely, bronchial sensitivity may sometimes be present in the absence of skin sensitivity, and when this is suspected RAST may indeed be useful. RAST also has undoubted value in investigating food allergy and in following patients for a quantitative fall in titres after control of exposure, for example to occupational allergen or to pets.

### Challenge testing

When it is necessary to investigate provocative factors, challenge testing may be desirable. Normally the first step is to demonstrate a response to a particular environment in terms of changes in PEF over a period. As the suspect environment in most such cases is the workplace, it is often necessary to record PEF four to eight times daily during periods off work, periods at work and periods again off work. The differences may be immediately obvious on looking at the record or particular patterns may be noticed [586]. Figure 34.28 illustrates one such test, where flow rates were persistently lower (and a bronchodilator was required frequently) when the patient was at work. More complex patterns may show increasing fall in flow rates as the week progresses, carry-over into the following week and intermittent falls, depending on such factors as the frequency and duration of exposure and the length of time the patient has had asthma. Sometimes in individuals in whom the asthmatic response has been over a prolonged period, recovery of flow rates may take weeks after exposure ceases (Fig. 34.29). Occasionally in these



**Fig. 34.28** Peak flow record of a patient with allergy to rubber gloves worn in laboratory work. Upper trace was recorded while he was on holiday, lower trace while at work. During the latter period he had frequent need of his inhaler. The one fall when at home followed a drink of red wine, to which he was also allergic.



**Fig. 34.29** Peak flow record of female electronic soldering supervisor. Full recovery and reduction in diurnal variability did not occur until about 2 weeks after cessation of exposure to colophony.

circumstances, where the aetiological diagnosis remains uncertain and when it is important to find out, challenge testing may be necessary.

As far as possible, all inhalation challenge tests should include exposure to an 'identical' placebo. The patient should be admitted to hospital overnight and the substance administered in a manner mimicking as closely as possible exposure at work. For example, isocyanate exposure may be produced by mixing certain two-component varnishes and applying them to a surface. Flour or sawdust exposure can be produced by pouring the dust from one bowl to another. In one study, a patient who thought he reacted to powder from his surgical gloves was challenged with placebo powder (talc), glove powder (starch), gloves of a different but apparently identical latex and gloves with which he worked [587]. He only reacted to the last, which were subsequently shown to give off

traces of carene vapour, previously known as a potent skin sensitizer.

The effects of the challenge are most conveniently monitored by peak flow rate, which the patient can carry out at home for a few days before and on the morning of challenge in order to obtain a baseline. The measurements should be carried out every 5–10 min after challenge until the immediate reaction is over (if necessary, a bronchodilator aerosol may be given if a severe attack is induced) and then every 30 min until it is certain that a late reaction will not occur. Such late reactions, starting after 3–4 h and lasting about 24 h, are common after challenge and may require treatment with corticosteroids (see Fig. 34.9).

In some cases the only convenient way of administering the challenge is by nebulized aerosol of extracts of the suspect material. It is difficult to judge the dose, and it is

therefore wise to start with high dilutions given for only a few minutes. The advantage of an exposure which mimics that in the workplace is that the patient is unlikely to be given a dose higher than that received previously. Nevertheless, length of administration is a matter for judgement, based on assessment of the patient's history. Severe reactions can occur, and nebulized bronchodilators for the initial reaction together with corticosteroids and bronchodilators for the late reaction should be available. Challenge tests are, of course, affected by drugs. The initial response is blocked by bronchodilators and cromoglicate and the late response by corticosteroids. These drugs should therefore be stopped before challenge and this may lead to difficulties in control of the asthma and in interpretation of the results. In general, challenge tests should be carried out on patients whose asthma is in remission and who are managing without regular medication. The techniques and problems of aerosol challenge testing have been reviewed by Burge [588].

Two other types of challenge test may occasionally be necessary. If ingested drug-related asthma is suspected, a small dose of the drug should be given orally. The above-mentioned precautions of hospitalization, baseline inves-

tigations, placebo tests and cessation of antiasthma treatment should be taken. The dose should be estimated from the severity of previous responses but initially should not be more than one-tenth of that contained in the preparation under suspicion. The other type of challenge test is that related to investigation of food allergy. In the simple case, the suspected food can be administered in a suitably disguised form (e.g. in a capsule or down a nasogastric tube). In complex cases, it may be necessary to establish the patient on an allergen-free diet and gradually introduce other foods one by one until reactions occur [589]. A typical such exclusion diet might consist of lamb or mutton, gluten-free bread or rice, fresh fruit and vegetables (though reactions to these are not unknown), tea, coffee, sugar and water. If this diet results in disappearance of symptoms and recovery of lung function over 2 weeks, foods under suspicion may be added. Those most likely to cause reactions are ones containing artificial flavours and colours, nuts, milk, eggs and wheat. The investigation of food allergy is complex and the results of such tests are subject to some variability in most cases; therefore clinical importance should only be attached to clear-cut results from placebo-controlled challenges.

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# ASTHMA: MANAGEMENT

GRAHAM CROMPTON

Asthma is a disease that affects people of all ages, in all parts of the world. Despite greatly increased knowledge of the immunopathological processes characteristic of the disease, and apparent improvements in treatment, morbidity (and in some countries mortality) is increasing rather than decreasing. It is extremely unlikely that a cure of asthma will be available for many years to come, but even without further pharmacological advance there is now great potential for improving the management of most asthmatic patients by encouraging more rational use of treatments already in existence. To encourage uniformity of asthma treatment, management plans and guidelines have been published in several countries. In general terms the contents of all the guidelines are similar, and it is hoped that a greater number of clinicians will become aware of these management recommendations in the future. A worldwide unified approach to the management of asthma would be the ideal. However, it is likely that the more wealthy nations will have to give the lead, since the resources necessary to educate patients and clinicians about management principles are considerable, and the financial burden of therapy would be too heavy for some of the less-developed nations.

The overall management of asthma has many similarities with that of diabetes, since in both diseases the aim is to allow the patient to be as independent as possible and to make treatment changes as appropriate to maintain clinical control. Professional advice should be readily available when self-management has not been successful, and for most patients there should be regular contact with a healthcare professional for review and advice.

## Aims and principles of management

The aims of management are to:

- recognize asthma;
- abolish symptoms;
- restore normal or best possible long-term airway function;
- reduce the risk of severe attacks;

- enable normal growth to occur in children;
- minimize absence from school or work.

The principles of management are:

- patient and family participation;
- avoidance of identified causes where possible;
- use of lowest effective doses of convenient medications minimizing short-term and long-term side-effects.

These aims and principles of management have been taken from British guidelines for the management of asthma [1] but are similar to statements in many other guidelines now in existence in many parts of the world. In general terms the major objectives are to allow all patients to lead symptom-free normal lives with the aid of treatments, free from side-effects, which can be adjusted and modified by informed patients themselves.

## Patient participation

Efficient management of asthma requires a partnership between the patient and family and the healthcare professional. At the outset it should be made clear that cure or spontaneous remission of chronic asthma in adults is unlikely and therefore treatment and supervision are likely to be required over a prolonged period. Education is essential to allow sharing of information about the nature of the disease and its treatment and to enable the patient and family to acquire understanding and management skills. An important stage of the education process is allowing and encouraging the patient and family to express fears and concerns about the disease and treatment, and to discuss both the clinician's and the patient's expectations of the condition and its management. Patients and parents require both verbal and written advice; ideally all asthmatics with more than mild disease should have a guided self-management plan.

## Self-management plans

All patients who have to make frequent decisions about the management of their asthma should be offered a

self-management plan, which in effect means most of those requiring treatment with an inhaled steroid in a dose of more than 800 µg daily. The common finding of controlled trials on patient education alone is that verbal, written, audio and video educational programmes can increase a patient's knowledge but without improvement in asthma morbidity [2–4]. Ideally the self-management plans should be written for, and tailored to, the needs of the individual patient, since these can be cost-effective in the short term if directed at those with moderate to severe disease [5]. However, this is rarely possible and standardized plans that can, in part, be tailored for each asthmatic are commonly used. The most popular plans are based on a three-colour system (green, amber and red) and carry advice about management actions depending upon symptoms and peak expiratory flow (PEF) values.

**1 Green.** Symptoms under control and PEF greater than 80% of predicted or best: continue to use steroid inhaler regularly in the same dose, and use bronchodilator inhaler as required.

**2 Amber.** Symptoms not well controlled or PEF less than 80% but greater than 50% of best or predicted: double dose of steroid inhaler and use bronchodilator inhaler as necessary or regularly every 4 h.

**3 Red.** Distressing symptoms not responding to the bronchodilator inhaler or PEF less than 50% of best or predicted: start oral steroid treatment immediately and obtain medical help.

Plans need to be tailored to individual patients and their local healthcare circumstances so that they know when to contact the general practitioner, call an ambulance by using the emergency telephone code, attend the nearest hospital emergency department or use a respiratory unit self-admission service [6–9]. Written personalized management plans are essential for patients with poorly controlled asthma; in these patients, if the three-colour system is used, it is probably appropriate to omit the amber zone to encourage early aggressive intervention in the event of deteriorating asthma. Written educational materials should be available to supplement self-management plans since these materials are likely to help patients accept their diagnosis and gain confidence in coping with its effects.

It is difficult to prove beyond doubt that self-management plans are effective in the long term. Controlled studies show evidence of benefit by their reduction of hospital admissions, courses of oral steroids and nebulized bronchodilators, although there are questions concerning 'enthusiast bias' compromising outcomes [10,11], i.e. patients who are perceived to be likely to benefit from plans tend to receive them and operate them [12,13]. This may be the explanation of the widespread clinical acceptance that self-management plans work despite the doubts raised by analysis of controlled trials [4,5]. It is likely that

the success of management strategies depends to a considerable extent upon the healthcare professional who issues the self-management plan. He or she should be known and trusted by the patient, be readily accessible by telephone and ideally should be the person who reviews the patient at follow-up. Appropriately trained practice nurses with the time, enthusiasm and accessibility to patients could be the ideal choice [13], although it is appreciated that in many areas these individuals may not exist. The major problem in asthma management is translating the theory of good asthma care into everyday practice. There are marked differences between patients' self-management knowledge and their actual behaviour in an acute attack [14]. Self-management plans appear to be the best available option at present [15,16], although these alone are unlikely to overcome the major problem of compliance known to exist in a large number of patients with asthma [17,18].

### Peak flow monitoring

The variable orifice PEF meter was introduced in 1959 [19]. Since then a number of lightweight PEF meters have become available, and are commonly used in both the diagnosis and management of asthma. In the last decade self-management plans using PEF monitoring have become widely used [11,13]. Peak flow monitoring is used for (i) diagnosis (see Chapter 34), (ii) monitoring the effect of treatment, particularly the effects of treatment changes, (iii) self-management plans, especially in patients with poor perception of symptom severity [20] and in the day-to-day management of the patient with brittle asthma, (iv) investigation of suspected occupational asthma (see Chapter 34) and (v) research.

### Avoidance of causes and non-specific triggers and aggravating factors

Specific causes of asthma are rarely known except for some occupational sensitizers and aeroallergens. Physical factors, such as exercise, strong smells, cold, sudden changes in ambient humidity and temperature, cigarette smoking and smoky atmospheres, can trigger episodes of asthma or make chronic symptoms more troublesome. All patients should, of course, be encouraged not to smoke and also to avoid passive smoking if possible. Unfortunately a surprising number of asthmatics continue to smoke even though they realize it aggravates their symptoms. It is difficult to modify climatic conditions; however, any suggestions about modifications to the home environment should include the advice that ideally there should be, as far as possible, an even temperature and humidity in all rooms. The control of exercise-induced asthma requires therapeutic intervention rather than avoidance of exercise.

### Allergy avoidance

The increase in prevalence and severity of asthma in westernized countries may be due partly to increase in exposure to indoor aeroallergens [21]. The logical approach to the treatment of asthma involves avoidance of allergens where possible, including occupational sensitizers, together with the early intervention of anti-inflammatory therapy, usually inhaled steroids. Evidence is now accumulating that aeroallergens, particularly the house-dust mite and animal danders, are major independent variables in the prediction of asthma in different populations [22,23]. Exposures during the neonatal period are thought to be critical in the development of atopic sensitization [24] and avoidance of perennial aeroallergens and/or food allergens during early life may delay or even prevent the onset of atopic sensitization and allergic manifestations [25,26]. An advance in the evaluation of allergen avoidance has been the identification and characterization of the major allergenic determinants of common perennial allergens, namely *Der pI* (dust mites), *Fel dI* (cats) and, more recently, *Can fI* (dogs). This has enabled the development of monoclonal antibodies that allow accurate measurement of major allergens in dust samples and airborne exposure [27–29]. Ideally the efficacy of any allergy avoidance measure should be assessed by measurement of the reduction or elimination of allergen as well as by clinical response [30,31]. Barrier bedding methods, removal of carpets, regular cleaning and application of liquid nitrogen to bedding and furnishing have been associated with a reduction in house-dust mite levels [32–35]. The value of acaricides in reducing mite allergen levels remains controversial [32,36] and on the evidence currently available these products cannot be recommended for routine use. In children, barrier bedding methods combined with regular cleaning and removal of carpets appear to be effective in reducing bronchial hyperresponsiveness [36,37], but unless these arduous and often expensive prophylactic measures can be carried out fastidiously they usually have little clinical benefit. Animal allergens are difficult to avoid and eradicate as long as the pets remain in the home. After the departure of a cat from a home environment, several months of vigorous cleaning is necessary in order to reduce cat allergen load to clinically acceptable levels [38]. Washing a cat every week for 4 weeks has been shown to reduce the airborne cat allergen levels when the washing was combined with vigorous cleaning measures and removal of bedroom carpets [39], although this cannot be regarded as a substitute for removal of the animal from the household environment. A major source of animal dander allergen is contaminated clothing. High levels of *Can fI* have been demonstrated on schoolroom desks and chairs but not on floors, suggesting contamination from children's clothing from pets at home [29].

It is impossible to avoid pollens. Simple advice includes

wearing spectacles or sunglasses, remaining indoors during periods of high pollen counts and keeping windows closed particularly in high buildings and cars. Walking in open grassy spaces should be avoided, especially during the evening and night when pollen counts tend to be at their highest. However, these lifestyle modifications are often unacceptable, particularly by those whose atopic symptoms are not severe and easily controlled by pharmacological agents.

Those asthmatics who give a history of symptoms on allergen exposure and who have a positive skin-prick test to the same allergen should be given advice about appropriate allergen avoidance measures, although advice about pets is rarely taken [30,31]. Such advice should not be given because of a positive skin-prick test in the absence of historical evidence of allergen hypersensitivity. Negative skin tests are helpful in excluding an allergic basis for asthma, providing they have been performed correctly at a time when the patient has not been taking an antihistamine. Serum allergen-specific IgE concentrations by radioallergosorbent test provide an alternative to skin tests, but in general are more expensive and perhaps less sensitive. Recognition of an occupational sensitizer is of extreme importance, since removal from exposure may result in improvement or remission of asthmatic symptoms; unfortunately this does not occur in every case. Food and food additives are a much less common, although important, cause of asthma. When genuine food allergy exists it is usually readily detected and the offending item of diet can be avoided. Many patients believe that certain foods have caused or made their asthma worse and modify their diets or those of their children. With these patients it is often difficult or impossible to confirm or exclude food allergy. Milk products and eggs are commonly incriminated and in some patients with severe disease a strict exclusion diet can be tried in an attempt to establish whether or not foods are causing asthma. Although the problem appears to be rare in adults, there can be no doubt that food allergens during early life play some role in the onset of atopic sensitization and allergic manifestations [25,26].

### Drug avoidance

All  $\beta$ -adrenoreceptor antagonists are absolutely contraindicated in all patients with asthma. Even eye-drops containing one of these drugs can precipitate severe acute asthma. Aspirin can also induce worsening of asthma, which can be severe and is sometimes, but by no means always, accompanied by urticaria. Aspirin-sensitive asthmatics are usually adults with a history of nasal symptoms often due to nasal polyps. Other non-steroidal anti-inflammatory drugs can make asthma worse and all should be used with great caution in asthmatic individuals.

### Patient compliance with treatment

Poor patient adherence to prescribed medications has been shown to be a widespread problem in asthma [40–42] and has been linked to increased morbidity [43] and mortality [44]. Poor compliance with treatment in general is difficult to identify by routine clinical assessment [45] and there does not appear to be any association between compliance and age, sex, socioeconomic group, personality traits or level of education [46]. Patients' attitudes to treatment are likely to influence how they cope with their illness and use their treatment [47]. Inappropriate over-emphasis of the side-effects of corticosteroids leading to rapid reduction of dose or withdrawal of treatment could be a factor contributing to the deaths of some patients from severe acute asthma [15,44,48]. There is no simple method of improving treatment compliance in asthma, nor is there any way of identifying patients likely to benefit from intervention programmes. All patients must therefore be assumed to be poor compliers and all should receive similar, but individually tailored, self-management plans and education about the disease and the treatments used to control it.

### Drug treatment

Avoidance of allergens and non-specific aggravating factors may result in the disappearance of symptoms in some patients but in the majority some form of drug treatment is also required. This may be intermittent in episodic or seasonal asthma, while in adults the disease is usually chronic and long-term treatment has to be planned. There are two principal aims in the treatment of all patients with chronic asthma: (i) the rapid achievement of symptom control and optimal or best lung function; and (ii) maintenance of symptom control and best lung function. Initially this usually requires the use of a steroid, either orally or by inhalation, to achieve rapid control of symptoms and best lung function. Once this has been achieved, a step-down of treatment is usually possible in all but those patients with very severe chronic disease. Long-term maintenance therapy in most patients has to be with an inhaled steroid since this is the most effective treatment available for the control of the asthmatic bronchial wall inflammation.

The drugs used in the treatment of asthma can be broadly split into two categories: the  $\beta_2$ -agonist bronchodilators, sometimes called 'relievers', and the antiasthma inflammatory agents, sometimes called 'preventers'. However, there are other bronchodilator drugs, such as the anticholinergics, which have a useful but less major role than the  $\beta_2$  agonists, and theophylline. Traditionally, this drug has been classed as a bronchodilator but has now been found to have some anti-inflammatory activity in addition, though its role in the

treatment of asthmatic inflammation has still to be established. The development of long-acting inhaled bronchodilators and the production of oral sustained-release preparations of shorter-acting drugs has made it more difficult to categorize drugs simply as relievers and preventers; nevertheless this naive classification is of value in the education of patients and in the production of management plans and educational literature.

## Management of chronic asthma

### Drugs used for the relief or suppression of symptoms (the relievers)

#### $\beta_2$ adrenoreceptor agonists

The  $\beta_2$  agonists are bronchodilators that give symptomatic relief but have no major beneficial effects on the underlying bronchial wall pathology. Indeed regular use of short-acting  $\beta_2$  agonists has been questioned because of the possibility that such treatment might have a detrimental effect on the control of asthma, possibly by increasing bronchial hyperresponsiveness either during treatment or soon after its withdrawal [49–53]. Since  $\beta_2$  agonists only give symptomatic relief, there seems little reason to encourage patients to take them regularly. If regular treatment is necessary for relief of symptoms this should stimulate the prescription of an anti-inflammatory preparation or an increase in its dose.

#### *Inhaled short-acting $\beta_2$ agonists*

The  $\beta_2$  agonists relax airway smooth muscle and enhance mucociliary clearance. They also decrease vascular permeability and may modulate mediator release from mast cells and basophils, but they do not have any clinically relevant beneficial effects on the underlying chronic inflammatory disorder of the asthmatic airways. Short-acting  $\beta_2$  agonist inhalers should be used as necessary to relieve symptoms. Regular treatment with these compounds should be avoided wherever possible, unless the results of clinical trials now in progress show that such treatment is not harmful in terms of increasing bronchial hyperresponsiveness or adversely affecting the overall control and prognosis of asthma [49–54]. The International Consensus Report on Diagnosis and Management of Asthma [55] suggests that if a patient has to use a short-acting bronchodilator more often than three times a week this indicates asthma of sufficient severity to warrant regular treatment with an anti-inflammatory or prophylactic drug. The British guidelines [1] suggest that this form of treatment would be appropriate if a bronchodilator inhaler has to be used more than once a day. It follows therefore that inhaled bronchodilator therapy alone should only be used by patients with mild asthma. However, all patients able to

use an inhaler should have one, to be used for symptom relief as necessary, irrespective of the other treatments required for their asthma. The inhalation of a short-acting bronchodilator prior to exercise is often necessary to prevent exercise-induced asthma.

All patients with asthma should be aware that a  $\beta_2$  agonist bronchodilator inhaler only provides short-term relief of symptoms, and that the development of asthmatic symptoms leading to more frequent use of this inhaler is a sure sign of worsening of asthma, which usually requires extra anti-inflammatory therapy. Little, short-lived or no response to a bronchodilator inhaler heralds the onset of potentially life-threatening asthma. All patients should be aware of this and should know that in this situation they should seek medical help at once.

The most commonly used  $\beta_2$  agonists are salbutamol, terbutaline and fenoterol. Fenoterol has recently lost some of its popularity because of the possibility that adverse effects may be more likely with this drug than other  $\beta_2$  selective bronchodilators [53,56–59]. For the relief of mild to moderate symptoms, the doses of salbutamol and terbutaline usually recommended are 100–200  $\mu\text{g}$  and 250–500  $\mu\text{g}$  respectively. Considerably larger doses are necessary for the treatment of severe acute asthma. The duration of action of these drugs is 4–6 h and the onset of activity is rapid, maximum bronchodilatation being achieved within 15 min after inhalation. Rimiterol is a  $\beta_2$  agonist with a shorter duration of action (1–2 h) because, unlike salbutamol and terbutaline, it is rapidly metabolized by the enzymes catechol-*O*-methyltransferase and monoamine oxidase. The recommended dose of this short-acting  $\beta_2$  agonist is 200–400  $\mu\text{g}$  as required for symptom relief.

### *Long-acting $\beta_2$ agonists*

Slow-release oral formulations of salbutamol and terbutaline are available and these increase the duration of activity of these bronchodilators considerably compared with conventional oral tablets. Prodrugs are also now available which, when given orally, also greatly increase the duration of bronchodilatation (e.g. bambuterol is a prodrug of terbutaline, to which it is metabolized by hydrolysis). In general, however, inhaled therapy is preferable to oral since the inhaled route allows more rapid onset of bronchodilator activity and with a minute fraction of the dose necessary to achieve a similar clinical response via the oral route; this therefore reduces the risks of adverse effects [60].

The production of  $\beta_2$  agonists with a long duration of action when administered by inhalation has created a new era of bronchodilator therapy [61]. Salmeterol has a molecule with a long lipophilic tail that adheres tightly to regions in the receptor or adjacent to it while its head engages the active site. Even when displaced by an antag-

onist its activity resumes after the antagonist is washed free [62]. Eformoterol is even more potent but less adherent, its high lipophilicity retaining it in the receptor region. These long-acting bronchodilators have the advantage of being effective when used twice daily, although their role in the routine management of the asthmatic patient is far from clear. They do not have any clinically relevant anti-inflammatory effects and therefore should not be used as primary treatment of asthma, since patients who require more than occasional use of a short-acting  $\beta_2$  agonist should be treated with an anti-inflammatory drug, usually an inhaled corticosteroid [1,55,63]. Salmeterol has been shown to be effective in the treatment of asthma of almost all degrees of severity [62–69], and its long duration of action is obvious convenient for patients. However, the controversy about the possible dangers of regular treatment with short-acting  $\beta_2$  agonists [49–59] must be considered before recommending the regular use of drugs like salmeterol and eformoterol. Indeed, it could be postulated that if short-acting  $\beta_2$  agonists are in any way detrimental when given regularly in the long-term management of asthma, there could be greater problems with long-acting  $\beta_2$  agonists because they are more potent bronchodilators [49,51,70]. The more effective and prolonged bronchodilator efficacy of drugs like salmeterol could allow more specific and non-specific bronchial insults with irritant or allergen triggers before bronchoconstriction breaks through and hence the resulting acute episode could be more severe than one prevented by short-acting bronchodilator therapy. This theoretical danger has not been a problem in clinical practice in postmarketing surveillance studies of salmeterol; nevertheless the drug's use should be restricted to patients whose asthmatic symptoms are not controlled by inhaled corticosteroid therapy in doses unlikely to be associated with long-term adverse effects. The major debate about long-acting inhaled bronchodilator treatment is whether to start salmeterol or eformoterol if asthma is not well controlled with low-dose or high-dose inhaled corticosteroid therapy [71]. It has been pointed out that the much-publicized asthma guidelines [1,55,63] vary somewhat with regard to recommendations about drug use as well as classification of asthma severity [72]. Salmeterol is recommended for patients who have local laryngeal or oropharyngeal adverse effects of inhaled corticosteroids that do not allow high-dose therapy to be used [1]. Also, it would appear to be sensible to use this form of treatment once daily at night for patients already on an inhaled corticosteroid but who continue to have more than occasional nocturnal symptoms [60]. The addition of salmeterol to the treatment of patients whose asthma was not well controlled by treatment with a low dose of inhaled beclomethasone (beclomethasone) dipropionate (200  $\mu\text{g}$  twice daily) has been shown to be at least as effective as increasing the dose of inhaled beclomethasone (500  $\mu\text{g}$  twice daily) [71]. Studies



are now in progress in which attempts are being made to assess the control, or the suppression, of markers of inflammation by low-dose inhaled corticosteroid therapy plus long-acting inhaled  $\beta_2$  agonists compared with high-dose inhaled corticosteroid therapy in the treatment of patients with asthma whose symptoms are not well controlled by inhaled corticosteroid treatment in conventional low doses. The preliminary results of these studies suggest that long-acting inhaled  $\beta_2$ -agonist bronchodilator preparations are not associated with adverse effects. The role of eformoterol is likely to be more controversial than that of salmeterol because it has a much more rapid onset of bronchodilator activity and could therefore be used as a relief inhaler with a long duration of activity.

#### *Side-effects of $\beta_2$ agonists*

Large doses of  $\beta_2$  agonists can produce adverse metabolic and cardiovascular effects [73–75]. However, these events only occur when very large doses are used and even then are rarely of clinical importance. The  $\beta_2$  agonists are extremely safe drugs even when large doses are used, especially when given by inhalation and with oxygen. Unwanted cardiovascular effects include tachycardia, increased cardiac output, inotropism and ECG changes. Cardiac dysrhythmias are usually asymptomatic and rarely occur in patients who do not have pre-existing heart disease. General systemic effects include hypokalaemia and hyperglycaemia, increased free fatty acids, hypomagnesaemia, increased blood lactate and uterine relaxation. The only general unwanted effect that often causes patient concern is skeletal muscle tremor which, while not serious, can be distressing [76]. The individual response to tremor is highly variable but to some extent is dose dependent and, unlike bronchodilatation, tachyphylaxis occurs rapidly in the majority of patients. Tremor therefore is usually only a problem when  $\beta_2$  agonists are being given for the first time.

The predictable physiological adverse effects of  $\beta_2$  agonists rarely cause any serious clinical events. Most depend on route of administration and dose. Conventional doses administered by an inhaler for 'as-necessary' relief of the symptoms of chronic asthma can be assumed to be free from all unwanted effects, except for tremor in a few patients. Larger doses given orally, by inhalation or intravenously are associated with demonstrable unwanted effects, but only rarely are these of clinical significance. High-dose treatment for the control of chronic persistent asthma should of course be avoided; however, large doses of  $\beta_2$  agonists, usually by inhalation, are essential for the treatment of severe acute asthma and patients should not be denied this treatment simply because of the theoretical risks of adverse effects.

#### **Theophylline**

In the USA in the 1970s and early 1980s, theophylline (1,3-dimethylxanthine) was the most commonly prescribed bronchodilator. Detailed study of its pharmacokinetics and the development of sustained-release preparations, often monitored by theophylline serum levels, improved the therapeutic value of this drug by increasing its efficacy and decreasing its adverse effects. However, emphasis on the importance of anti-inflammatory therapy coupled with the simplicity and assumed safety of inhaled  $\beta_2$  agonists led to a decline in its use. It still has a role in the management of nocturnal asthma resistant to other forms of treatment, and is prescribed for many patients with severe chronic asthma in an attempt to avoid oral corticosteroid therapy. Paediatricians use theophylline more often than clinicians treating adult patients with asthma, mainly because it is easier for children to be treated with oral preparations, because many are unable to use inhalers and perhaps also because young children are less likely to be aware of side-effects. Theophylline relaxes smooth muscle by inhibition of phosphodiesterase and probably via other mechanisms [77]. A serum theophylline concentration of 10–20  $\mu\text{g/mL}$  was recommended, since below this range bronchodilatation is unlikely and above it symptoms of toxicity are common [78,79]. A dose–response relationship can be shown in chronic stable asthma with increasing serum concentrations of theophylline up to 20  $\mu\text{g/mL}$ , serum concentrations of 15 and 20  $\mu\text{g/mL}$  achieving bronchodilatation similar to that of conventional doses of salbutamol administered by metered dose inhaler (MDI) [80]. In most patients there is also a direct relationship between serum theophylline levels and side-effects, the most troublesome being nausea, vomiting, headache, nervousness and irritability. Because these toxic effects are common, the popularity of theophylline has declined markedly. There is an additive bronchodilator effect when theophylline is given in combination with  $\beta_2$  agonists [81–83], and in an attempt to decrease adverse effects low doses of theophylline preparations have been used in combination with salbutamol or terbutaline. However, this therapeutic approach requires regular  $\beta_2$  agonist, which should be avoided in the treatment of asthma whenever possible. Theophylline has been shown to increase the contractility of the diaphragm and render it less susceptible to fatigue [84], and also to increase maximal transdiaphragmatic pressure [85]. However, these actions of the drug are not likely to be of much clinical significance in asthma, except perhaps in severe acute episodes. Of much more interest recently has been the discovery that theophylline has anti-inflammatory properties, although the relevance of these to the treatment of asthma is far from clear. Type IV phosphodiesterase inhibitors, including theophylline, have been shown to effect changes in the activity and function of macrophages

[86,87] and lymphocytes [88,89]. Theophylline has been shown to reduce eosinophil infiltration of the airway [90] and to produce a reduction in eosinophil activity after prolonged treatment [91]. Also, unlike  $\beta_2$  agonists, theophylline modulates the late asthmatic response [92–95]. It has been suggested that theophylline may provide clinical effects comparable to those of low-dose inhaled corticosteroids in selected asthmatics [96,97]. The evidence suggests that theophylline has anti-inflammatory properties at doses lower than those necessary to achieve the conventional therapeutic serum level (10–20  $\mu\text{g/mL}$ ) required for optimal bronchodilatation. However, the role of theophylline in the treatment of the basic underlying eosinophilic inflammation of asthma has yet to be determined, and may be minimal. In the future, low-dose theophylline in combination with other drugs may become more established in the management of mild to moderate chronic asthma, although until more knowledge of the efficacy of such treatment is available oral theophylline therapy should be reserved for patients whose asthma is not controlled with conventional doses of inhaled corticosteroids. However, intravenous aminophylline continues to have an important role in the management of patients with severe acute asthma.

#### Anticholinergic agents

The drugs of this category (muscarinic antagonists) most widely used in the treatment of reversible airways disease are ipratropium bromide and oxitropium bromide. It is generally accepted that they are more effective in chronic obstructive pulmonary disease, i.e. chronic bronchitis and emphysema, than in chronic asthma [61]. In chronic stable asthma, ipratropium bromide produces a smaller response of delayed onset compared with salbutamol [98], although older asthmatics may respond better to anticholinergic agents than do younger patients [99,100]. In chronic asthma these drugs are usually reserved for use in patients who have not responded to conventional doses of an inhaled corticosteroid, when they are added to the treatment regimen as regular inhaled therapy (ipratropium bromide 20–40  $\mu\text{g}$  three or four times daily, or oxitropium bromide 200  $\mu\text{g}$  two or three times daily). Ipratropium bromide is of much greater value in the treatment of the severe acute episode than it is in the routine treatment of most patients with chronic asthma.

#### Drugs with anti-inflammatory properties used to influence the underlying inflammatory mechanisms of asthma (the preventers)

##### Sodium cromoglycate (cromoglycate) and nedocromil sodium

Sodium cromoglycate was first synthesized and its use in

asthma reported in a small trial in 1967 [101]. Its clinical efficacy was established in both adults and children in a series of clinical trials performed in different parts of the world [102–111], although in recent years its use has been almost completely restricted to the treatment of childhood asthma [112–114]. In the main this has been due to the often irrational fears of treating children with inhaled corticosteroids, sodium cromoglycate being preferred because it is virtually free from side-effects. This drug continues to be prescribed as first-choice treatment for atopic asthmatic children, particularly those with exercise-induced asthma, despite reports of early treatment failure and greater efficacy of low-dose inhaled corticosteroids [115–119]. To be optimally effective it has to be taken regularly at least four times daily and this very frequently leads to problems with compliance, which may be the explanation of treatment failure in some patients. Sodium cromoglycate has no role in the treatment of severe acute asthma.

Nedocromil has an extremely good safety record, although some patients find its taste unpleasant. An attempt to disguise this has been made by adding mint flavouring to the inhaler. The role of this drug in the management of chronic asthma is difficult to define [120–123]. It has little place in primary treatment, since its anti-inflammatory properties and clinical efficacy are inferior to those of inhaled corticosteroids. However, it may be of value in patients not well controlled by conventional doses of an inhaled corticosteroid and should be used as a corticosteroid-sparing agent in patients on oral and high-dose inhaled corticosteroids [124,125]. Compared with sodium cromoglycate, the evidence suggests that it is at least as good, or even superior, in the treatment of adult chronic asthmatics [126–128]. Like sodium cromoglycate it has no role in the treatment of severe acute asthma.

##### $H_1$ -receptor antagonists

Although effective in the treatment of allergic rhinitis, antihistamines have little place in the treatment of asthma. The evidence for and against the use of these drugs in asthma has been extensively reviewed and it is apparent that the few patients who may benefit from these compounds are young atopic individuals with mild seasonal symptoms [129].

Ketotifen is a commonly used drug, especially in under-developed countries. It is a non-competitive  $H_1$ -receptor antagonist and *in vitro* has an inhibitory effect on mast cells similar to that of sodium cromoglycate. In challenge studies ketotifen has an immediate bronchoprotective effect, although there are no convincing clinical trial data to confirm its value in the long-term treatment of asthma. Like many of the early antihistamines, the most common side-effect of ketotifen is drowsiness, which occurs in over 20% of patients [129].



### Inhaled corticosteroids

Corticosteroids have been used in the treatment of asthma for nearly half a century [130,131]. The early treatment of both acute and chronic asthma was with adrenocorticotrophin (ACTH). However, following the development of a number of glucocorticosteroids, prednisolone became the standard oral therapy, and hydrocortisone and methylprednisolone have become established as the most commonly chosen corticosteroids for intravenous administration. The treatment of asthma with systemic corticosteroids in sufficiently high doses to control symptoms led to the development in many patients of numerous adverse effects, which ironically were all outside the respiratory tract. This stimulated the pharmaceutical search for a drug that was locally active in the control of asthma when inhaled but not absorbed from the lungs or gastrointestinal tract in sufficient quantities to have the same degree of systemic side-effects. The breakthrough came in the early 1970s when beclomethasone dipropionate and betamethasone valerate were found to have high topical activity in the bronchi with low systemic availability. Very soon after this, triamcinolone acetonide and flunisolide were found to possess similar pharmacokinetic profiles, and almost a decade later budesonide was introduced as a corticosteroid with a higher topical activity than those already established in the treatment of chronic asthma. Recently, approximately a decade further on, fluticasone propionate was marketed as a more potent drug than budesonide. The role of this drug has yet to be established since it appears to have greater topical activity than budesonide in terms of control of asthmatic symptoms, but may also have greater systemic activity when absorbed from the lungs.

There can be no doubt that the development of inhaled corticosteroids revolutionized asthma therapy. In the early 1970s there were enthusiastic reports of the efficacy of inhaled corticosteroids assessed in uncontrolled studies [132,133], followed by confirmation of efficacy by the publication of the results of well-designed placebo-controlled studies [134–136]. These showed that withdrawal of oral prednisolone and substitution with an inhaled corticosteroid did not result in poorer control of asthmatic symptoms but did allow worsening of atopic nasal and skin problems, thus confirming the topical, rather than systemic, activity of inhaled corticosteroid therapy. Beclomethasone dipropionate was first introduced into clinical practice in a recommended dose of 400 µg daily (100 µg four times daily). The careful controlled clinical trials in which this drug was substituted for oral prednisolone indicated that this four-times-daily dose of beclomethasone dipropionate, and also betamethasone valerate, was equivalent to 7 or 8 mg of prednisolone [137]. The introduction of topical inhaled corticosteroid therapy thus allowed withdrawal of systemic corticosteroid

therapy in the majority of patients previously treated with these drugs and allowed a considerable reduction in dose in those patients with very severe disease requiring treatment with high doses of prednisolone.

Inhaled glucocorticosteroids have now become first-line therapy for the treatment of chronic asthma in most countries. They are the most effective therapy available and have been shown to have beneficial effects on bronchial wall inflammation and airway hyperresponsiveness as well as symptoms. Bronchial biopsies of patients being treated with inhaled corticosteroids have shown a reduction in the number and activation of inflammatory cells in the airway [138–141] and also restoration of the disrupted epithelium and normalization of the ratio of ciliated cells to goblet cells [138]. Inhaled corticosteroids reduce airway responsiveness to both direct and indirect stimuli. In acute challenge studies, the late response to allergen and the accompanying increase in airway responsiveness is reduced [142] and prolonged therapy protects against the early asthmatic response [143]. A single dose of inhaled corticosteroid fails to protect against exercise-induced asthma, but more prolonged therapy does [144,145]. Chronic treatment reduces airway responsiveness to inhaled histamine and methacholine, although this may take up to 3 months or even longer [143,145–150]. Corticosteroids presumably improve airway responsiveness by reducing the underlying inflammation, although any component of the airways disease caused by structural changes in the bronchial wall, such as thickening of the basement membrane and airway muscle hypertrophy, may be irreversible. Indeed there is now evidence which suggests that if inhaled corticosteroid therapy for asthma is delayed the response, as judged by objective measurements of pulmonary function, is less good than when this treatment is given quickly after the diagnosis has been made [151–153]. It has not yet been established whether prolonged therapy with inhaled corticosteroids can overcome this problem, or whether this indicates irreversible bronchial wall changes that cannot be remodelled. One study showed that there was no 'catch up' in the delayed treatment group after 1 year [151]. These findings have led to the concept of early intervention with inhaled corticosteroids in the treatment of asthma.

Numerous controlled clinical trials have now established that corticosteroids are effective in controlling symptoms of asthma and in reducing the number and severity of exacerbations. This proven efficacy of inhaled corticosteroids, coupled with our knowledge that inflammation is found even in patients with very mild asthma, has indeed led to the use of these drugs at a much earlier stage in treatment [154]. A low dose of an inhaled corticosteroid (e.g. budesonide 200 µg daily) is effective in mild asthma [155], as is once-daily therapy [156]. The various guidelines for asthma therapy recommend this form of treatment for any patient symptomatic enough to require

the use of a bronchodilator inhaler more than once daily [1,55,157].

High-dose inhaled corticosteroid is now frequently used in many countries for treatment of patients with more severe disease [158]. This significantly reduces the need for maintenance oral corticosteroids, and many patients with 'difficult to control' chronic asthma have benefited from this treatment [158–161], although the value of high-dose compared with low-dose therapy has been questioned [162]. Inhaled corticosteroids are effective in the treatment of asthma because they control bronchial wall inflammation, although this may take many weeks to be achieved [138]. When treatment is withdrawn, there is usually an increase in airway responsiveness and recurrence of symptoms to pretreatment levels presumably because of recurrence of bronchial inflammation [147,163–165]. The longer treatment is given, the more likely the possibility of a prolonged remission; indeed, the ultimate aim of treatment is the induction of a complete remission by inhibition of the inflammatory process, or of prolonged remissions by intermittent courses of therapy. A clinically worthwhile prolonged remission is more likely in mild asthmatics treated soon after the onset of their disease. Early treatment is also important since it has been shown that objective response to inhaled corticosteroid therapy is significantly better in patients treated soon after the onset of symptoms compared with treatment delayed by 2 years or more [151–153]. The evidence that there is a better objective response when inhaled corticosteroids are given early after the onset of asthmatic symptoms suggests that irreversible and permanent pathological changes, possibly fibrosis in the bronchial wall, occur at an early stage even in patients with mild asthma. Theoretically this treatment should reduce the irreversible component of airway narrowing seen in patients with more severe poorly controlled disease [166–168]. Whether inhaled corticosteroids reduce the mortality from asthma remains to be demonstrated. The Saskatchewan study of asthma deaths and near-death attacks [169] suggested that this therapy does have this effect, although the numbers studied were too small to reach a firm conclusion.

Although most patients with asthma respond to corticosteroids, there is a small minority who appear to be resistant or much less responsive to these drugs. Disease of this type has been called steroid-resistant asthma [170]. This problem is not explained by pharmacokinetic abnormalities such as impaired absorption or rapid elimination of oral corticosteroids. Compared with normal individuals and corticosteroid-sensitive asthmatics, these patients have been found to have a significantly different response to beclomethasone dipropionate applied to their skin [171], suggesting that this phenomenon is not organ-specific. Corticosteroid-resistant asthma can be defined as a less than 15% improvement in forced expiratory

volume in 1 s (FEV<sub>1</sub>) or PEF to treatment with oral prednisolone in a daily dose of 40 mg given for a period of at least 2 weeks in a patient in whom all other exacerbating asthma factors have been excluded or removed. Patients with asthma resistant to the beneficial effects of corticosteroids have been the focus of much *in vitro* research and abnormalities of peripheral blood cell behaviour have been detected [172]. It is anticipated that if the crucial defect in these patients can be determined, this will lead to the discovery of how corticosteroids exert their beneficial effects in asthma and thus to a focused approach in searching for a cure of this common disease. Corticosteroid-resistant asthma has been comprehensively reviewed [172].

### *Local side-effects*

The most frequent side-effects of inhaled corticosteroids are local effects on the upper airways caused directly by oropharyngeal deposition; these are discussed below.

### *Oropharyngeal candidiasis*

The reported incidence of oropharyngeal candidiasis has varied greatly (5–77%) because of the different criteria used for diagnosis, ranging from a throat swab positive on culture for *Candida albicans* to clinical thrush requiring treatment, and also whether cross-sectional or cumulative analyses have been made [173–177]. Oropharyngeal candidiasis is much less common in children than it is in adults [178,179]. The incidence of thrush is related to the daily dose of inhaled corticosteroid and possibly also to dosing frequency [177,180,181]. The combined use of oral and inhaled corticosteroids does not appear to increase the incidence of candidiasis [173,174,181]. The use of large-volume spacer attachments to the conventional MDI appears to offer some protection against the development of thrush [182,183]. Oropharyngeal candidiasis tends to develop more readily in patients who have a positive *C. albicans* throat swab [184] but is seldom a major clinical problem, can usually be controlled with topical treatment using nystatin or amphotericin, and rarely necessitates withdrawal of inhaled corticosteroid therapy [185]. Oesophageal candidiasis is a very rare complication of inhaled corticosteroid therapy [186]. Candidiasis of the lower respiratory tract has not been reported to have been caused by inhaled corticosteroid treatment.

### *Dysphonia*

Dysphonia or hoarseness of the voice is a much more common problem than candidiasis in patients being treated with inhaled corticosteroids. It occurs to some degree in one-third to half of patients [177,187] and has been reported to be due to a local corticosteroid myopathy

of the vocal cord muscles, which is reversible after withdrawal of treatment [188] but which, unlike thrush, tends to recur when treatment is restarted [189]. The occurrence of dysphonia is related to the total daily dose of inhaled corticosteroid but not to dose frequency [177,187]. Large-volume spacers do not provide any protection against the development of voice problems [180,187], since they increase rather than decrease drug deposition in the region of the larynx and could therefore theoretically make the problem worse. There is some evidence that dry powder inhalers (DPIs) cause fewer voice problems than conventional pressurized MDIs with or without spacer attachments [190,191].

#### *Cough and throat irritation*

Cough and non-specific throat irritation are also common complaints of patients using inhaled corticosteroids [187]. Corticosteroid inhaler-induced cough is much more common with pressurized MDIs than with DPIs and is more often caused by the additives in the inhaler, such as surfactants, rather than the drugs [192,193]. Inhaler-induced cough is often associated with bronchoconstriction [192,194] and pressurized aerosol inhalers should be changed to dry powder systems whenever patients have this problem [193]. Non-specific throat irritation is quite common in patients being treated with inhaled corticosteroids [187], although this is rarely of more than nuisance value and tends to be less of a problem when DPIs are used.

#### *Other local side-effects*

There is no evidence to suggest an increase in infections, including tuberculosis, of the lower respiratory tract after prolonged use of inhaled corticosteroids [178,179], and this treatment does not adversely influence pre-existing colonization of the bronchi with *Aspergillus fumigatus* in patients with allergic bronchopulmonary aspergillosis [195]; indeed it is useful in the long-term management of this condition [196]. Biopsy studies have failed to demonstrate any bronchial mucosal abnormalities, even after treatment for over 10 years [138,197].

#### *Systemic side-effects*

Inhaled corticosteroid treatment was first introduced in a recommended dose of 100 µg four times daily. Subsequently it was found that a dose regimen of 200 µg twice daily was as effective as administration four times daily in maintaining control of chronic asthma. In low doses of up to 400 µg daily it is possible to detect evidence of systemic absorption and activity by assessment of hypothalamic–pituitary–adrenal (HPA) axis function [198], although these minor changes are of no clinical

importance even after prolonged therapy [178]. Indeed the lack of systemic activity allows recurrence of disorders such as eczema and allergic rhinitis when beclomethasone dipropionate or betamethasone valerate is substituted for oral steroids in atopic asthmatics. Despite initial fears regarding the potential side-effects of long-term inhaled corticosteroids, only the minor local upper respiratory problems of oropharyngeal candidiasis and dysphonia have occurred [178].

In recent years, however, much larger doses of inhaled corticosteroids have been used in the treatment of asthmatic patients whose symptoms are not controlled by low-dose therapy, and high doses of these drugs are inevitably associated with systemic effects. These arise from absorption of drug from the lung and the gastrointestinal tract. Adverse effects from swallowed drug depend upon first-pass liver metabolism. Budesonide is more efficiently inactivated by the liver than is beclomethasone dipropionate. The recently introduced fluticasone propionate is almost completely inactivated by the liver when ingested [199] but, like all corticosteroids clinically effective in the treatment of asthma by the inhaled route, gives rise to systemic effects from the fraction deposited in the lung. This is because drug reaching the lung is very rapidly absorbed without metabolism and is consequently available for systemic activity [200]. Therefore, all inhaled corticosteroid preparations in clinical use give rise to systemic effects if high enough doses are inhaled. The differentiation between 'low-dose' and 'high-dose' therapy is now generally accepted. In effect this separates therapy assumed to be safe (low dose) and free from systemic effects from high-dose therapy that might be associated with unwanted systemic corticosteroid effects if given long term. However, the advantages and disadvantages of long-term low-dose and high-dose inhaled corticosteroid therapy are somewhat controversial [201]. It is generally accepted that in adults total daily doses of beclomethasone dipropionate or budesonide up to and including 800 µg are safe and are defined as 'low dose', while 'high-dose' therapy is 800–2000 µg daily [1]. Long-term treatment with doses in excess of 2000 µg (or 1000 µg of fluticasone propionate) should be assumed to be able to cause systemic adverse effects in some of the patients. However, it must be emphasized that, in the main, the amount of drug absorbed from the lung determines the magnitude of systemic activity, and the pulmonary deposition efficiency of different inhalation delivery systems varies considerably. Hence, it is inappropriate to assume that the nominal doses of different inhalers achieve similar therapeutic and adverse effects. Thus, a clinically very effective inhaler must also be expected to have a higher systemic effect than a device that achieves a lower pulmonary deposition [154]. There is a great need for the equivalence of inhaled drugs to be assessed in order to lessen the confusion in this important area of asthma management [202,203].

*HPA axis function*

A large number of studies have assessed the effects of inhaled corticosteroids on HPA axis function. Researchers have focused on the HPA axis because assessments of its function are very much more simple to make than any other estimation of the systemic activity of corticosteroid treatment. However, it is not possible to use HPA axis function abnormalities induced by exogenous corticosteroid treatment to assess the risk of other adverse effects of long-term treatment, such as osteoporosis. Few studies have compared the effects on HPA axis function of the various inhaled corticosteroid preparations available for clinical use, and the findings of these studies are conflicting [154]. However, as one would expect, there appears to be a dose-dependent effect and it has to be assumed that the risk of all systemic adverse effects is dose dependent. Undoubted improvement in HPA function has been established when oral corticosteroid therapy has been replaced by inhaled treatment with beclomethasone dipropionate or budesonide in doses of up to 2000 µg daily [204–206]. Considering all the published data on beclomethasone dipropionate and budesonide and HPA axis function, it can be assumed that clinically significant HPA suppression is unlikely to occur with daily doses up to and including 1500 µg in adults and 400–800 µg in children [154].

*Osteoporosis*

One of the most feared unwanted effects of systemic corticosteroids is osteoporosis [207]. Although low-dose inhaled therapy in adults has been proved to be safe (except perhaps in patients who have received oral corticosteroid treatment prior to substitution with inhaled drugs), the recent increased use of inhaled drugs in high dose has given rise to some doubt about its effect upon bone metabolism. The effects of inhaled corticosteroids on biochemical markers of bone metabolism, such as bone-specific serum alkaline phosphatase, serum osteocalcin, urinary hydroxyproline, calcium and pyridinium cross-links, have been assessed in many short-term studies, even though the relevance of these markers to the risk of development of osteoporosis in the distant future is far from clear. The results of long-term studies of bone density in patients being treated with different doses of different inhaled corticosteroids will have to be awaited before any conclusions about the risks of high-dose therapy and osteoporosis can be made. Clinical trial data so far available raise the possibility of clinically significant osteoporosis developing as a result of long-term high-dose inhaled corticosteroid treatment, although skeletal fracture has not yet been reported as a direct result of such treatment [154]. Those patients at greatest risk are postmenopausal women, the inactive and smokers.

*Growth in children*

Knemometry studies have made it possible to measure accurately linear growth velocity of the lower leg over short periods of time. However, the relationship of this measurement to long-term statural growth has not been determined. However, knemometry is a sensitive method of assessing systemic activity of corticosteroid treatments. It has been shown that budesonide delivered via a large-volume spacer in a dose of 400 µg does not adversely affect lower leg growth velocity [208–210]. Knemometry is extremely sensitive since it has been found that prednisolone in the small dose of 2.5 mg totally suppresses short-term lower leg growth [211]. However, this emphasizes the fact that knemometry is not a measurement of statural growth since although small doses of prednisolone may suppress growth, complete suppression is unlikely. Long-term treatment with budesonide in doses of 400–800 µg daily does not suppress statural growth in children [152].

*Other systemic effects*

The increased risk of the development of subcapsular cataracts in patients being treated with systemic corticosteroids is well known, although despite isolated reports there is no convincing evidence that inhaled corticosteroids cause cataracts in adults or children [154]. Similarly, although minor metabolic effects can be detected, there is no evidence that inhaled corticosteroids result in clinically significant changes in glucose or lipid metabolism.

**Leukotriene antagonists**

Several orally administered leukotriene antagonists have recently been released on the market, and it is likely that other variants will soon be available. It is possible that they may have a role in the treatment of mild asthma or as corticosteroid-sparing drugs, although it is premature to assess their therapeutic role or safety in long-term use. Their actions are considered in Chapter 9.

**Systemic corticosteroids**

Corticosteroids are used in asthma on account of their anti-inflammatory properties, and it is unfortunate that no drug has yet been synthesized that separates these from the metabolic effects responsible for many of their side-effects. The drugs act in a common way. Steroids diffuse through the cell membrane and bind to intracytoplasmic (rather than membrane) receptors. The steroid–receptor complex binds with nuclear chromatin, inducing the production of an mRNA that promotes the synthesis of an effector protein responsible for the steroid

actions. The anti-inflammatory actions include reduction in permeability and dilatation of blood vessels and suppression of accumulation of neutrophils; other effects include reduction in the numbers of circulating monocytes, eosinophils and basophils and extravascular sequestration of lymphocytes, together with inhibition of fibroblast proliferation. Steroids are considered in more detail in Chapter 9.

Oral corticosteroids, usually prednisolone, are the mainstay for aborting and treating acute exacerbations of asthma. Most patients who have suffered a severe attack can recognize the early signs, especially increasing tightness in the chest and failure to respond other than partially to their usual bronchodilator. Such patients should be provided with a supply of prednisolone and told to take it as soon as they realize an attack is starting. The dose may be judged on the patient's size and experience of previous attacks, although it is the author's practice to advise 30–60 mg daily until the chest feels normal, then reducing by 5 mg daily. This is discussed further in the section on acute exacerbations.

Oral corticosteroids are also necessary for the long-term management of patients with chronic asthma. Attempts should always be made to avoid this by maximizing other treatment and by using short intermittent courses, but in some patients control is impossible without regular prednisolone. When this is necessary, the dose should be kept as low as possible and periodic attempts should be made to wean the patient from the drug. The patient should be given a 'steroid card', on which is recorded the dose, duration of treatment, name and telephone number of the doctor and a brief list of emergency instructions. In many subjects this form of treatment is far from satisfactory, requiring as it does a balance between acceptable control of the disease and limitation of side-effects. Hospital asthma clinics are unfortunately full of patients with steroid facies, cataracts, osteoporotic vertebral crush fractures, bruised fragile skin, hypertension and diabetes; some alternative to this treatment is therefore highly desirable.

Parenteral hydrocortisone is used primarily in the management of the acute severe attack. The drug takes at least several hours to have a measurable effect on the airways, presumably depending on the severity of the mucosal inflammation and plugging of the lumen. Depending on an assessment of the severity of the condition at presentation, the dose varies from 100 mg to as high as 1 g. This is usually then repeated either in a constant infusion or as 6-hourly pulses until recovery occurs. This is discussed further in the section on acute severe asthma.

Other uses of parenteral steroids are in the occasional management of chronic severe asthma and patients incapable of taking their medicines reliably (see below). In addition, intermittent injections of ACTH have been used in the management of severe childhood asthma in the hope of avoiding long-term adrenal suppression.

Fortunately the need for this therapy has been much reduced by the advent of cromoglycate and inhaled corticosteroids.

As stated above, patients on long-term steroids should be maintained on the smallest dose consistent with proper control of the asthma. This is judged from the history of symptoms and from regular assessment of PEF or FEV<sub>1</sub>, and no attempt should be made to wean patients from steroids without such careful monitoring. If it seems possible that a patient will manage without long-term steroids, the daily dose should be reduced very gradually (by 1 mg prednisolone each week) and adrenal function assessed periodically by short Synacthen tests. If the patient is successfully weaned from the drugs, he or she should be warned of possible adrenal hypofunction at times of future stress (e.g. operations) and should be told that future acute attacks of asthma will undoubtedly require short courses of steroids. Such patients are understandably reluctant to restart these drugs, and tragic deaths have occurred as a consequence.

In order to prevent the major side-effects of long-term treatment, patients with a history of indigestion should have concomitant therapy with an H<sub>2</sub> antagonist and considered for eradication therapy if there is evidence of *Helicobacter pylori* infection. Postmenopausal women should be encouraged to keep physically active and considered for hormone replacement therapy or other measures to prevent osteoporosis (discussed in Chapter 9).

### General principles of drug use in the treatment of chronic asthma

The principles of management are based on the guidelines produced by the British Thoracic Society [1], the International Consensus Report on the Diagnosis and Management of Asthma [55] and Australian guidelines [63].

The stepwise approach to the treatment of asthma is based on the use of corticosteroids. It is now common practice to use long-acting  $\beta_2$  agonists at an earlier stage than step 3 or 4, although it is accepted that they should always be used in combination with an inhaled corticosteroid. A rare exception to this would be the patient with severe dysphonia or, if less serious, interfering with their occupation, for example a professional singer. The initial management of asthma should be based on the principal aim of achieving optimal lung function and symptom control as quickly as possible initially, and subsequently deciding on the therapy required to maintain symptom control. On many occasions this would require the use of oral prednisolone or high-dose inhaled corticosteroid treatment initially with a subsequent titrated step-down thereafter according to symptoms and PEF recordings. PEF monitoring is essential in the early management of asthma especially when prednisolone or high-dose

inhaled corticosteroid therapy is being used to achieve optimal asthma control.

### Step 1

Occasional use of inhaled short-acting  $\beta_2$ -agonist bronchodilators. If more than occasional use (more than once daily or three times each week) is necessary, treatment with inhaled drugs that have a beneficial effect on the underlying asthmatic inflammatory process should be prescribed (Step 2 treatment). Treatment with an inhaled  $\beta_2$  agonist alone is recommended if it is only used occasionally by a patient with mild asthma who is leading a normal active life and who is free from nocturnal and exercise-induced symptoms.

### Step 2

Regular inhaled corticosteroid in a low dose of up to 800  $\mu\text{g}$  daily (or 400  $\mu\text{g}$  of fluticasone propionate) together with an inhaled  $\beta_2$  agonist to be used as required. Alternatively, sodium cromoglycate or nedocromil sodium can be used instead of an inhaled corticosteroid, although these drugs are rarely as effective. Sodium cromoglycate is mainly used in the treatment of asthma in childhood.

### Step 3

Inhaled short-acting  $\beta_2$  agonist as required plus an inhaled corticosteroid in the dose range 800–2000  $\mu\text{g}$  daily (or 400–1000  $\mu\text{g}$  daily for fluticasone propionate). Large-volume spacers are recommended for use with the conventional pressurized MDI in order to reduce both local and systemic corticosteroid side-effects. The alternative to high-dose inhaled corticosteroid therapy is addition of a long-acting bronchodilator to low-dose inhaled corticosteroid.

### Step 4

Inhaled short-acting  $\beta_2$  agonist as required with an inhaled corticosteroid (800–2000  $\mu\text{g}$  daily) plus a sequential therapeutic trial of one or more of (i) an inhaled long-acting  $\beta_2$  agonist such as salmeterol xinafoate or formoterol, (ii) a sustained-release theophylline, (iii) inhaled ipratropium bromide or oxitropium bromide, (iv) a long-acting oral  $\beta_2$  agonist such as bambuterol, (v) nedocromil sodium or sodium cromoglycate or (vi) high-dose inhaled bronchodilators.

### Step 5

The addition of oral corticosteroid (prednisolone) therapy to high-dose inhaled corticosteroid therapy and the other

drug(s) found to be of benefit during the sequential therapeutic trial in step 4.

### Increasing the dose of inhaled corticosteroid

Doubling the dose of inhaled corticosteroid irrespective of the actual maintenance dose appears to be an effective way of controlling minor exacerbations of asthma. This advice is given to most patients even though there is no clinical trial evidence to prove its effectiveness.

### Short-course oral prednisolone treatment

Short courses of 'rescue' prednisolone are often required to regain control of symptoms during exacerbations. Prednisolone in a dose of 30–40 mg daily can be given to adults until 2 or 3 days after symptom control has been regained. Tapering of the dose is not necessary unless treatment has been required for more than 3 weeks [212].

## Management of severe acute asthma

The clinical features of acute severe asthma are described in Chapter 34. The presentation can range from the moribund patient who has developed respiratory arrest to the apparently distressed breathless asthmatic whose disease is not life-threatening but who is hyperventilating in response to relatively mild airflow obstruction. It is therefore extremely important that an accurate assessment of the degree of severity of the acute episode is made, since the treatment necessary depends on the severity.

### General measures

The majority of patients with severe acute asthma are frightened and distressed by their breathing difficulties, and this may stimulate the uninitiated to attempt relief by the administration of some form of sedative or anxiolytic drug. This is the most culpable mistake that can be made in the management of the distressed asthmatic [213,214]. Sedation must be avoided in all patients outside an intensive care area. Patients suffering a severe acute episode of asthma breathe with maximally efficient use of their respiratory muscles and despite this are unable to maintain normal arterial blood gas tensions. To suppress ventilation with any form of sedation is therefore likely to lead to deterioration. Very occasionally a patient with a mild attack of asthma can become excessively agitated and distressed and this can lead to inappropriate hyperventilation. In this situation the judicious use of a benzodiazepine by the experienced clinician may be of benefit, after the severity of the patient's asthma has been fully assessed objectively. In general terms, however, sedation of any type is contraindicated in severe acute asthma.

Prolonged severe asthma can lead to dehydration

because of lack of intake coupled with an increase in obligatory fluid loss. While intravenous replacement is rarely necessary, it is wise to have an intravenous access in all sick patients, the main purpose of this being to provide a route for drug administration should this become necessary, perhaps unexpectedly.

Electrolyte imbalance is theoretically possible in many patients because of side-effects of drug therapy but, like dehydration, is rarely a clinically significant problem. In particular, hypokalaemia should always be kept in mind since this can be induced by  $\beta_2$ -agonist and corticosteroid therapy in the doses used to treat some patients with severe acute asthma; this can be made worse by the overzealous use of potassium-free solutions for the treatment of theoretical dehydration or for the delivery of intravenous drugs such as aminophylline.

Physiotherapy is of no benefit in the treatment of the severe acute episode unless the patient also has another condition requiring a physiotherapist's assistance, such as bronchiectasis perhaps as a result of coexisting allergic bronchopulmonary aspergillosis. Even then the physiotherapy used must be gentle since the gymnastic rituals of treatments such as postural drainage are absolutely contraindicated in the distressed asthmatic.

Antibiotic treatment is very rarely necessary in the treatment of severe acute asthma, even though a majority of patients are prescribed an antibiotic such as amoxicillin (amoxycillin). Many exacerbations of asthma are triggered by upper respiratory tract viral infections and this often induces the clinician to prescribe antibiotic treatment. However, antibiotics are rarely necessary even if the patient produces scanty apparently purulent sputum. Bronchoconstriction itself, no matter what has triggered it, causes retention of bronchial secretions that might appear to be purulent, either because of minor bacterial infection or because of the presence of large numbers of eosinophils. In either case, treatment should be aimed at improving bronchoconstriction in order to allow the retained bronchial secretions to expectorated.

### Specific treatment

There is no precise order for listing the essential treatments for severe acute asthma, since in critically ill patients most drugs and oxygen should be given at the same time. In the less severely ill, bronchodilator therapy alone may be the only treatment necessary. However, the majority of patients require a combination of treatments. Assessment of the degree of severity of the episode is essential and response to treatment must be assessed carefully with both clinical and objective measurements. The response to treatment of all patients with severe acute asthma should, when possible, include measurement of arterial blood gases (if abnormal initially) and PEF.

### Oxygen

All dangerously ill patients with severe acute asthma are hypoxaemic, or are capable of suddenly becoming hypoxaemic, and oxygen treatment should therefore be routine. Patients with asthma become hypoxaemic and then hypercapnic because of asphyxia caused by severe airflow obstruction and not because of any pre-existing brainstem abnormality of response to oxygen or carbon dioxide (unlike the patient with severe chronic obstructive pulmonary disease). Oxygen should therefore be given by face mask in high concentration, and should only be adjusted according to  $P_{aO_2}$  measurements irrespective of any degree of carbon dioxide retention and respiratory acidosis. The most severely ill asthmatic, prior to death, has respiratory acidosis because of carbon dioxide retention as a result of alveolar hypoventilation caused by severe diffuse airways narrowing leading to asphyxia. These moribund patients are also hypoxaemic for the same reason (asphyxia) and are in need of treatment with oxygen in high concentrations, which unfortunately they are often denied because of the false assumption that high-concentration oxygen therapy in the presence of carbon dioxide retention in asthmatics is dangerous.

The aim should be to maintain a  $P_{aO_2}$  of at least 9 kPa (70 mmHg) and therefore blood gas monitoring of treatment is essential in all patients whose first blood gas analysis is abnormal. When hypoxaemia persists and hypercapnia worsens despite drug treatment (see below), assisted ventilation may be required. Most distressed asthmatics dislike closely fitting face masks and should be treated with masks designed to use the Venturi principle, or even nasal prongs if face masks cannot be tolerated. Those delivering 35% oxygen should be the ones used in the initial treatment of severe acute asthma, and masks delivering higher oxygen concentrations may be necessary. Oxygen tents may have to be used for the treatment of young children.

The administration of bronchodilator drugs, particularly when given intravenously, can theoretically result in worsening of hypoxaemia [215,216] and it is therefore prudent to administer oxygen before, during and after such treatment. Oxygen should be given in the ambulance during transfer from home to hospital, and general practitioners should be encouraged to give oxygen to sick asthmatics whenever possible.

### $\beta_2$ Agonists

Nebulized administration of  $\beta_2$  agonists has now become established as first-line treatment of severe acute asthma [217]. A large dose of one of these preparations, nebulized in oxygen, is at least as effective as the same drug given intravenously but is associated with less unwanted effects [218–220]. The dose of intravenous salbutamol



required to achieve a better response than nebulized treatment is associated with unacceptable side-effects [221]. However, in one study of the early management of acute severe asthma in children, intravenous salbutamol was found to be more effective than when given by the nebulized route [222]. In most circumstances a combination of nebulized and intravenous administration of the same drug should be avoided; similarly, because of the unpredictable onset of activity of a subcutaneously injected  $\beta_2$  agonist, this route of administration should also be avoided. Large doses of salbutamol (5 mg) or terbutaline (10 mg) should be nebulized as initial treatment, since the actual amount of drug reaching the bronchi is unpredictable. In patients who have the most severe airflow obstruction, the amount of drug reaching their bronchi is likely to be less than in those with less severe disease and it is therefore illogical to give all patients the same dose of inhaled  $\beta_2$  agonist. The dose and frequency of administration should be tailored to disease severity and adherence to a strict drug-dose protocol must be avoided. Indeed, continuous nebulization may be successful in patients in whom repeated single treatments have failed [223]. Treatment with a nebulized  $\beta_2$  agonist is unlikely to result in worsening of hypoxaemia [224], but oxygen therapy should not be interrupted during treatment of the hypoxaemic patient. Therefore ultrasonic nebulizers and air compressors driving jet nebulizers should not be used in hospitals for the treatment of severe acute asthma. Aerosol therapy delivered by intermittent positive-pressure breathing has no advantages over simple jet nebulizer treatment [225]. The response to a large dose of a nebulized  $\beta_2$  agonist is rapid, and continued improvement of ventilatory function should not be expected to occur for more than 10–20 min [224,225]. Hence, if a patient remains unwell 10–20 min after this treatment, it should be repeated, possibly in combination with ipratropium bromide; in the very ill asthmatic, intravenous aminophylline should also be considered.

Large-volume spacers designed for use with the conventional MDI provide an alternative to the jet nebulizer for administration of large doses of  $\beta_2$  agonists in the treatment of severe acute asthma [226]. Spacer devices can be used for the treatment of severe acute asthma outside hospital. Face masks allow young children to use large-volume spacers.

Occasionally it is necessary to give therapy intravenously. Salbutamol (4  $\mu$ g/kg) or terbutaline (250–500  $\mu$ g) can be given by slow intravenous injection and also by continuous intravenous infusion.

### Anticholinergic agents

The quaternary ammonium compound ipratropium bromide is of limited therapeutic value in the treatment of chronic asthma but has an important role in the manage-

ment of severe acute asthma. The onset of bronchodilator action of this drug is considerably slower than that of an inhaled  $\beta_2$  agonist but it is as effective as salbutamol [227,228]. Because of the slow onset of action of ipratropium bromide it should not be used alone as primary treatment of a severe attack; when used in conjunction with a  $\beta_2$  agonist, there is evidence that this combination is at least as good as, or better than, either drug given alone [227–231]. The value of this combination therapy has been questioned [232–234], although its use is recommended for patients whose asthma does not respond well to initial treatment with a nebulized  $\beta_2$  agonist [1]. The dose of ipratropium most commonly used is 0.5 mg and there does not appear to be additional benefit if the dose is increased [235]. There are no data available to indicate how long ipratropium bromide should be continued in the treatment of severe acute asthma. However, it is unlikely that it needs to be used for more than 24 h in patients who respond satisfactorily to conventional therapy in the first few hours. Ipratropium bromide is usually given regularly every 4–6 h in combination with salbutamol or terbutaline.

### Xanthine derivatives

Aminophylline has been used for many years in the treatment of severe acute asthma. However, nebulized  $\beta_2$ -agonist therapy has replaced intravenous theophyllines as first-line treatment of severe asthma for reasons of efficacy and safety. Aminophylline is of value in the moribund asthmatic and in the less severely ill patient who does not respond rapidly to treatment with oxygen, parenteral corticosteroids and nebulized bronchodilator therapy. An aminophylline infusion is recommended in a dose of 0.5–0.9 mg/kg/h, or 750 mg over 24 h in small patients and 1500 mg over 24 h in large individuals if the weight of the patient is unknown [1]. In the very severely ill patient a loading dose may be necessary (250 mg by slow intravenous injection, preferably over 20 min), although this should be avoided in the patient known to be taking an oral theophylline preparation. Lower doses may be needed in patients with liver or heart disease and in those taking cimetidine and most quinolone and macrolide antibiotics. Higher doses may be appropriate in smokers. If intravenous aminophylline therapy is necessary for more than a few hours, the dose should be adjusted according to theophylline blood levels.

### Corticosteroids

The value of corticosteroid therapy in the management of severe asthma was first reported in 1949 [236] and confirmed by clinical trial in 1956 [237]. The value of these drugs in the treatment of the severely ill asthmatic has rarely been questioned [238] and their use should be

routine in all patients who do not rapidly respond fully to bronchodilator therapy [239,240]. Large doses of intravenous hydrocortisone or methylprednisolone are usually given empirically since short-course high-dose systemic corticosteroid therapy is rarely responsible for adverse effects, except in the diabetic or patient with cardiac failure. Very high doses of these drugs are probably not necessary [241,242] and might occasionally give rise to an acute steroid myopathy [243]. Occasionally, patients on such doses also develop steroid psychosis, requiring rapid reduction of the dose. Doses of hydrocortisone producing blood levels that exceed stress-induced physiological levels have been recommended [244], i.e. 3–4 mg/kg loading dose followed by the same dose by intravenous infusion every 6 h. However, standard empirical doses of 100 or 200 mg every 4–6 h are used most frequently, intravenous therapy being rapidly replaced with prednisolone in doses of 40 or 60 mg daily. Oral prednisolone is usually given immediately at the same time as hydrocortisone and may be as effective as intravenous therapy in all but the most extremely ill patients [245].

### Assisted ventilation

Assisted mechanical ventilation is rarely necessary but has to be used as a life-saving procedure in some patients who are either moribund on admission to hospital or deteriorate even though they have been treated as outlined above. The indications for assisted ventilation are difficult to define, since they range from the elective decision to ventilate because of lack of response to standard treatment in a patient who is becoming exhausted to the acute emergency resuscitation of the patient who has had a respiratory arrest. The generally accepted indications for the institution of mechanical ventilation include:

- 1  $P_{aCO_2}$  of more than 6.6 kPa (50 mmHg) and rising;
- 2  $P_{aO_2}$  of less than 6.6 kPa (50 mmHg) and falling;
- 3 pH of 7.3 or less and falling;
- 4 intolerable respiratory distress;
- 5 exhaustion because of lack of response to conventional treatment;
- 6 respiratory arrest;
- 7 cardiorespiratory arrest.

The clinically dramatic indications for assisted ventilation in asthma, such as respiratory arrest, are obvious, although mechanical assistance of breathing should also be considered in the less obvious emergency. Physical exhaustion, especially when associated with systemic hypotension, is a dangerous combination and when there is any doubt about the necessity for assisted ventilation the safest course of action must be to ventilate rather than to procrastinate. When a patient with severe asthma has to be ventilated, there is some controversy about the method of assisted ventilation that should be employed. The use of high inflation pressures can theoretically cause baro-

trauma, and the use of controlled hypoventilation carries the risks of prolonged assisted mechanical ventilation [246–249]. The debate about the advantages and disadvantages of adopting policies of planned hypoventilation or the more aggressive approach of trying to normalize arterial blood gas tensions as quickly as possible will continue, and the decisions will depend upon local expertise and facilities available. However, there appears to be no doubt about the dangers of therapeutic lavage of asthmatic patients requiring assisted ventilation [250].

### Inhalation delivery systems

Inhaled remedies have been used for centuries in the treatment of respiratory disorders and bronchodilator aerosols have been used for the treatment of asthma since at least 1935 [251]. In the early days, a number of ways were used to allow the inhalation of medicaments and aerosol inhalation was achieved by hand-held nebulizers driven by air generated by squeezing a rubber bulb. The conventional pressurized MDI was introduced into clinical practice as long ago as 1956 and its basic design has changed little in the last four decades.

### Pressurized metered-dose inhaler

The pressurized MDI is the most commonly prescribed inhaler. It consists of a canister and a plastic actuator. When the canister is depressed into the actuator a measured amount of aerosol is released, the amount of which is determined by the valve in the actuator into which the canister nozzle is seated. Within the canister is drug either as a suspension or as a solution in volatile propellants under pressure (approximately 303 kPa in the case of chlorofluorocarbon, CFC, propellants). The canister of most inhalers also contains a dispersant or lubricant to ensure accurate dose delivery by the valve during multiple actuations of the inhaler. When the valve is actuated, the propellants and drug leave the inhaler at high velocity. The propellants evaporate very rapidly as soon as they leave the canister and this 'flashing' breaks up the liquid stream into droplets that continue to evaporate as they move away from the valve. Because of the high velocity of the aerosol cloud, together with the anatomical structure of the upper respiratory tract and the physical characteristics of the drug particles, the majority of the drug impacts in the oropharynx even when the pressurized MDI is used efficiently. Less than 25% of drug reaches the lung [252,253].

The most efficient way of using a pressurized MDI is as follows [254].

- 1 Shake the canister thoroughly (after removing the mouthpiece cover).
- 2 Place the mouthpiece of the actuator between the lips.
- 3 Breathe out steadily.

- 4 Release the dose while taking a slow, deep breath in.
- 5 Hold the breath in while counting to 10.

These instructions appear to be simple but many, if not the majority, of adults cannot use a pressurized MDI efficiently if the only instruction they receive is the manufacturer's package insert [255–259]. Also, more than 10% of patients develop an inefficient technique with prolonged use of the pressurized MDI [255,259], the majority of these being those who had some difficulty in using the device when it was first prescribed [260]. The main problem experienced is the coordination of dose release during inspiration [259], although a significant number of patients cannot continue to inhale through the mouth when the propellants are released into the mouth ('cold freon effect') [259]. It is rarely possible to teach these patients how to overcome this problem unless a spacer attachment to the pressurized MDI is used. Young children and the elderly experience the greatest difficulties using the conventional pressurized MDI, and for many of these patients spacers or holding chambers have to be used with the pressurized aerosol or alternative inhalation devices have to be prescribed.

Until recently all pressurized MDIs used CFCs as propellants, but because of the effect of these compounds on the ozone layer 80 nations agreed to ban their use before the beginning of the twenty-first century [261]. In some Western countries this ban was brought forward to 1995, with a temporary exemption for medicinal aerosols. Alternative propellants, such as tetrafluoroethane, have been produced and are now in clinical use or undergoing clinical trials. It is likely that because of the enforced change in the contents of the pressurized MDI brought about by the CFC ban, the opportunity will be taken to change or reduce the amounts of lubricants/surfactants in these inhalers, since these have been shown to produce cough and bronchoconstriction in a high proportion of patients [187,192–194].

### Spacers or holding chambers

The principle behind the use of spacers is the fact that the drug aerosol cloud released from a pressurized MDI remains in suspension for many seconds before it is dispersed by gravity and other factors. Also the droplet size of aerosols is dependent on the distance from the actuator orifice. Experiments with tubes and holding chambers of different sizes led to the discovery that these devices could result in an increase in drug availability to the lungs and at the same time decrease the unwanted drug deposition in the oropharynx [262–264]. Large-volume spacers have proved to be of greater clinical value than small 'tube spacer' devices [263,265,266]. A one-way valve at the mouthpiece of a large-volume spacer enables it to contain the aerosol cloud before inhalation, and this overcomes the problem of coordinating dose-release and inhalation,

which therefore do not have to be synchronized when using spacer systems. The efficiency of spacer devices in terms of increasing pulmonary deposition of drug depends upon many factors, including their size, the presence or absence and characteristics of the one-way valve, the electrostatic charge of the plastics used to manufacture the device and the hygroscopic properties of the drug particles. The amount of drug available from the many different spacer systems varies enormously and it is recommended that each device be evaluated for each drug used [267–271]. Large-volume spacers decrease oropharyngeal deposition of drug and their use is recommended for inhaled corticosteroids in order to decrease systemic side-effects (if they are not inactivated by first-pass liver metabolism when swallowed) and also to minimize the risk of oropharyngeal candidiasis [1,182,272–276]. The use of spacers for inhalation of corticosteroids does not cause too much inconvenience, since most treatment regimens are twice daily, although bulky spacer devices are much less convenient for the 'as-required' use of a bronchodilator. Spacers are now most often used in the treatment of children with asthma. In adults their main use is when corticosteroid therapy via the pressurized MDI has to be taken in high dose [1]. However, they can be used as alternatives to nebulizers in chronic [277,278] and severe [226] asthma. Spacers do not decrease the amount of drug deposited in the region of the larynx and do not protect against dysphonia, the most common local side-effect of inhaled corticosteroids [187,251].

### Breath-actuated metered-dose inhaler

The conventional pressurized MDI has been made easier to use by making it breath-actuated. The canister is completely enclosed within the body of the actuator and, depending on the design, is primed by opening a hinged mouthpiece cover or lifting a latching lever on top of the device. When primed, the valve is actuated by a low inspiratory flow in the region of 30 L/min. These devices are easier to use than the conventional pressurized MDI [279,280] and can be triggered by patients with severe airflow obstruction [281].

### Dry powder inhalers

DPIs depend entirely upon the patient's inspiratory effort and are generally easier to use than the conventional pressurized MDI [260]. The first DPIs to be introduced were single dose (Spinhaler soon followed by the Rotahaler) and had to be reloaded with a cartridge/capsule containing micronized drug in a large particle carrier powder, usually lactose.

The second generation of DPIs carry multiple doses (range 4–200) and are more convenient than single-dose inhalers. The four-dose and eight-dose Diskhalers

have to be reloaded after all the foil blisters on the Rotadisk have been punctured; other devices such as the Accuhaler, which like the Diskhaler uses the aluminium foil blister system, are disposable after its 60 doses have been used. The multidose DPIs that use a drug reservoir from which drug is fed by gravity into the dosing mechanism, such as the Turbuhaler (Turbuhaler in the USA) and Klickhaler, contain up to 200 doses and are discarded when empty.

DPIs are less bulky than spacers and are as easy to use as the breath-actuated pressurized MDI, although some DPIs are less convenient because of the need to reload capsules/cartridges or discs frequently. Clinical comparisons of different DPIs indicate that patients prefer multidose devices to single-dose inhalers [282,283], and a meta-analysis of all available studies showed that 58% of 530 patients preferred a multidose DPI to the pressurized MDI [284]. The major drawback of DPIs is that their efficient use depends upon the patient being able to generate sufficient inspiratory flow to allow the drug to reach the lungs in therapeutic amounts. The various DPIs have vastly different inspiratory resistances, but there have been few comparisons of intrapulmonary drug deposition and clinical efficacy of these devices used at different inspiratory flow rates. This makes it difficult to give informed recommendations about the advantages and disadvantages of the numerous DPIs now available [260]. Children under the age of 6 years may not be able to generate sufficient inspiratory flow to use the Turbuhaler; the younger the child, the more likely this is the case [285]. It is known that the Turbuhaler is less efficient at an inspiratory flow rate of 30 L/min than at 60 L/min [285,286], and the Rotahaler has only about 10% of its maximum bronchodilator effect at inspiratory flow rates of 40 L/min [287]. Until direct comparisons of all DPIs have been made and data about optimal inspiratory flow rates are available, it has to be assumed that, unlike the pressurized MDI, the most efficient way of using a DPI is to breathe in through the device from residual volume as quickly and as deeply as possible. There is a need for more research on DPIs, especially with regard to the proportion of the dose reaching the lung, since this is extremely important when corticosteroid preparations are being inhaled. There is already evidence that the Turbuhaler is twice as efficient as the pressurized MDI for the inhalation of budesonide [288], while another study has suggested that another DPI is only about half as efficient as the pressurized MDI [253]. Immediately after DPIs are used for corticosteroid administration, gargling and mouth rinsing should be advised since this has been shown to decrease systemic effects from drug deposited in the oropharynx [289].

### Nebulizers

Nebulizers are of two types: jet and ultrasonic. Jet nebu-

lizers have widely differing characteristics with regard to the generation of particles within the respirable range [290] and the performance of individual nebulizers is influenced by many factors, such as the flow rate of the driving gas (air or oxygen), the nature of the drug solution or suspension, the fill-volume of the nebulizer chamber and, of course, the nebulization time [290–295]. For basic clinical purposes it is essential to be familiar with the characteristics of one nebulizer system, particularly the flow rate at which it functions most efficiently. For most clinical purposes jet nebulizers are more efficient than ultrasonic nebulizers. An ultrasonic nebulizer should be chosen for the administration of hypertonic saline to induce the production of sputum. For full details concerning the use of nebulizers the publication produced by the British Thoracic Society is recommended [296].

### Immunotherapy

The treatment of asthma by antigen injection goes back to 1911, before its allergic basis was described, and such treatment remains in widespread and often uncritical use in some countries [297]. This continued use without clear evidence of value, together with the success achieved by bronchodilator drugs, has given immunotherapy a reputation of unorthodoxy. Nevertheless, there is evidence of efficacy in certain cases and it would be a pity if further research in this subject were to cease [298,299].

The principle of immunotherapy is to give initially small, then increasing, doses of pure antigen to a patient who is sensitive to that antigen in the hope of producing interference with the IgE-antigen-mediated reaction responsible for the symptoms. Whether this effect, when it occurs, is due to IgG blocking-antibody formation, a decrease in the sensitivity of mast cells to challenge or some other mechanism is not known [300,301]. Success of such therapy might therefore be expected to depend on selection of a patient in whom the symptoms are entirely or very largely due to the antigen in question and on the availability of a sufficiently pure form of the antigen in the vaccine. In keeping with these criteria, there is no evidence of the efficacy of immunotherapy in non-atopic asthma, asthma associated primarily with infection or in asthma with multiple allergic factors. The use of blunderbuss-type vaccines is strongly to be condemned, as is the use of vaccines in circumstances where treatment for anaphylactic reactions is not readily available. Indeed, use of such vaccines outside hospitals has been effectively prohibited in the UK [297].

There is some evidence of efficacy of immunotherapy in the treatment of hay fever and asthma associated with grass pollen and ragweed sensitivity, rhinitis and asthma associated with house-dust mite sensitivity, and similar symptoms related to exposure to cats and laboratory animals [302–308]. However, it has to be admitted that

several equally well-controlled studies have failed to show differences between groups treated with active and placebo preparations, and a strong placebo effect has been present in most investigations [309,310]. It is to be expected that research will lead to the production of increasingly pure vaccines that, in turn, will increase the range of allergies treatable and the overall efficacy of the treatment.

At present, it is recommended that treatment be reserved for those few patients with clear evidence of sensitivity to house-dust mites or grass pollen (or ragweed pollen) in whom drug therapy proves ineffective or unacceptable. Such patients usually have conjunctival and nasal symptoms as well as asthma. Careful explanation of the likely outcome is advisable before starting: it is reasonable to predict an even chance of some improvement and a small chance of a big improvement. Epinephrine (adrenaline) should be available for anaphylaxis and the patient should remain under observation for 2h after the injection, although almost all reactions occur immediately. If the injections cause worsening of the asthma or any other suspicious symptoms, it is very unwise to continue the course. Use of such treatment for other allergic factors in asthma is best confined to allergy specialists engaged in research.

## Miscellaneous problems in asthma management

### Bronchopulmonary aspergillosis

The clinical manifestations of this syndrome vary from asthma associated with very occasional episodes of pulmonary eosinophilia to a severe progressive condition leading to lung fibrosis and bronchiectasis (see Chapter 34). Treatment should be judged by the response of the individual and not on the basis of studies that have shown average effects or lack of effects on groups of patients. Thus it is perfectly possible to maintain patients with milder manifestations on inhaled bronchodilators and inhaled steroids, so long as they are taught to treat exacerbations early with courses of high-dose oral steroids [196]. Asymptomatic episodes of pulmonary eosinophilia do occur in patients not on long-term oral steroids but only very rarely. If these are occurring, they may be detected at annual clinic visits by evidence of radiographic and functional deterioration. Such episodes, or frequent symptomatic attacks, or persistent presence of hyphae in the sputum require long-term oral steroids, again with increase in dose to cover exacerbations. It is in such patients, where the persisting antigenic stimulus due to survival and germination of the fungus in the airways leads to chronic disease, that consideration should be given to eradication of the organism. Newer oral antifungals are available (see Chapter 21) and promising results

have been reported with ketoconazole [311]. In severe cases where there is a risk of high-dose steroids leading to invasive disease, a course of amphotericin should be considered. A patient treated successfully with antifungal drugs would of course still remain sensitized to *A. fumigatus* and therefore liable to an exacerbation next time adequate numbers of spores are present in the air. Trials of pulsed antifungal therapy are ongoing, the aim being to eradicate the fungus with the first treatment and then to prevent recolonization with shorter courses of treatment every few months. The long-term outlook, and the effect of antifungal treatment on it, must therefore remain uncertain, although experience suggests that many such patients can be maintained well and without deterioration in lung function for many years on routine treatment of chronic asthma. It is probable that early diagnosis, before significant lung damage has occurred, is the secret of successful management.

### Pregnancy

Many young female patients with asthma are understandably anxious about the effects of their illness on pregnancy and vice versa. Three problems merit discussion: the effects of asthma on pregnancy, the effects of drugs on the child and the chances of having an asthmatic child. The course of asthma during pregnancy is impossible to predict but usually is no different to that when the patient is not pregnant, improving in a few cases and requiring additional treatment in others [312,313]. It is wise to reassure the patient and to make oneself available for help with attacks should they occur. It is possible that very high steroid doses may have a deleterious effect on the early fetus, although it is likely that a severe asthma attack could have similar consequences. Either or both seem to increase the risk of mild pre-eclampsia [313]. The patient should be encouraged to use steroids in adequate dose early, so as to avoid the large doses that might be required in hospital. The other drugs used in asthma are not known to be toxic to the fetus, although clearly it is wise to confine treatment to inhaled drugs as far as possible except during acute exacerbations. Finally, patients who have had severe asthma are often worried that their children will suffer the same problem. It has to be admitted that this is possible, though the severity of asthma in several affected members is usually very different. There is no good genetic reason for an asthmatic patient to deny herself children.

Having discussed these matters, the management of asthma in pregnancy should be exactly as in the non-pregnant state. Care should be taken to explain this to the patient, who has a natural tendency to withdraw treatment and avoid drugs for the exacerbations that may ensue as a result. As always, time spent explaining this to the patient is time well spent.

## Heart disease

The asthma patient who develops angina or hypertension is at risk of having  $\beta$ -blocking drugs prescribed and thus being made worse, sometimes acutely. Alternatives for hypertension are diuretics, methyldopa, reserpine, captopril, prazosin or nifedipine. For angina, vasodilators such as nitrates, verapamil or nifedipine are acceptable. From the cardiologist's point of view, drugs used in asthma may be undesirable;  $\beta_2$  agonists in high dose may worsen angina and steroids commonly promote fluid retention and hypertension. Judgement is therefore necessary in deciding on an optimal dose.

## Surgery

The majority of patients with asthma have no problems even with thoracic surgery, so long as they, the surgeon and the anaesthetist are adequately prepared. The patient should be treated vigorously for a week or two preopera-

tively in order to achieve normal or near-normal flow rates, and appropriate inhaled medications continued over the postoperative period. Corticosteroid cover should be provided if the patient is likely to have suppressed adrenal function and acute exacerbations of asthma should be treated along routine lines.

## Other problems

An asthmatic on oral corticosteroids who develops tuberculosis and is given rifampicin probably needs to double the dose of steroid to obtain the same effect, because of drug interaction. Senile, psychotic or retarded patients cause particular problems with drug compliance. Treatment should be kept as simple as possible and supervised by a nurse or relative. Those requiring long-term oral steroids may sometimes be most reliably treated with depot injections. Visually impaired patients should be provided with inhalers that have different shapes for different functions.

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# REACTIVE AIRWAYS DYSFUNCTION SYNDROME

ANTHONY SEATON

Exposure of the respiratory tract to irritant gases or fumes may lead to one or more of a number of adverse consequences, although in the majority of cases no long-term harm ensues. To some extent, the site of pathological change is determined by the solubility of the gas, in that the most soluble exert their effects proximally in the nose, throat and main airways while the less soluble cause damage more distally in the acinus. These different responses and the agents that most frequently cause them are discussed in Chapter 54 and summarized in Table 36.1. It is important to recognize that in practice such responses may occur in combination and mixed syndromes, not fitting neatly into any one classification, are quite common.

Of all the possible lung responses, the one most frequently seen is an asthmatic type of reaction that has acquired the name of reactive airways dysfunction syndrome (RADS). Asthma has been recognized for many years as an occasional consequence of accidental exposure to high concentrations of airborne irritants, and such exposure was included by Gandevia in 1970 [1] as one of the causes of occupational asthma, although he did not regard this as true asthma. From the late 1970s a series of papers reported the development of asthma after exposure to sulphur dioxide, ammonia and chlorine [2–5], and in 1985 the term RADS was coined to describe the syndrome and to draw attention to it as a response to a wide range of toxic inhalation episodes [6].

## Definition

There is an obvious danger in defining any disease, since it results in an arbitrary cut-off between health and normality in what is often a continuum. It thus leads to exclusion of individuals with obvious ill-health who do not quite fit into the definition. Definition should therefore be specific to the purpose for which it is intended and should not be used for other purposes. When Brooks and colleagues [6] first defined RADS, they correctly indicated the criteria that they had used to identify their cases in

order to clarify their methods for the reader. These criteria were:

- 1 a documented absence of previous respiratory complaints;
- 2 onset of symptoms occurring after a specific exposure incident or accident;
- 3 exposure to a gas, smoke, fume or vapour present in high concentration and with irritant properties;
- 4 onset of symptoms occurring within 24 h of the exposure and persisting for at least 3 months;
- 5 symptoms simulating asthma, with cough, wheeze and dyspnoea;
- 6 pulmonary function tests 'may show airflow obstruction';
- 7 other pulmonary disease ruled out.

Since that time there has been debate about the possibility of RADS occurring after repeated or chronic relatively low exposures [7]; it is also clear that someone with pre-existing asthma or airways disease may worsen after an exposure to irritant chemicals [8]. The above criteria should not therefore be looked upon as a definition of the disease. Rather, it is appropriate to define RADS for clinical purposes simply and broadly as non-allergic asthma occurring following exposure to airborne irritant chemicals. For a discussion of the definition of asthma see Chapter 34.

## Clinical features

In the classical case, a patient who has been well previously is exposed to a spill of irritant chemical, for between seconds and hours, and within the next few days develops cough, wheeze and breathlessness. The symptoms at first are often rather mild and may be dismissed by the patient and doctors as unimportant, but as time goes by they become more rather than less troublesome [6,9]. Cough is often the most prominent symptom and may cause disturbed sleep. The patient usually complains that laughing, raising the voice, exertion and exposure to smoke or strong scents precipitates cough and wheeze. Severe

**Table 36.1** Syndromes associated with exposure to irritant substances.

Site of lesion	Pathological response
Nose	Rhinitis
Larynx	Acute laryngitis, laryngeal oedema
Trachea	Tracheitis
Bronchi	Acute bronchitis, asthma, irritable airways
Bronchioles	Obliterative bronchiolitis
Alveoli	Pulmonary oedema

attacks of asthma may occur, although these are usually confined to the first few weeks after the exposure.

Lung function testing often, though not always, shows a reduction in forced expiratory volume in 1 s (FEV<sub>1</sub>) and an increase in residual volume. The airflow obstruction is usually partially reversible. A methacholine challenge test would be expected to be positive, and this has been viewed by some as a necessity for making the diagnosis [8,10]. In general, diffusing capacity is normal, although different patients may show different patterns of abnormality in keeping with the combination of syndromes that follow toxic gas exposure [11]. The chest radiograph is normal in the absence of pulmonary oedema.

As time passes, personal experience suggests that the majority of patients find their symptoms less troublesome, though adequate follow-up studies unclouded by litigation issues are few. One such study reported the examination and lung function testing of 20 patients up to 12 years after exposure to a spill of chlorine in a pulp mill [12]. All had suffered acute symptoms including dry cough and none had been treated with corticosteroids. In general, they had shown an obstructive pattern of lung function immediately after the episode, with raised residual volume. Thereafter, the FEV<sub>1</sub> improved initially and then showed a slow decline, while the residual volume progressively declined, suggesting that the long-term consequences were not trivial and that some permanent damage to small airways had occurred. In another study of 64 workers exposed repeatedly to chlorine over several months in another pulp mill, 58 had symptoms, 16 airflow obstruction and 29 bronchial hyperreactivity when examined 18–24 months after exposure had ceased [8].

Because of the paucity of good long-term studies, it is necessary to rely on personal experience to comment on the outcome and this is inevitably coloured by one's practice and local referral patterns. The large majority of workers exposed to irritant gases or fumes never present for specialist care and make a full recovery after a few hours or days of coughing and perhaps a visit to the local accident department, as indicated by the relatively small proportion of those subjects reported by occupational

physicians to the SWORD project (see below) who develop asthma [13]. Those seen by a specialist present the more typical features described above and are usually treated for asthma with satisfactory results. They slowly recover and can often stop their medications over the course of a couple of years. However, some present more severe symptoms, never respond adequately to anti-asthma medication and become progressively more breathless with irreversible airflow obstruction; these patients fall into the classification of obliterative bronchiolitis (see Chapter 29). Between the two extremes are a few patients who continue with persistent and typical asthma.

In the author's opinion, the chest physician should keep an open mind about the possibility of a similar syndrome occurring as a response to repeated lower-dose exposures to irritant fumes or gases. Recent studies have confirmed that cigarette smoking is, after a family history of atopic disease, the most important risk factor for adult-onset wheezy illness [14]. It would not be surprising if similar consequences occasionally followed long-term exposure to other irritants, and the author's experience suggests that this is so. Several reports in the literature support this view. For example, Kippen and colleagues [7] described 32 patients seen in an occupational clinic with asthma, of whom seven had classical RADS while 10 had a similar syndrome following low-dose exposure on a frequent basis. Chia and colleagues [15] showed that regular fire-fighters were more likely to show increased airway reactivity after experimental exposure to smoke than were recruits, suggesting that recurrent exposure had rendered them more susceptible. The construction workers described by Bh  rer and colleagues [8] who developed bronchial hyperreactivity from working in a pulp mill gave a history of recurrent exposures to chlorine rather than a single severe exposure. All these examples suggest that increased airway reactivity may follow a wide range of types of airway irritant damage apart from that caused by inhaling tobacco smoke.

## Frequency

The best indication of the frequency of the syndrome to date comes from the UK SWORD project, in which respiratory and occupational physicians report clinical diagnoses of occupational and work-related diseases [16]. Among these are two categories, inhalation accidents and occupational asthma, the latter being divided into allergic and RADS. Approximately 180 inhalation accidents are reported each year, leading to an estimated annual incidence of about 230 [17]. This probably represents a minimum figure, as it is likely to exclude many of those treated by non-respiratory physicians and of those occurring in industries without an occupational physician. One study of these reports has shown that of

623 patients, 50 developed asthma lasting for a month or more [13]. Among 47 of these cases in whom data were available, 34 were confirmed as having developed asthma as a consequence of the exposure. Thus, some 5–6% of people reported as having had an exposure to toxic gases or fumes in the UK seem to develop asthma. In addition, among the reports of occupational asthma, some 15% appear to be ascribed to irritants rather than to allergens, suggesting that around 110 such cases are reported each year. In total, therefore, about 150–200 patients develop asthma severe enough to be reported to the SWORD scheme each year, from a total UK workforce of about 20 million, or 1 per 100 000 per annum. This might be regarded as a minimum incidence of the condition.

In a survey in 1978 by the US Social Security Administration, a question was asked about work-related ill-health. The survey was biased towards people with disabilities. Of the 6000 respondents 7.7% said they had asthma, most of whom reported a physician diagnosis [18]. This prevalence was roughly double that recorded in a contemporary national health survey. Of those with asthma, 15% attributed it to bad working conditions. These would have included many with true allergic occupational asthma but presumably some had asthma due to irritants. If this proportion approximates to that in the SWOKD study, it suggests that some 2 per 1000 respondents might have had RADS. In view of the deliberate bias in sampling towards disabled people, this is a substantial overestimate of the prevalence in the working population. In a survey in the UK in 1990, a random sample of adults in 60 000 households was asked if they had any illness that they related to their work [19]. From the responses it was estimated that about 30 000 people believed that they had work-caused asthma, and on the same 15% basis this suggests that some 5000 may have RADS, or 2–3 per 10 000 of the current workforce.

In practical terms for those who see patients with asthma, it has been reported that of 154 patients referred to an occupational medicine clinic with a possible diagnosis of occupational asthma, the diagnosis was confirmed in 59, in 10 of whom it had been induced by high-dose exposure to irritant chemicals [20]. This experience tallies with that of the SWORD project in suggesting that some one in five or six people with occupational asthma have it as a consequence of exposure to irritants rather than sensitizers.

## Causes

On reading the literature one is struck by the wide range of exposures reported as having led to RADS, and personal experience supports this. In the original paper by Brooks and colleagues [6], the illness was reported after exposure to uranium hexafluoride, floor sealant, ammonia, smoke,

and various fumigating and surface coat-removing substances. The most common reported causes are spills of strong acid and alkali, escape of chlorine and ammonia, and sulphur dioxide. However, any irritant smoke or fume seems able to initiate the process, and it is not uncommon to see patients with it after inadvertent mixing of household cleansing chemicals. Some well-known sensitizers, such as isocyanates, are also irritants in high concentrations and exposures may lead to either RADS or true sensitization [21].

## Pathology

There are few reports of the pathology of RADS. In the original description, bronchial biopsies in two cases showed some epithelial desquamation and primarily lymphocytic inflammation [6]. More recently, Gautrin and colleagues [22] have reported on the bronchial biopsies in five subjects with RADS, in whom they showed focal epithelial desquamation, squamous cell metaplasia, some subepithelial fibrosis, thickening of the basement membrane and mainly lymphocytic inflammation. Bronchoalveolar lavage fluid showed mainly lymphocytes. They considered these changes to be consistent with the generally reduced reversibility and lability of the airflow obstruction in such patients compared to those with sensitization, and therefore concluded that the two types of occupational asthma are pathologically distinct.

## Management

There are no clear guidelines for either acute or long-term management of RADS. Since airway inflammation is the basis of the initial pathological damage, it would seem sensible to treat patients who are symptomatic following acute irritant exposure with high-dose oral corticosteroids. Once RADS has developed, it is usual to treat it along conventional lines for asthma, and partial reversibility is to be expected. Progressive irreversible obstruction suggests obliterative bronchiolitis and in these circumstances high-dose steroids should be continued until it becomes apparent that no benefit is occurring.

In the majority of patients treated personally, slow improvement from RADS has occurred, the need for inhaled steroids and bronchodilators progressively diminishing. Ultimately, most are able to lead a normal life with only intermittent episodes of wheeze provoked by infections or further exposure to irritants. Long-term oral steroids have not been of benefit in either those with RADS or those with obliterative bronchiolitis.



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# HYPERSENSITIVITY LUNG DISEASES

ANTHONY SEATON

The history of hypersensitivity lung diseases goes back to 1932, when Campbell [1] described acute respiratory symptoms in farmers after work with hay and Tower and colleagues [2] described similar symptoms in maple bark peelers. The association of the conditions with inhalation of microbial spores was recognized and, in the case of maple bark disease, it was speculated that the pathogenesis might be a form of hypersensitivity reaction to *Cryptostroma corticale*. Farmer's lung was subsequently shown to be due to the inhalation of spores of thermophilic actinomycetes (now classified as bacteria) and of species of *Aspergillus*. The finding of precipitating antibody to such organisms led to the concept that the disease was an example of a pulmonary type 3 allergic reaction, although study of lung biopsies, animal models and bronchoalveolar lavage (BAL) fluid has shown that cell-mediated reactions are also crucial to the development of the condition.

Study of the pathogenesis of farmer's lung led to considerable interest in other possible causes of hypersensitivity pneumonitis; bagassosis had been described (as a bronchiolitis) in 1946 [3] and it became apparent that this disease was similar in aetiology to farmer's lung. The occurrence of similar syndromes in response to animal antigen was recognized when bird fancier's lung was described in 1960 [4,5], while more recently sporadic examples of a similar condition have been described in response to exposure to certain chemicals of relatively low molecular weight [6–8]. A very large number of causes, mostly related to inhalation of fungal spores, have been recorded and undoubtedly more remain to be described.

It is important to recognize that the syndrome of hypersensitivity pneumonitis covers a range of reactions, varying from the classical severe acute episodes of farmer's lung to a much more chronic illness such as occurs most frequently in response to bird antigen. In addition, variations on the theme occur in people exposed to aerosols from air conditioners and humidifiers, to dust in grain silos and to sewage sludge. These other condi-

tions are discussed further in Chapter 54. Moreover, very similar reactions may occur in response to treatment with certain drugs and these are discussed in Chapter 55.

## Clinical features

The classical acute presentation occurs mainly in individuals exposed to high doses of microbial spores, as seen typically in farmers feeding cattle with mouldy hay [9,10]. The onset of symptoms is about 4–9 h after exposure, with chills, dry cough and an influenzal feeling. Rigors may occur and the patient notices breathlessness on normal exertion. Severe attacks may result in profound dyspnoea but in most cases general malaise is the predominant symptom. The main findings on examination are repetitive mid- and late-inspiratory crackles and tachypnoea. Polyphonic wheezes may be heard and should not deter one from making the diagnosis. Precipitating antibodies are commonly found in the blood.

Such acute attacks usually settle after 48 h. However some episodes may be much more persistent and the patient may remain ill and breathless for several weeks. In very rare instances the acute attack may be fatal [11]. Another variant, related to the removal of mouldy grain from the tops of silos prior to emptying the silage, presents with cough, fever, chest tightness, malaise and headache about 2–8 h after exposure [12,13]. Crackles are less frequent and precipitins are absent. This syndrome has been called mycotoxicosis or organic dust toxicity. However, despite differences in immunopathogenesis, its similar aetiological, clinical and pathological features to farmer's lung suggest that it should be regarded as a variant of that form of hypersensitivity pneumonitis.

At the other extreme of the spectrum of clinical presentation is the usual response to budgerigar (parakeet) antigen. Such patients present with insidious malaise, breathlessness, unproductive cough and sometimes loss of weight, often over months or even years [14,15]. Again, repetitive inspiratory crackles are the characteristic physical sign. Polyphonic wheezes may also occur and, in the

more chronic cases, a high-pitched, short, late inspiratory squeak is often heard [16]. This sign, which also occurs in other chronic pulmonary fibroses and in rheumatoid bronchiolitis, usually follows an inspiratory crackle and is probably caused by vibration in the wall of a bronchiole as it opens following abnormal closure. The presence of such signs of airway disease serves as a reminder that so-called allergic alveolitis affects bronchioles as well as alveoli.

A proportion of patients with allergic alveolitis of any sort may progress to a chronic form of the disease, characterized particularly by increasing exertional dyspnoea over years [9,17]. Inspiratory crackles are usually present but some of these patients may develop the clinical, radiological and physiological features of generalized emphysema. Patients with chronic allergic alveolitis may progress to fatal cardiorespiratory failure [11]. Finger clubbing is not a feature at any stage. In contrast, some patients who continue to be exposed to antigen despite medical advice do not progress to chronic disease and may even show evidence of spontaneous desensitization.

In most patients with allergic alveolitis, the most important diagnostic clues come from the history and the finding of inspiratory crackles. Acute episodes bear a clear relationship to exposures to antigen, such as mouldy hay, pigeons or work in maltings. If a more insidious type is suspected, attention should be paid in history-taking to exposure on a regular basis to known causes. Periodicity of symptoms is important; in Japan, *Trichosporon cutaneum* commonly grows in damp wooden houses and sporulates in the warm summer temperatures, causing outbreaks of seasonal alveolitis [18]. Patients with budgerigars improve when they (or the budgerigars) leave home for a while, and work-related symptoms may improve over holidays.

Allergic alveolitis may occur at any age; children who help their parents on farms or in pigeon lofts or who are exposed to antigen in the house may present with the disease. In several surveys cigarette smokers have been shown to be less susceptible than non-smokers [19,20].

## Radiographic features

In acute episodes, the chest radiograph commonly shows a bilateral, diffuse, micronodular infiltrate, usually denser towards the hila (Fig. 37.1). An irregular and linear infiltrate may also be present in the lower zones. In severe attacks it may mimic acute pulmonary oedema, *Mycoplasma* pneumonia or pneumonitis due to inhalation of toxic gases, although it should be noted that in some of the precipitin-negative cases occurring in workers clearing the tops of silos the radiograph remains normal even when the systemic illness is quite severe. The changes usually resolve rapidly on removal from exposure and treatment with corticosteroids. As mentioned above, in

some cases resolution is slow, taking several weeks and giving rise to diagnostic difficulties. If the patient is a farmer, silo-filler's lung (pneumonitis due to nitrogen dioxide) needs to be considered in the differential diagnosis and lung biopsy may be necessary. *Mycoplasma* or other atypical pneumonia may also be confused clinically and radiologically, especially as such patients occasionally produce false-positive precipitating antibody to farmer's lung antigens [21].

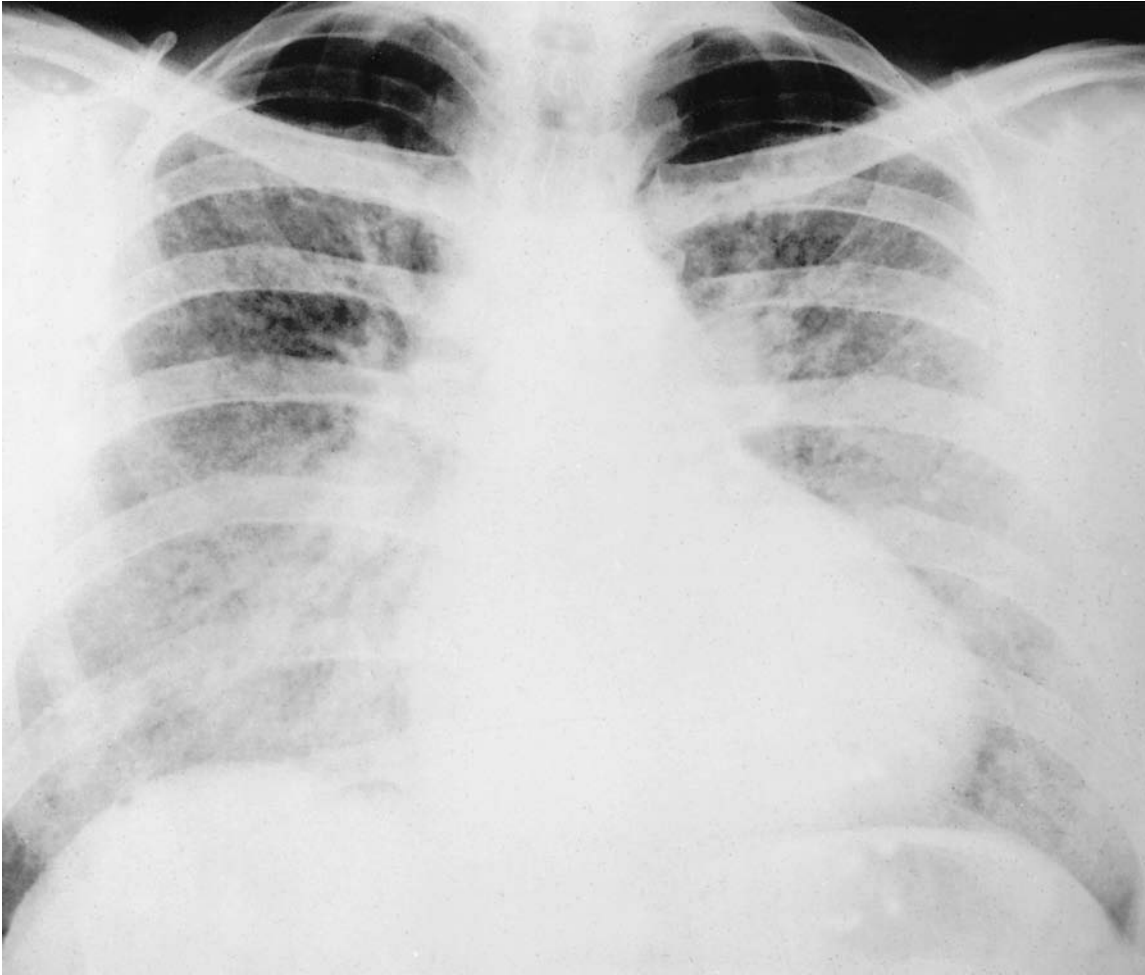
In less acute cases, the radiographic signs may be more subtle and sometimes even absent. A very sparse micronodular infiltrate, perhaps indistinguishable from a normal film, should not prevent the diagnosis in the presence of an appropriate history and the finding of inspiratory crackles. Some patients, particularly those with disease related to inhalation of chemicals, may present with dense, patchy consolidation easily confused with an infective pneumonia. The first patient described as having alveolitis due to isocyanates presented in this way [6] (Fig. 37.2).

Chronic allergic alveolitis may progress to pulmonary fibrosis, which characteristically affects upper zones predominantly. Coarse, irregular shadows extend from hila to apices with attendant bronchiectatic change, retraction upwards of pulmonary vessels and, often, well-marked emphysema in the lower zones (Fig. 37.3). In some of these patients the fibrosis may be invisible radiologically, the appearances being indistinguishable from those of cigarette-related emphysema [9]. In the more usual type, the radiological appearances resemble those of old tuberculosis, chronic sarcoidosis, ankylosing spondylitis lung or accelerated silicosis. High-resolution CT may assist in the differential diagnosis by showing a peribronchiolar or centriacinar distribution of nodular change [22].

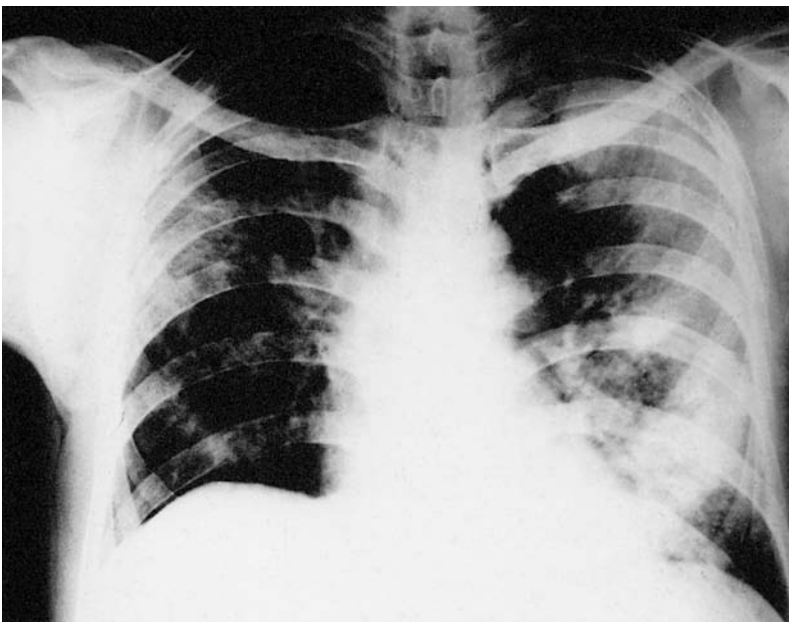
## Pulmonary function

The typical changes in an acute attack are reductions in lung volumes, carbon monoxide diffusing capacity and  $PO_2$  [9,23]. In milder cases, only a slight fall in diffusing capacity and  $PO_2$  during exercise may be found. If compliance is measured it is found to be decreased, as would be expected. The reduction in diffusing capacity is a more sensitive test of acinar disease than the chest radiograph, and in the more subacute syndromes (e.g. in people exposed to budgerigars) it is often present when the radiograph is normal. Sometimes the patients with the so-called organic dust toxicity syndrome or mycotoxicosis have normal chest films and lung function, showing only slight oxygen desaturation [13].

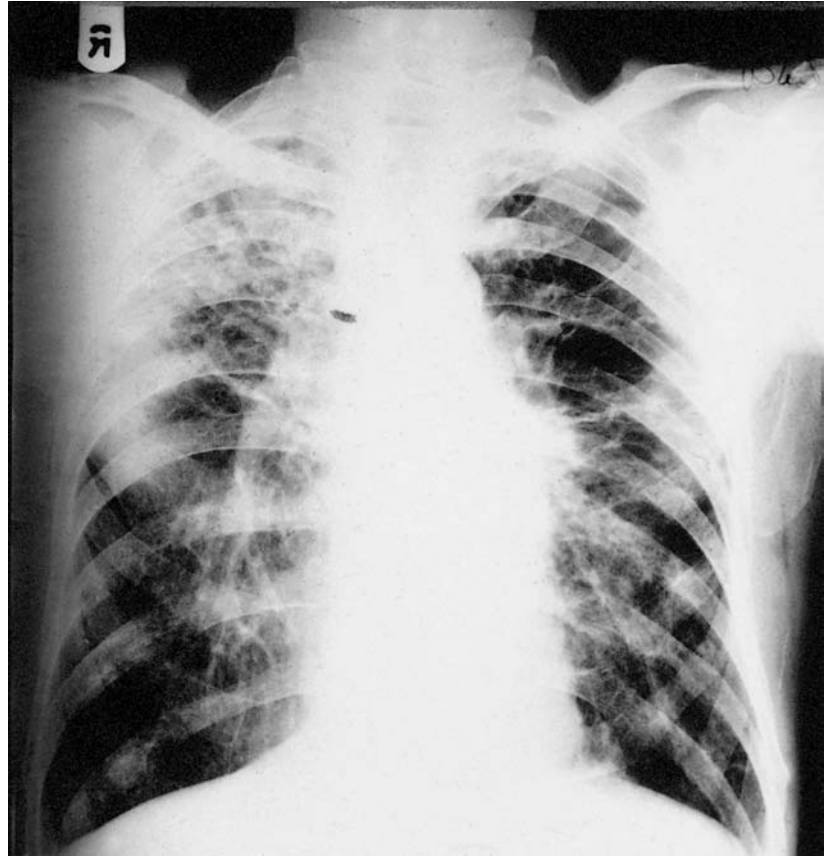
In most patients with acute episodes the volumes, codiffusion and  $PO_2$  abnormalities recover over a few days or weeks, though increases in diffusing capacity may still occur after a year [24]. However, in those with subacute or chronic disease recovery may be slow and incomplete,



**Fig. 37.1** Diffuse bilateral ground-glass appearance of acute farmer's lung.



**Fig. 37.2** Dense pneumonic infiltrates throughout left lung and in right mid zone. This proved to be an acute hypersensitivity reaction to toluene diisocyanate.



**Fig. 37.3** Irregular upper zone fibrosis in patient with chronic farmer's lung.

leaving the patient with chronic impairment of function. Evidence of airflow obstruction may be present in a number of these patients, not always explicable on the basis of smoking or concomitant asthma [25]. While bronchiolitis is the likely explanation in some, up to one-third of patients with well-developed chronic allergic alveolitis develop a pattern of irreversible airflow obstruction, reduction in diffusing capacity and pathological emphysema [9,26,27].

### Pathology

In keeping with the inhalational route of exposure, the pathological changes in acute allergic alveolitis are most marked at the centre of the acinus and least at the periphery [10,27]. When a biopsy shows non-specific changes, this pattern of distribution may be an important clue as to aetiology. In the very acute cases described as mycotoxicosis, intense inflammatory change with polymorphonuclear leucocytes has been noted in bronchioles [12], although one such patient studied personally has also shown typical non-caseating granulomas. In typical acute cases, the alveolar inflammation extends to the bronchioles where it is somewhat less marked, and is usually characterized by a lymphocytic and granulomatous reaction. Sometimes this may occlude the smallest airways. In

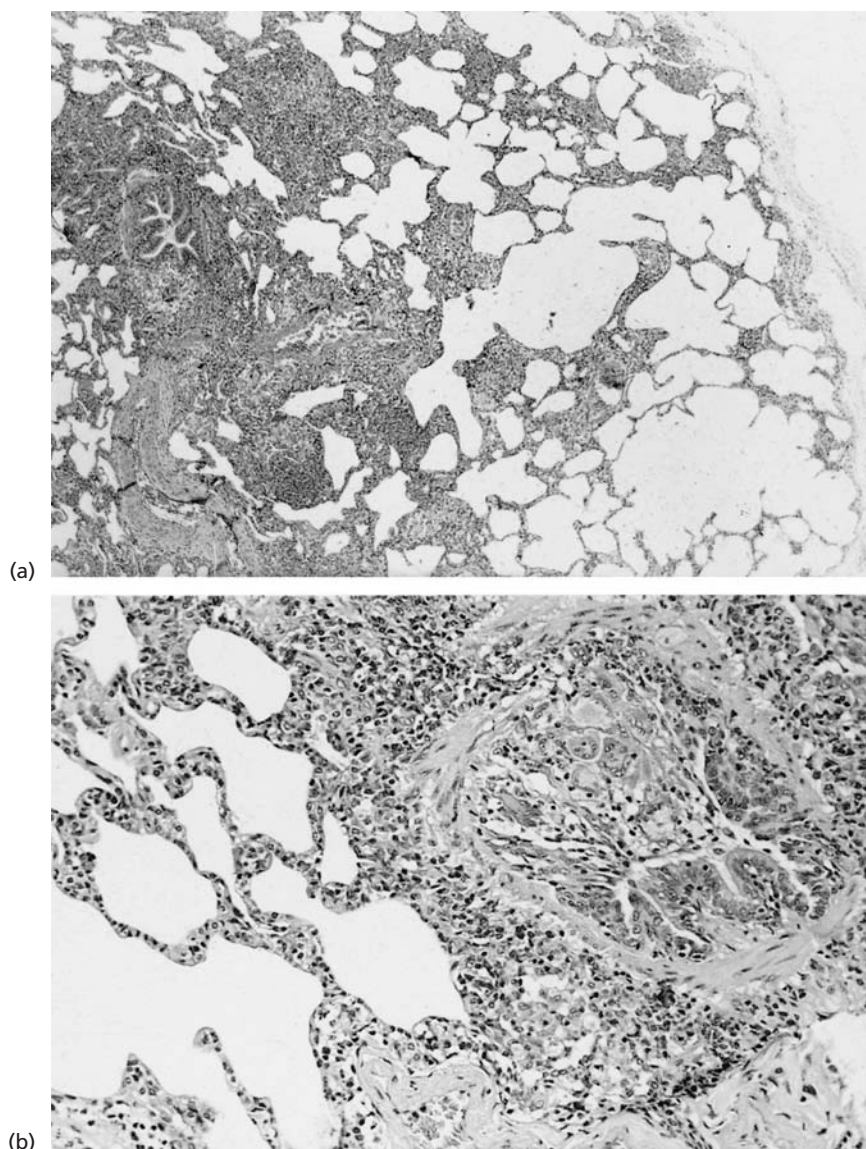
addition, non-caseating granulomas including Langhans-type giant cells, lymphocytes and plasma cells are found predominantly at the centre of the acinus (Fig. 37.4). The alveolar walls are thickened, with oedema and chronic inflammatory cells; foamy macrophages may fill the alveoli. Fibrin deposition may be demonstrated and, depending on the length of the illness, it is not uncommon to see some mature collagen in alveolar walls. In contrast to immune complex disease, vascular changes do not normally occur. In a unique case, a lady with allergic alveolitis due to dust from sea snail shells was shown to have deposition of amyloid in her alveolar septa [28]. Ultrastructural studies show swelling of alveolar epithelial cells and disruption of basement membrane in association with the inflammation [29].

In chronic disease, the granulomatous changes may disappear. The lungs become fibrosed and secondary cystic change due to bronchiolectasis occurs. The fibrosis is usually more marked in upper zones and secondary emphysema is common. Secondary vascular changes reflect the pulmonary hypertension.

### Pathogenesis

Despite its relative rarity and the ease with which the condition may be treated and prevented, the pathogenesis of



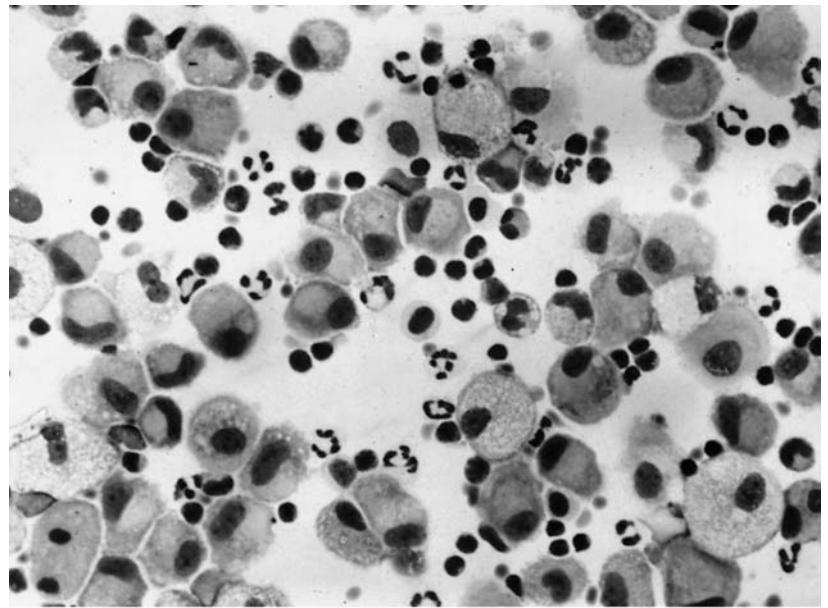


**Fig. 37.4** Histological appearances of acute allergic alveolitis: (a) centriacinar distribution of mononuclear cell infiltrate with poorly formed granulomas (haematoxylin & eosin  $\times 25$ ); (b) higher power demonstrating granuloma within the bronchiolar wall as well as the interstitial mononuclear cell infiltrate (haematoxylin & eosin  $\times 115$ )

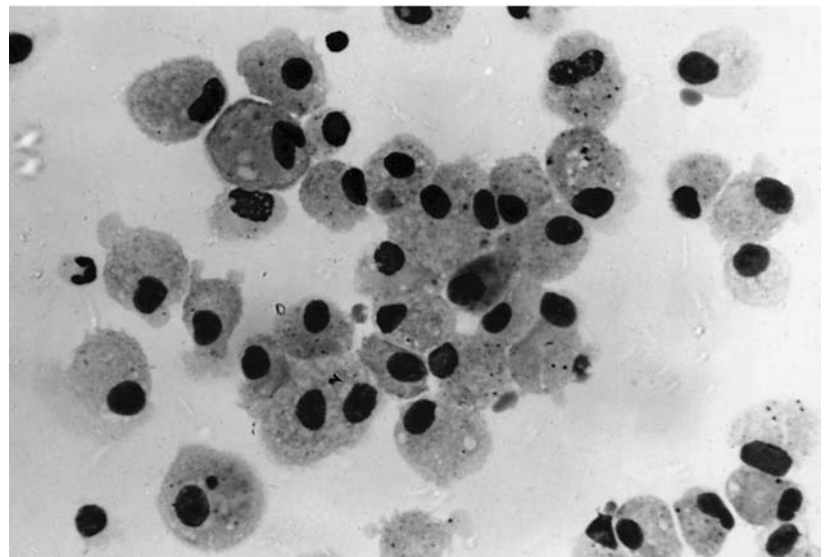
hypersensitivity pneumonitis has attracted a huge amount of interest among immunologists [30]. Nevertheless, the mechanisms of the disease remain obscure. The earliest concept of pathogenesis was that allergic alveolitis was an example of a type 3, complement-fixing, immune complex reaction in the lung [31]. In support of this concept was the frequent finding of precipitating antibodies to the inhaled antigen in the blood of farmers, pigeon fanciers and others with the disease. However, many patients, especially among those exposed to budgerigars, did not show such antibodies, while they were found in a surprising number of exposed but well subjects [32,33]. Moreover, the histopathological features suggested that the aetiology was more complex, since vasculitis was usually absent and granulomas were present. Interest therefore started to centre on cell-mediated reactions and, in particular, on the roles of macrophages and lympho-

cytes [34]. The popularization of the technique of BAL allowed study of the cellular reactions within the acinus, including studies of the functional status of cells so obtained. Even so, the precise immunological or para-immunological mechanisms have still not been clearly defined.

Features that seem to be usual in patients with allergic alveolitis are a response to inhalational challenge with the offending antigen in terms of fever, polymorphonuclear leucocytosis with fall in total blood lymphocyte count, and evidence of impairment of acinar lung function [35]. Bronchial washings in patients with active allergic alveolitis (Fig. 37.5) show an increased proportion of lymphocytes up to about 80% of the total count and averaging about 60% [36,37]. Studies of T-cell subtypes in BAL fluid have shown findings similar to those in peripheral blood, with a relative excess of suppressor CD8 over helper CD4



(a)



(b)

**Fig. 37.5** Bronchoalveolar lavage from (a) patient with allergic alveolitis showing large numbers of lymphocytes together with macrophages and some polymorphonuclear leucocytes and (b) from normal subject showing macrophages.

T lymphocytes [38]. Curiously, exposed but unaffected subjects have also been shown to have raised lymphocyte counts and proportions in their alveolar fluid [39]. However, functional tests of BAL lymphocytes *in vitro* have shown that those from symptomatic subjects with bird fancier's lung increase markedly in blastogenic activity when stimulated with phytohaemagglutinin or pigeon serum compared with the response of cells from exposed but asymptomatic subjects [40]. A soluble protein associated with suppressor T lymphocytes, sCD8, has been shown to augment proliferation of lymphocytes when stimulated with relevant antigen [41], while the proinflammatory cytokines macrophage inhibitory factor and interleukin (IL)-8 (which attract CD8 T lymphocytes and neutrophils respectively) have been demonstrated in high concentrations in BAL fluid from patients with allergic

alveolitis [42]. Other macrophage cytokines identified in various animal models include IL-1 and tumour necrosis factor  $\gamma$  and various growth factors [30], some of which can be released by immune complexes and lead to the formation of granulomas.

In addition to increased numbers of lymphocytes in BAL fluid of exposed subjects, those with disease may also show high counts of mast cells, up to about 5% of the total cell count [43–45]. In different studies, the proportions of these cells have been shown to fall to normal, but the absolute numbers to rise, when exposure ceases [43,44]. Increases in neutrophil leucocytes, averaging 10% of the total cells, may also be observed in the exposed individual, falling when exposure ceases. Indeed, a transient and often severe bronchoalveolar neutrophil leucocytosis has been shown to be an important component of the initial



response to bronchial challenge, appearing within 24 h of exposure and clearing within a week [46]. Finally, plasma cells may be found in BAL fluid from patients with acute allergic alveolitis and are rarely found in any other condition [47,48]. They may therefore be of some diagnostic value.

The evidence suggests that people exposed to these organic antigens may develop a complement-fixing, IgG-mediated reaction detectable by precipitating antibodies in serum. In addition, and despite remaining perfectly well, they may have a lymphocytic alveolitis following release of cytokines from alveolar macrophages challenged by the antigen. In those in whom disease develops, the functional activity of the lymphocytes is altered; it may be that this is responsible for the formation of granulomas, since these cells produce lymphokines that inhibit macrophage migration. Furthermore, the T cell may also produce other lymphokines and leukotrienes that attract mast cells and cause them to release their mediators [49,50]; this would provide an alternative explanation to a type 3 reaction for the oedema, though the absence of eosinophils in the pathology of the disease is a point against an important role for mast cells. Nevertheless, degranulation of mast cells may contribute towards the disease [44,45].

Bronchoalveolar neutrophil leucocytosis seems to be a common response to inhalation of a number of irritant and toxic particles. The histology of so-called mycotoxicosis shows neutrophils and, as mentioned above, many subjects with acute allergic alveolitis have blood and bronchoalveolar neutrophilia early in the course of the disease. There is good evidence that in some subjects activation of the alternative pathway of complement may occur in response to dust inhalation; it may be that this could be important in some of the more acute, precipitin-negative cases [51].

The question remains why some exposed individuals develop neither disease nor immunological response, some develop the response in terms of antibodies and/or lymphocytic alveolitis but no disease, and some develop disease with striking changes in both proportions and functions of alveolar inflammatory cells. Dose of antigen exposure probably plays a part [52], as does the immunomodulatory (in this case, suppressive) effect of cigarette smoke [53]. Genetic factors have not yet been identified and, despite the sacrifice of many rats, mice and rabbits, the question remains unanswered. It is perhaps fortunate that satisfactory management of the condition does not depend on understanding its mechanisms.

## Diagnosis

A physician scanning the literature on allergic alveolitis might get the impression that diagnosis is complicated and requires the use of many sophisticated and, for the

patient, uncomfortable tests. Happily this is not so, as in most cases the diagnosis can be made by taking a competent history and by the use of stethoscope, simple laboratory tests, chest radiograph and lung function testing, supplemented if necessary by a visit to the site of the suspected antigen source. Only occasionally are challenge testing, bronchoscopy with lavage and transbronchial biopsy necessary.

## History

Acute episodes usually bear a clear relationship to the exposure and are recognized by the patient. The more subacute presentation is often regarded as recurrent bronchitis or asthma by the primary care physician and is more difficult to pin down to antigen exposure. All patients with respiratory symptoms suggestive of allergic alveolitis should be asked about exposures at work or home to dusts and moulds, birds and small animals, and volatile chemicals (as well as drugs, see Chapter 55). One potential source of antigen that may be overlooked is feathers in cushions or pillows. This was the proven cause of chronic allergic alveolitis in the first patient with the condition investigated by the author many years ago, and a similar case resulting from exposure to goose feathers in a duvet has been described more recently [54,55]. Attention should be paid to any improvement in symptoms that may occur with the season or on holiday. However, apart from suggesting a possible source of antigen, the history in subacute and chronic allergic alveolitis is often of non-specific respiratory symptoms with little or no diurnal variation.

## Physical examination

The crucial finding is of repetitive inspiratory crackles. If these are persistent, they indicate disease and justify further investigation. They are virtually always present in acute, subacute and chronic disease and their absence should cast doubt on the diagnosis, tipping the scales in favour of sarcoidosis. Other causes of such crackles in the relatively young and middle-aged people who predominantly suffer from allergic alveolitis are nowadays quite uncommon. The finding of finger clubbing is a strong pointer against allergic alveolitis and towards cryptogenic pulmonary fibrosis.

## Blood tests

In someone with appropriate clinical features, the finding of precipitins to the suspected antigen in the serum can normally be taken to clinch the diagnosis. The straightforward gel diffusion test may not be adequate to detect antibody in a number of subjects, and many laboratories now favour a quantitative radioimmunoassay [56]. This

technique is more sensitive but detects antibody in a higher proportion of exposed but unaffected subjects. However, the higher the titre, the greater the likelihood that disease is present, and in the clinical setting sensitivity is invaluable in a test used to complement clinical findings.

### **Radiology and lung function testing**

As stated before, the chest radiograph may be misleadingly normal in subacute disease; indeed the presence of a relatively normal film in a patient with diffuse inspiratory crackles should alert the physician to the possibility of allergic alveolitis as a diagnosis. In acute episodes the film is usually convincingly abnormal, and here the problem is differentiating allergic alveolitis from other causes of diffuse shadowing. To this extent, the radiographic changes are non-specific. The usual abnormality of lung function, a reduced carbon monoxide diffusing capacity, is also non-specific but is a useful indication of parenchymal disease justifying further investigation. The chief value of chest radiography and lung function testing lies in follow-up of the patient after removal from exposure in order to assess response.

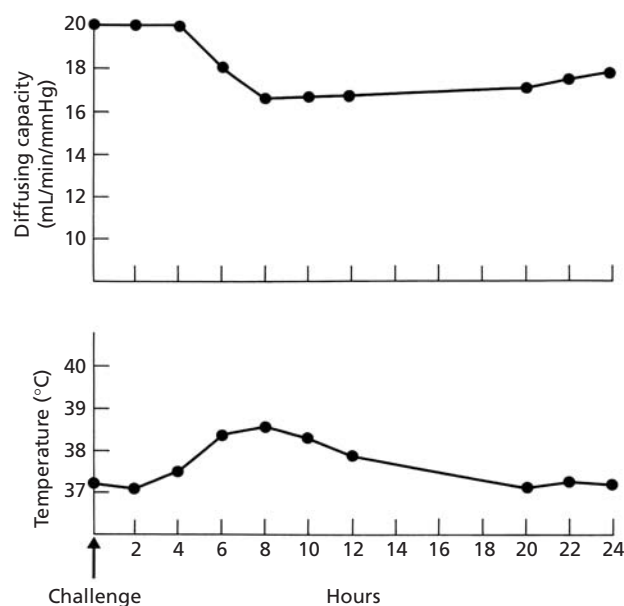
### **More complex investigations**

In most patients the cause of the disease is clear from the above investigations, and the physician is able to plan appropriate management monitored by the same tests. Occasionally, however, the cause is not clear and further investigations are necessary. The first essential is to establish the diagnosis and to exclude other causes of interstitial lung disease. This may be done by biopsy or immunological testing. Biopsy requires an adequate specimen and the transbronchial method is rarely satisfactory in this respect; increasingly, surgeons are offering thoracoscopic biopsy, enabling several good-sized specimens to be taken with control of bleeding and air leaks by stapling [57]. It seems likely that this method will displace all others where appropriate surgical expertise is available. However, biopsy does not always enable a certain diagnosis of allergic alveolitis, especially if a granuloma is not included in the sample or in more chronic cases, and never helps establish the cause. It therefore has its main application in patients in whom there is a serious likelihood of some other disease being present. BAL is frequently performed as part of the investigation, although the usually lymphocytic alveolitis (with a ratio of suppressor to helper T cells greater than unity and with plasma cells sometimes present) is no more than a guide to the diagnosis without usually giving specific aetiological information. However, if a likely antigen has been identified it can then be used not only to search for precipitating antibodies in the blood but also to look at specific proliferative responses of bron-

choalveolar lymphocytes to antigen stimulation [58]. It can also be used in challenge testing, where a small dose is administered to the subject by nebulizer and response measured in terms of white cell count, temperature and lung function tests (see later).

If an antigen is suspected but unknown, a visit to likely sources is worth while. Search of a patient's house for fungi, air conditioners or exotic pets may sometimes be revealing, as may a careful look around the workplace. In doing this, the physician should not confine the search to seeking known antigens; any organic material capable of generating particles of respirable size should come under suspicion, including dusts that might contain fungi or animal material, and fumes at work. Particular attention should be paid to stored organic matter that could have become damp and mouldy, to damp places or rotten wood where fungi could sporulate and to ducted or blown air conditioning or heating systems. Furnishings may contain feathers or straw; the author has diagnosed allergic alveolitis in a housewife due to feathers in cushions, as mentioned above, and also in an upholsterer due to contaminated straw in antique furniture. If a source of antigen is detected in a workplace, further study of all those exposed using epidemiological techniques is usually desirable. Ultimate confirmation of the diagnosis may depend on demonstration of a response to either withdrawal from exposure or challenge with the suspected antigen. The simplest procedure, and that most usually practised, is to remove the antigen source or to have the patient change his or her work practice and to follow the response in terms of lung function. A slow but steady improvement would be anticipated, although complete recovery may never occur in more chronic disease. Alternatively, a challenge test may be carried out. The simplest form of this is to expose the subject to antigen in the normal way, for example a farmer is exposed to mouldy hay or a worker exposed to the suspect fumes or dust in the workplace, and appropriate measurements made. Alternatively, the exposure may take place in the laboratory, either to crude antigen or to purified extracts. The latter is appropriate if the subject is exposed to a known antigen but if it is not certain whether or not the disease is present.

Laboratory challenge tests require decisions about dose of exposure. It is always wise to precede them with a skin-prick test, since if immediate hypersensitivity is present a severe bronchial reaction may occur. The dose of antigen may be estimated very roughly from the history, in terms of severity of reaction, and may be adjusted by time, by concentration or both. For example, using budgerigar or pigeon serum it is usual to challenge first with a 1/100 dilution, then (if no reaction occurs) on another day with a 1/20 dilution and finally with a 1/5 dilution of 1 mL neat serum. Similar dilutions can be made of mouldy hay extract and of fungal antigens. Clearly, laboratory



**Fig. 37.6** Rise in temperature and fall in lung diffusing capacity following challenge with budgerigar antigen. Ideally, a smaller dose might have been given to avoid too great a fall in diffusing capacity.

challenge testing is not an exact science and should be approached with caution. The subject should remain in hospital under observation for 36h and corticosteroids should be available to treat severe reactions. The response to challenge tests may not be as clear-cut as one would anticipate. The most obvious response is a feeling of malaise, with fever, aches and exertional dyspnoea (Fig. 37.6). These are associated with a rise in exercise ventilation, temperature, neutrophil count in the blood and respiratory frequency during exercise, together with a fall in circulating lymphocytes and forced vital capacity [35]. Changes in diffusing capacity and the chest radiograph may occur, but only in severe reactions that are best avoided. Criteria for a positive response proposed by Hendrick and colleagues are shown in Table 37.1. If three or more of these tests are positive within 36h of the challenge test, there is a high likelihood that the antigen has been found. A scheme for the investigation of suspected allergic alveolitis is given in Fig. 37.7.

## Management

Acute episodes of allergic alveolitis may require hospitalization and oxygen therapy to help the patient during the reaction; occasionally hypoxaemia may be so severe and the lungs so stiff as to necessitate assisted ventilation. Corticosteroids should be given for all but the mildest attacks, in a dose of 40mg prednisolone daily until lung function and  $PO_2$  have improved to clinically adequate levels. A controlled trial in acute farmer's lung

**Table 37.1** Response to challenge testing [35].

Test	Change	Specificity (%)	Sensitivity (%)
Exercise minute ventilation	>+25%	94	40
Exercise respiratory frequency	>+25%	94	30
Body temperature	>37.2°C	95	78
Neutrophil count	+2.5×10 <sup>9</sup> /L	96	68
Lymphocyte count	>-0.5×10 <sup>9</sup> /L*	97	52
Vital capacity	>-15%	97	48

\*When combined with absolute lymphocyte count of <1.5×10<sup>9</sup>/L.

has shown that an 8-week course of corticosteroids speeded functional recovery but that longer-term lung function did not differ between the active and placebo groups [59].

Further exposure to antigen should if possible be prevented. In the case of exposure to birds, the creatures must be removed if possible. Unfortunately, for financial and social reasons, many pigeon breeders are unwilling to do this; in such cases effective oronasal respirators should be used whenever the loft is entered. Cross-reactivity occurs, so that pigeon breeders may get exacerbations when they visit houses with budgerigars and they should be warned of this possibility. It should be noted that after a bird has been removed from a patient's house it may find a home with a relative whom the patient visits; in the author's experience this has caused recurrent disease, sometimes manifesting as quite severe attacks. Moreover, bird antigen may persist for months in a room after the bird has been removed, despite careful cleaning, and this may explain persisting symptoms in some very sensitive patients [60]. Farmers often require respirators, but should also be given advice about keeping hay dry or changing to making silage (though this may require some education also on avoidance of silo-filler's lung and mycotoxicosis). Colleges of agriculture can usually give appropriate advice, as can the Health and Safety Executive in the UK.

The use of respirators requires some comment [61,62]. These should be well fitting and well maintained. Filters should be changed regularly and should be adequate to exclude respirable-sized particles; in the UK and the USA, they are subject to testing against standards and should not allow penetration of more than 1–2% of a standard aerosol. If a subject is advised to obtain a respirator, an appropriate one should be recommended and the patient instructed in its fitting, use and maintenance. Care should be taken to ensure that one is chosen that provides a good seal without too much discomfort or respiratory resistance. Powered helmet-type respirators, as opposed to

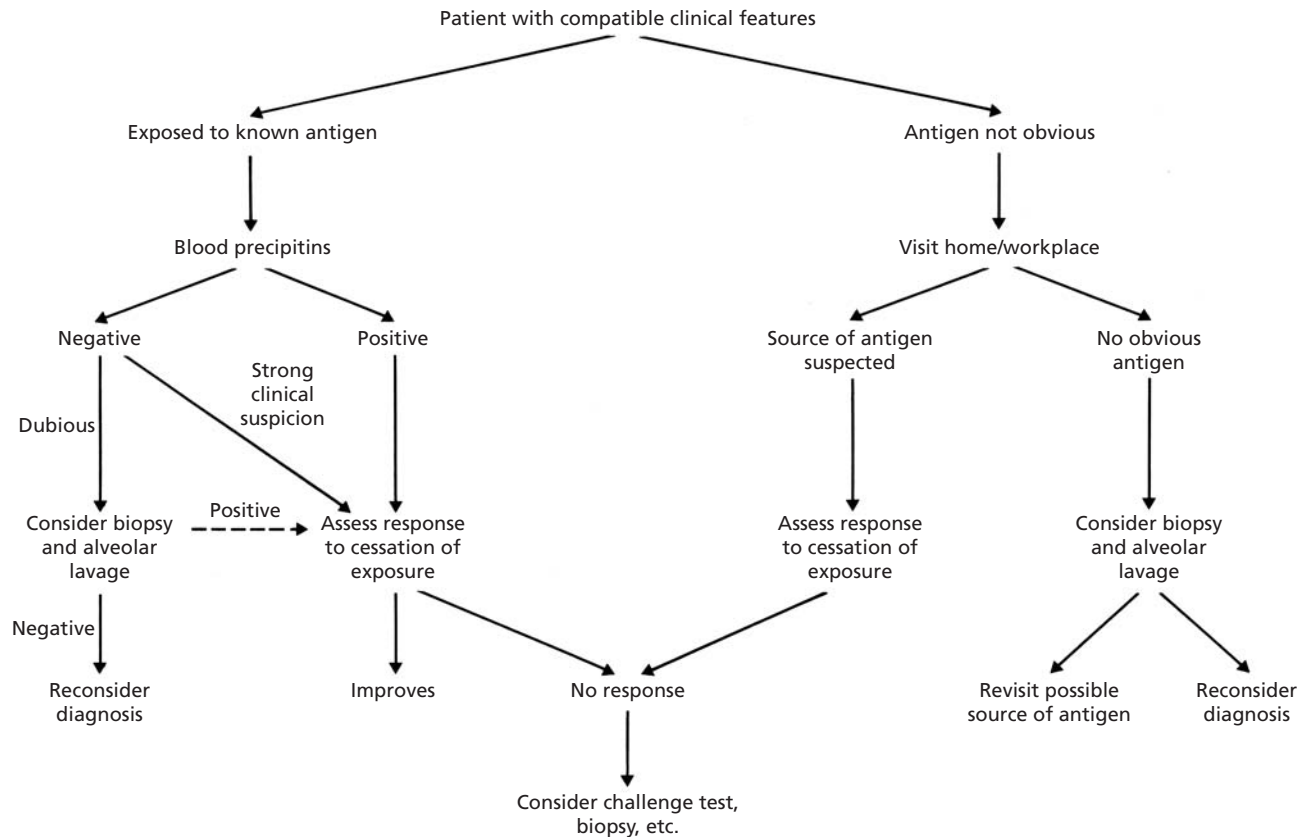


Fig. 37.7 Investigation of suspected allergic alveolitis.

mask types, may be adequate, depending on the efficiency of the filter and the sensitivity of the patient to antigen. Before the subject purchases a respirator, it is wise to test its efficacy in preventing symptoms under normal exposure conditions. Chronic allergic alveolitis should be treated with a prolonged course of corticosteroids, usually for several months, until it is clear that no further functional improvement will occur. The drugs should then be stopped, assuming that further exposure can be prevented. The airways' obstructive component does not respond adequately to corticosteroids, and there is no point in continuing these drugs long term in the hope that it will. However, it should be remembered that asthma sometimes coexists with allergic alveolitis and trials of antiasthma therapy are always justified in such patients.

### Causes of allergic alveolitis

The causes of allergic alveolitis may be separated into three main types: microbial, animal and chemical. In addition there is a small group in which the antigens have not been identified. The main causes are listed in Table 37.2.

### Microbial causes

#### Farmer's lung

Farmer's lung commonly presents in the acute form, although chronic cases may go unrecognized for long periods [9,10,27]. It is usually caused by inhalation of spores of thermophilic actinomycetes, higher bacteria of a filamentous appearance that grow in hay or other organic matter that has been stored in a damp condition. The two most usual organisms in the UK are *Micropolyspora faeni* (now known as *Faenia rectivirgula*) and *Thermoactinomyces vulgaris*, though other organisms including fungi of *Aspergillus* species may sometimes cause the syndrome. The spores are liberated into the air when the dried mouldy hay is fed to cattle, usually in the winter. The condition occurs most commonly in countries where rain is frequent at harvest time and among farmers unaware of the problem. Studies of the epidemiology have shown a prevalence of 3–5% of farmers in agricultural areas of Britain and the USA, most cases occurring in the areas of highest rainfall [20,32,63,64]. Precipitating antibodies in the absence of disease are found in approximately twice as many subjects, and can therefore only be taken as an indication of exposure unless the farmer has appropriate symptoms and signs as well. As with other types

**Table 37.2** Principal causes of allergic alveolitis.

Antigen source	Disease
<b>Microbial</b>	
Thermophilic actinomycetes ( <i>Micropolyspora faeni</i> , <i>Thermoactinomyces vulgaris</i> )	Farmer's lung Bagassosis Mushroom worker's lung
<i>Aspergillus clavatus</i>	Air conditioner lung
<i>Aspergillus fumigatus</i>	Maltworker's lung
<i>Aspergillus versicolor</i>	Allergic aspergillosis
<i>Alternaria</i> spp., <i>Trichoderma</i> <i>koningii</i>	Doghouse disease
<i>Aureobasidium pullulans</i> , <i>Graphium</i> sp.	Wood-pulp worker's lung
<i>Cryptostroma corticale</i>	Sequoiosis
<i>Penicillium frequentens</i>	Maple bark stripper's lung
<i>Merulius lacrimans</i>	Suberosis
<i>Mucor</i> spp.	Dry rot lung
<i>Penicillium casei</i> , <i>P. roqueforti</i>	Paprika splitter's lung
<i>Lycoperdon</i> spp.	Cheeseworker's lung
<i>Trichosporon cutaneum</i>	Puff-ball lung
<i>Bacillus subtilis</i>	Summer pneumonitis
<i>Bacillus cereus</i> , <i>Cephalosporium</i> <i>acrimonium</i> , <i>Klebsiella oxytoca</i>	Washing powder lung Humidifier lung
<b>Animal</b>	
Budgerigar, pigeon, hen, turkey, owl, etc.	Bird fancier's lung
Fish protein	Fishmeal lung
Animal pituitary	Pituitary snuff-taker's lung
Animal pancreas	Enzyme worker's lung
Rodents	Rodent handler's lung
Wheat weevil	Weevil alveolitis
<b>Chemical</b>	
Bordeaux mixture	Vineyard sprayer's lung
Cobalt	Hard-metal disease
Isocyanates	Isocyanate alveolitis
Pauli's reagent	Pauli's reagent alveolitis
Pyrethrum	Insecticide lung
Trimellitic anhydride, hexahydrophthalic anhydride	Acid anhydride lung
<b>Uncertain</b>	
Lake water	Sauna lung
Hut thatch	New Guinea lung
Boxwood	Ramin lung

of allergic alveolitis, smokers are less likely to have the disease than non-smokers [64].

It is worth noting that farmers are subject to a number of respiratory disorders as a result of their work [65] (Table 37.3). Farmer's lung, both acute and chronic, may be associated also with asthma due to hay or its contaminants. On the acute side, with negative precipitins, farmer's lung merges into the acute organic dust (mycotoxicosis) syndrome [13]. Farmers may also have asthma and rhinitis due to exposure to fungi in harvesting grains and to mites in stored grains [66,67]. If they keep livestock

**Table 37.3** Respiratory diseases of farmers.

Farmer's lung, farmer's fever	Actinomycetes
Mycotoxicosis	Fungi
Asthma/rhinitis	Fungi, storage mites
Swine fever	?Endotoxin in excreta
Silo-filler's disease	Nitrogen dioxide
Organophosphate poisoning	Insecticides

under conditions of intensive rearing, they may be subject to alveolitis or febrile reactions due to excreta and their contaminants [68], while chemical pneumonitis may occur as a result of exposure to oxides of nitrogen in silos [69]. To make life more difficult for the clinician, they may also present like anyone else with *Mycoplasma pneumonia*, which mimics either farmer's lung or silo-filler's lung [21]. A febrile illness like farmer's lung but without the pulmonary component has been described [70] and farm workers are of course at risk of poisoning by organophosphorus compounds, which can in severe cases lead to neuromuscular paralysis.

The diagnosis of farmer's lung is usually easy; indeed it is often made by the patient. If it is made sufficiently early in the course of the disease, preventive measures should be effective and progression should not occur. However, continued exposure is associated with a high risk of progression [71]. Only in difficult, precipitin-negative cases are further investigations necessary, and these should usually be preceded by a visit to the farm to make sure there is no other source of antigen that has been overlooked in the history.

Management is as discussed above. Since farmers are rarely able to retire or change jobs, it is important that they be educated in preventive measures. Equally, they should not simply hand over the dusty job to their wife or other assistant, as that is likely to produce a second case. Transfer from hay to silage, proper drying of damp hay and use of a respirator when exposure cannot be prevented [72] are the principles of management. In the UK, employed farmers with the disease (not self-employed, who have to make their own insurance arrangements) are eligible for industrial injuries benefit under the national social security scheme.

### Mushroom worker's lung

Mushrooms are grown commercially on compost, often made of straw and horse droppings that is allowed to ferment, which is then heated in moist air to just below 60°C. While these conditions suit the mushroom mycelia with which it is seeded, they are also ideal for the growth of thermophilic actinomycetes. Workers may be exposed to spores when compost and mycelia are mechanically mixed or when the sheds are being cleaned. The manifes-

tations of the disease are clinically indistinguishable from those of farmer's lung [73–76].

### Bagassosis

Bagasse is the residue after sugar is extracted from cane. It is a fibrous material used in the manufacture of paper, boards and building materials. Typically it becomes contaminated with thermophilic actinomycetes when lying in the hot and humid conditions of Louisiana, the West Indies and other tropical and subtropical areas where sugar cane is processed. Although the disease commonly affects workers handling the bagasse in these countries, it may also occur wherever mouldy material is imported [77–79]. Indeed, it was first described in London, in workers handling bagasse imported from Louisiana [3]. Again, the disease is a variant of farmer's lung.

### Air conditioner and humidifier lung

(see also Chapter 54)

Many workers exposed to 'conditioned' air (air in which the humidity and temperature have been controlled to produce comfortable conditions) suffer mild general malaise known as humidifier fever [80,81], particularly on the first day of the week; however, some develop a true allergic alveolitis [82–86]. Various organisms have from time to time been incriminated, since conditions differ in different conditioning and humidifying systems, leading to preferential growth of different organisms. In some episodes, thermophilic actinomycetes have been thought to be responsible, in some *Aspergillus* spp., in others *Penicillium* spp. and thermotolerant bacteria resembling *Bacillus cereus* [87], while in some the cause has not been identified [88]. In general, humidifier fever, in which the predominant antigen source is *Naegleria gruberi* or other amoebae, is not associated with evidence of interstitial lung disease, although at least one patient with typical radiological and physiological changes has been described [86].

This spectrum of responses, from classical allergic alveolitis to humidifier fever, results from exposure to droplets from humidifying systems in which the water is sprayed into a moving stream of air. The drops that fall and the larger droplets removed by a baffle are collected in a sump and then recirculated and sprayed again. The sump and the baffle plates form a culture medium for microorganisms, and a food chain develops depending on temperature and nutrients. In theory this can be prevented by spraying steam or fresh (rather than recirculated) water, although these options are often expensive. Alternatively, the incoming and outgoing air can be filtered and/or subjected to ultraviolet light and biocides can be added to the water. Measures taken depend on the system and on economic factors, but must include regular cleaning of the

whole system. If the water is heated, the temperature should also be raised above 60°C in order to discourage the growth of *Legionella* spp. (see Chapter 13).

An identical range of syndromes may occur from exposure to contaminated aerosol from home ultrasonic nebulizers. An outbreak in Japan has been associated with an aerosol containing *Cephalosporium* and *Candida* spp. [89], while one in the USA has been caused by *Klebsiella oxytoca* [90].

### Maltworker's lung

Malt is used as a source of carbohydrate for fermentation in the manufacture of whisky. It is barley that has been dried, stored and then rehydrated and allowed to germinate in conditions of controlled temperature and humidity. The process may take place on the floor of a large room, the maltings, where the material is turned regularly to allow carbon dioxide to escape. Alternatively, it can be carried out in rotating drums. In the former situation, the malt may become contaminated with *Aspergillus clavatus* and workers may inhale spores of this organism [91–93]. The condition has been shown to cause a farmer's lung-like illness in up to 5% of those workers who turn the malt.

### Woodworker's lung

Allergic alveolitis has been described in several different groups of woodworkers. Indeed, maple bark stripper's lung was described in the same year as farmer's lung [2]. These workers were exposed to the spores of *Cryptostroma corticale*, a fungus that grows under the bark and which is pathogenic to the tree [94]. The spores are liberated when the bark is mechanically removed in lumber mills [95–97]. The incidence of the disease may be controlled by hygiene measures, such as extract ventilation and spraying of the dusty process. Similar illnesses have been described in workers in paper mills due to inhalation of spores of *Alternaria* spp. [98], in sawyers of redwood (sequoiosis) due to *Graphium* spp. or *Aureobasidium pullulans* [99], in other sawmill workers due to *Trichoderma koningii* [100], and in workers making cork (suberosis) due to *Penicillium frequentans* [101,102]. One subject working with ramin dust has also been described as developing allergic alveolitis, probably due to the wood dust itself rather than to a fungus [103].

### Aspergillosis

Allergic bronchopulmonary aspergillosis is discussed in detail in Chapter 34 and other diseases related to *Aspergillus* spp. in Chapter 21. Since *Aspergillus* spp. grow on dead organic matter, they can be found in mouldy hay and in compost heaps and may therefore cause episodes of

allergic alveolitis in farmers and market gardeners. A severe episode, requiring assisted ventilation, occurred in a patient as a result of changing straw contaminated with *A. versicolor* in her dog's kennel [104].

### Cheeseworker's disease

This relatively mild and chronic form of allergic alveolitis was described originally in Swiss cheese washers, whose job was to wash off mould that had grown on the surface of some cheeses aged in damp cellars. On the basis of blood serology the condition was thought to be due to sensitization to *Penicillium casei* [105–107]. Although the condition was thought unlikely to occur in industries in which cheese was aged by wrapping in plastic, it has subsequently been described in a worker in the USA who was engaged in crumbling blue cheese in the production of salad dressing; in this case the organism was the *P. roqueforti* used to give the cheese its distinctive flavour [108].

### Japanese summer pneumonitis and other domestic causes

A distinctive type of allergic alveolitis, in which the symptoms occur in the patient's home during the summer months, has been described in Japan where it is the commonest form of allergic alveolitis [18,109,110]. This is caused by *Trichosporon cutaneum* in the houses, particularly in bird droppings, which enhance the organism's growth. In one case, the mould was growing in bed-clothes. As with other forms of allergic alveolitis, the condition is less common in cigarette smokers [53]. Immunological studies in these cases have shown antibodies cross-reacting with *Cryptococcus neoformans*, a related yeast, and a particular rise in IgA antibodies to *T. cutaneum* in both blood and BAL fluid [111,112]. The antigen has been characterized as a polysaccharide with glucuronic acid residues on side-chains forming the epitope [113].

It would not be surprising if other episodes of alveolitis occur as a result of exposure to fungi in houses. Several such have been described, including reactions to the dry rot fungus, *Merulius lacrimans*, and to *Penicillium* spp. growing in wet rot [114,115]. *Bacillus subtilis* growing in rotten wood has also been shown to cause the disease in a family [116].

### Other causes

An entomologist who developed allergic alveolitis in response to workplace exposure to antigen of *Penicillium* spp. and from humidifiers has been described [117]. Some of the workers exposed to *B. subtilis* in the manufacture of biological washing powders may have developed alveoli-

tis as well as asthma; certainly precipitating antibodies were found in their blood [118,119]. Workers splitting red peppers, or paprika, used to be exposed to heavy doses of spores of *Mucor* spp. and several cases of what was probably alveolitis were described among them [120]. An alveolitis associated with fever was also described in children using inhalation of puff-ball (*Lycoperdon*) spores to stop nose bleeds [121]. This last case report made the interesting suggestion that the disease could be prevented if the puff-balls were picked when young, sautéed in butter and garlic, and eaten rather than inhaled!

### Animal causes

#### Bird fancier's lung

This condition was first described in 1960 in people plucking ducks and those exposed to budgerigars, and in 1965 in people breeding pigeons [4,5,122,123]. Chicken and turkey farmers may occasionally develop the disease and it has also been described in a bird ringer [124–126]. The presentation in people who keep the birds in their houses is often insidious and may be mistaken for neurosis, recurrent chest infections or asthma. In children, loss of weight or failure to thrive may be the presenting feature. Acute attacks occur most commonly in pigeon breeders, following visits to the loft. Re-exposure to a bird after exposure has ceased may also provoke a severe attack, and cross-reactivity may mean that a pigeon fancier suffers an attack on visiting a house where a budgerigar is kept. Otherwise the symptoms do not differ from those associated with other types of allergic alveolitis, shortness of breath, cough, malaise, wheeze and fever being the important ones [127]. The radiograph is often within normal limits in the more chronic cases, although crackles are usually audible at the bases. Lung function commonly shows a restrictive pattern with reduced diffusing capacity, but an obstructive syndrome can occur [128–130].

The frequency with which the condition occurs depends on the prevalence of bird exposure and the extent of that exposure; this is presumably why budgerigars (kept in some 12% of British homes) and pigeons are the most common sensitizers, since exposure to budgerigar antigen is unavoidable if the creature lives in the house while pigeon fanciers have intimate contact with their animals. Among pigeon fanciers, alveolitis has been estimated to occur in about 10–20% of those regularly visiting the lofts [131]. While precipitating antibodies often occur in exposed people without disease [132], the intensity of IgG response measured by radioimmunoassay is a good guide to the likelihood of disease being present [133].

The sensitized patient has precipitating antibody to bird serum protein and droppings. At least in pigeons, IgA seems to be the most important antigen; it was originally thought that this would be inhaled in dried bird faeces,

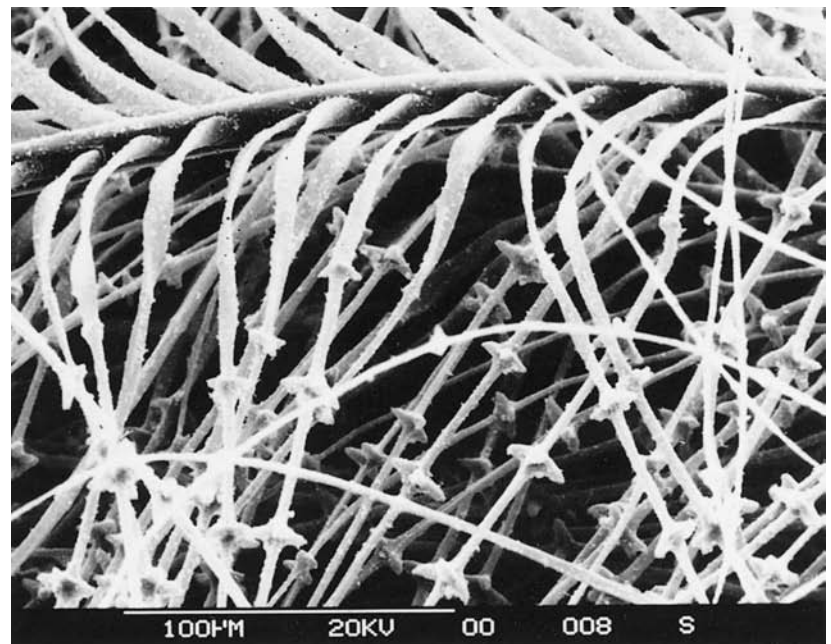


although it now seems likely that bloom from feathers is the principal source [134,135]. Bloom consists of <1.0- $\mu\text{m}$  spherical particles of keratin coated with IgA that cover the feathers and give them their glossy appearance (Fig. 37.8). It relates to the appearance of the bird and its ability to fly efficiently, and is therefore abundant on the wings of ornamental and sporting birds.

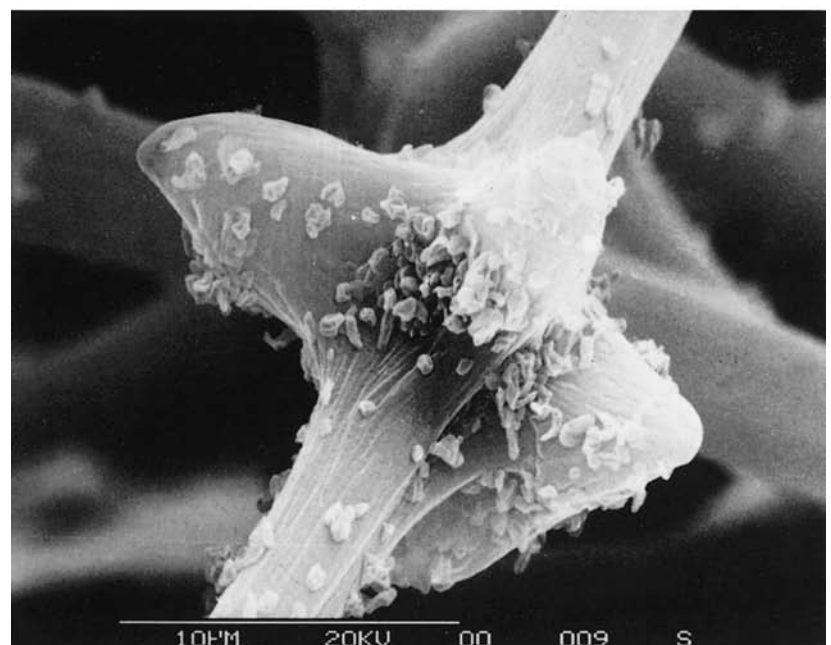
Two practical problems may occur in the diagnosis of bird fancier's lung. Firstly, false-positive titres of viral complement-fixing antibodies may be found due to either polyclonal stimulation of antibody formation or cross-reactions with proteins in the egg on which the virus was

grown, leading to confusion with viral pneumonia [15,136]. Secondly, patients with coeliac disease may have precipitins in their serum to bird antigen, probably derived from egg protein in their food [137]. However, it appears that there is an association between bird fancier's lung and coeliac disease as well, and therefore the coincidence of coeliac disease with interstitial lung disease is one situation where inhalation challenge may be invaluable [138-140].

Management of bird fancier's lung is by preventing further exposure. Usually this may be achieved by removal of the birds; if this involves serious financial or



(a)



(b)

**Fig. 37.8** Scanning electron micrographs of pigeon feather: (a) low power showing structure of the feather; (b) high power showing particles of bloom. The bars at the bottom show the scale. (Courtesy of Dr Gavin Boyd.)

emotional hardship, use of effective respirators may be a compromise [62]. As noted above, residual antigen in rooms vacated by birds may persist for months despite cleaning [60], and patients should be advised to keep out of the room in which the bird has been kept if possible. All patients should be warned of the dangers of irreversible pulmonary fibrosis if they are contemplating continued exposure. Corticosteroids are effective treatment for acute episodes and bring about partial improvement in most chronic cases if exposure is stopped.

### Other animal causes

Apart from those caused by birds, episodes of allergic alveolitis due to exposure to animal protein have been described rarely. Small laboratory mammals frequently provoke asthma as a consequence of sensitization to urinary protein, and an occasional case of allergic alveolitis has been described in people exposed to rats and gerbils [141,142]. A granulomatous interstitial pneumonitis (probably of foreign body rather than immunological aetiology) has been described in a person handling animal furs [143], and a patient exposed to the wheat weevil, *Sitophilus granarius*, developed alveolitis as well as the more typical asthmatic reaction [144]. Workers making fishmeal as animal food may become sensitized and develop allergic alveolitis [145].

Alveolitis has been described in the production and use of two therapeutic substances. Pituitary snuff-taker's lung occurred in patients with diabetes insipidus taking extracts of porcine or bovine pituitary by nasal insufflation [146,147]. The particles of this were mostly below 50 µm, and some were small enough to reach alveoli and cause a chronic allergic alveolitis. Sensitization was usually to contaminating ox or pig protein but in one case was to the hormone itself [148]. Since synthetic vasopressin has been introduced the problem has not recurred. More recently, workers producing pancreatic extract have been described as developing alveolitis [149]. This substance has been known to cause asthma and is under suspicion of provoking emphysema in exposed workers, although one report has also documented a late alveolitic reaction to challenge testing and radiological evidence of interstitial disease in a few people employed in its production [149].

### Chemical causes

In view of the relatively large numbers of subjects who

develop asthma as a consequence of exposure to volatile reactive chemicals, it is surprising that so few have been described as developing alveolitis. This is particularly remarkable because the atopic state is not an important determinant of occupational asthma due to low molecular weight chemicals and their particle size is such that deposition is not likely to be preferentially in airways. Nevertheless, few chemical causes of alveolitis have been described and few patients have suffered these effects. Several volatile isocyanates have caused alveolitis, combined in some subjects with asthma [6,8,150–153]. A haemorrhagic pneumonitis has been associated with exposure to trimellitic anhydride, and allergic alveolitis and haemorrhagic rhinitis associated with IgG antibodies with exposure to hexahydrophthallic anhydride, acid anhydrides used in epoxy resin systems [154,155]. Typical allergic alveolitis and asthma have occurred in a laboratory technician using Pauli's reagent (sodium diazobenzene sulphonate) in chromatography [7]. Cobalt, to which workers in the hard-metal industry may be exposed because of its presence in coolant sprays in grinding and also in small amounts in the tungsten carbide metal itself, may cause both asthma and alveolitis, the latter sometimes leading to pulmonary fibrosis [156,157]. Pyrethrum, an extract of autumn crocus used in insecticides, has caused alveolitis in one subject [158], and exposure to Bordeaux mixture (copper sulphate neutralized with lime) in spraying vines has also caused a similar reaction [159].

### Possible causes and some non-causes

Chronic lung disease in Papua New Guinea, though probably usually due to smoke inhalation, may occasionally be an allergic alveolitis due to inhalation of fungi or other contaminants in thatch [160]. Lake water constituents may be the cause of alveolitis described in Finland in people using saunas [161]. Three possible episodes of alveolitis have now been discounted: smallpox worker's lung turned out to have been a pneumonia modified by vaccination [162]; coffee worker's lung was a pulmonary fibrosis in association with rheumatoid disease [163]; and blackfat tobacco smoker's lung turned out to be a lipid pneumonia [164]. As mentioned above, furrier's lung seems likely to have been a foreign body granulomatous, rather than allergic, reaction.

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# PULMONARY EOSINOPHILIAS

A. GORDON LEITCH

## Definition

The term 'pulmonary eosinophilia' was originally applied as a general one to a group of diseases in which lung shadows were observed radiologically and were accompanied by a blood eosinophilia. Resolving pneumonia, sarcoidosis, hydatid disease and Hodgkin's disease were excluded [1]. Some workers have used the term 'pulmonary infiltration with eosinophilia' (PIE syndrome) [2] and because eosinophilic infiltration of the lung can exist in the absence of blood eosinophilia, it has been suggested that the term 'the eosinophilic pneumonias' might be even more appropriate [3]. The terms are interchangeable but pulmonary eosinophilia is retained in this chapter for historical reasons.

Opinions vary on the level of blood eosinophil count that constitutes eosinophilia. In one study 95% of healthy non-allergic subjects had eosinophil counts of less than  $0.27 \times 10^9/L$ , whereas counts of greater than  $0.35 \times 10^9/L$  were usually seen in patients with active asthma [4]. Total eosinophil counts of greater than  $0.5 \times 10^9/L$  (and often much higher) are usually seen in patients with pulmonary eosinophilia.

## The eosinophil

The eosinophil polymorphonuclear leucocyte is 12–15  $\mu m$  in diameter, containing a bilobed nucleus, rich endoplasmic reticulum, an active Golgi complex and two types of eosinophilic granules (Fig. 38.1). The larger granules, of which there are about 200 in each cell, are  $1 \times 0.6 \mu m$  in size and comprise an electron-dense crystalloid matrix in which are found a number of enzymes, including a unique peroxidase [5],  $\beta$ -glucuronidase, acid phosphatase and histaminase [6–8]; 25–50% of the mass of the granules consists of the major basic protein (MBP), a 13.8-kDa protein [7,9]. In addition the granules contain eosinophil cationic protein (ECP) (18–21 kDa) [10] and eosinophil protein X (eosinophil-derived neurotoxin) (18 kDa) [11]. The smaller granules, which are more prominent in mature

eosinophils, measure  $0.2 \times 0.2 \mu m$  and are rich in arylsulphatase B and acid phosphatase. The cell membrane contains lysolecithinase, an enzyme that spontaneously forms Charcot–Leyden crystals in tissues and fluids [12] (Fig. 38.2).

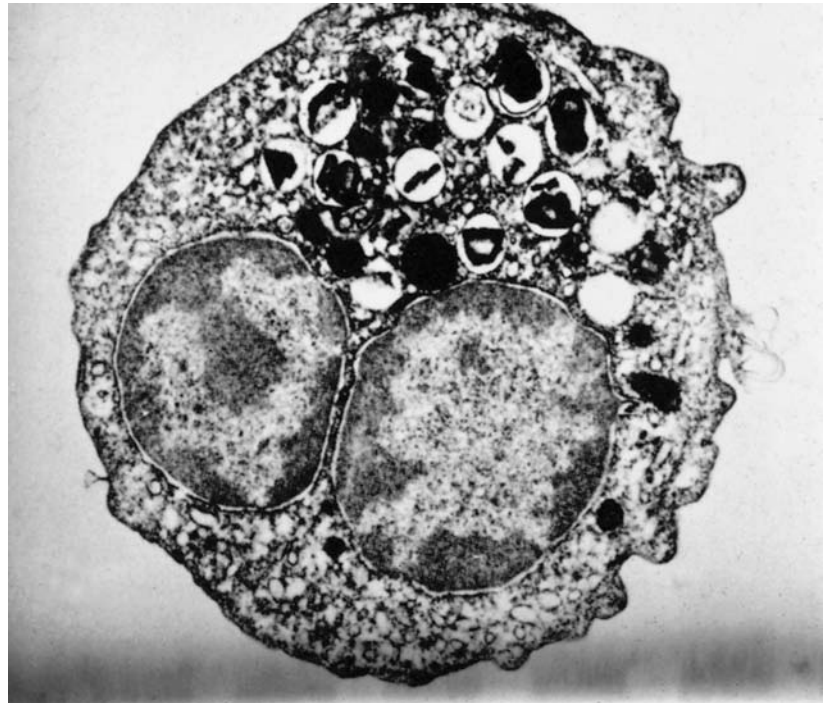
Eosinophils are produced in the bone marrow, circulate for 4–10 h and then localize in the tissues, being most prominent in the submucosal sites of the respiratory, gastrointestinal and genitourinary tracts [13]. Their behaviour is influenced by chemotactic factors, chemokinetic factors and deactivation factors. Chemotactic factors cause migration towards a cell-sensed concentration gradient, while chemokinetic factors enhance random motility. Deactivation factors induce unresponsiveness to subsequent chemotactic stimuli, a property that localizes and immobilizes eosinophils in the tissues. Both complement-derived products C3a, C5a and C567 (which may be generated by the classical or alternative pathways [14]) and the mast-cell derived products ECF-A and ECF-A oligopeptide [15] demonstrate the combination of chemotactic and deactivation activities. Chemotactic activity is also shown by lipoxygenase pathway products, such as several of the monohydroxyeicosatetraenoic acids and leukotriene  $B_4$ , which may be generated by several cell types [16]. Eosinophils may therefore be attracted to tissues by many mechanisms, including mast cell activation, complement activation, lymphocyte-derived products and generation of arachidonic products via the lipoxygenase pathway by a variety of cells.

Blood eosinophil counts are depressed by glucocorticosteroids, which also inhibit eosinophil chemotaxis and facilitate eosinophil margination and tissue destruction [17]. Propranolol induces a modest peripheral blood eosinophilia in many patients, suggesting direct  $\beta$ -adrenergic control of eosinophil levels [18].

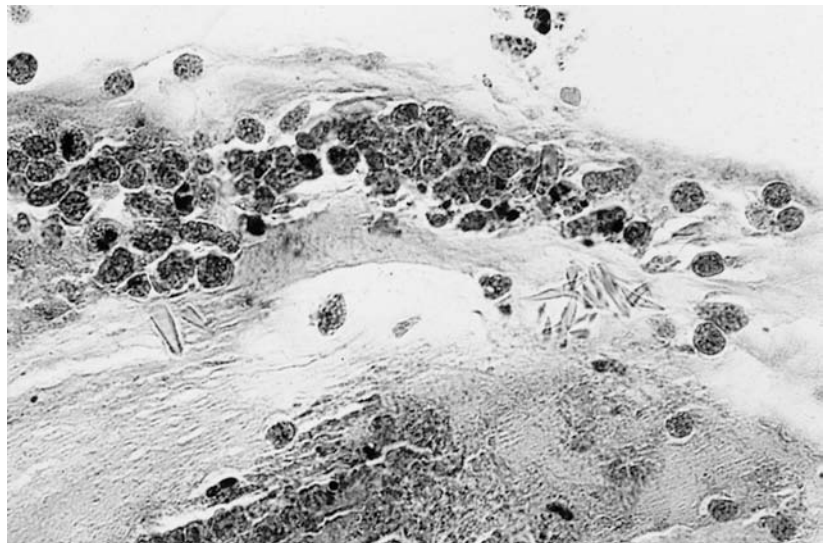
## Function

The eosinophil is equipped to modulate mast cell-dependent reactions by virtue of the enzymes that it





**Fig. 38.1** Electron micrograph of an eosinophil showing bilobed nucleus, endoplasmic reticulum and prominent intracytoplasmic granules.



**Fig. 38.2** Mucous plug from asthmatic airway showing eosinophils and Charcot-Leyden crystals (haematoxylin & eosin  $\times 335$ ).

produces [19]; histaminase degrades histamine, phospholipase D degrades platelet-activating factor and, in addition, the eosinophil can ingest mast cell granules and IgE-antigen complexes. An eosinophil-derived inhibitor of histamine release, which is probably prostaglandin  $E_2$ , also exists [20]. The marked eosinophilia found in many parasitic conditions suggests a role for the eosinophil in the destruction of parasites [21]. This has been shown to be the case in schistosomiasis, in which eosinophils inflict IgG antibody-dependent damage on the schistosomula [22]. Complement also enhances this process and mast

cells enhance both complement and IgG-dependent eosinophil-mediated schistosomal killing *in vitro* [23]. The eosinophil may function similarly in other parasitic diseases.

Not all the activities of the eosinophil are beneficial. Prolonged hypereosinophilia may be associated with tissue damage and a possible mechanism for this adverse effect has now been identified. Low concentrations of eosinophil MBP have been shown to damage a wide variety of mammalian cells and organs [24]. Concentrations of MBP comparable to those found in the sputum of patients with



asthma have been shown to be ciliostatic and to damage tracheal mucosal cells [25]. Furthermore, using immunofluorescent techniques, MBP has been localized to areas of mucosal damage in the bronchi of patients with asthma [26]. It seems possible that deposition of MBP in the interstitium or vascular tree could cause pulmonary parenchymal or vascular damage in a similar fashion. Other constituents of the eosinophil that could exert a pathogenic effect include superoxide, lysosomal hydrolase, ECP, eosinophil protein X and the inflammatory products of arachidonic acid [27,28].

While knowledge of the factors regulating eosinophil behaviour and function continues to grow, it would be wrong to conclude that more than a start has been made in uncovering the mechanisms that underly the several varieties of pulmonary eosinophilia.

### Classification

In the fourth edition of this book, the pulmonary eosinophilic disorders were classified into seven categories largely on the basis of clinical manifestations. Since then, acute eosinophilic pneumonia has been described [29,30] and the present classification of pulmonary eosinophilias is as shown in Table 38.1 [31].

#### Loeffler's syndrome or simple pulmonary eosinophilia

##### Definition

Originally described by Loeffler in 1932 [32], this syndrome is characterized by transient radiographic shadows and by blood eosinophilia that is usually relatively slight, although high counts have been recorded. The illness usually lasts less than 2 weeks and always less than 1 month and is related to the passage of parasitic larvae, most commonly *Ascaris lumbricoides*, through the lung.

##### Aetiology

The life cycle of *A. lumbricoides* in humans begins with

the ingestion of eggs and subsequent development of larvae in the intestine. Some 10–14 days after ingestion the larvae migrate to the liver and the lung, thence to the alveoli and up the bronchial tree to be swallowed into the intestine where they develop into the mature roundworm.

Koino, a Japanese investigator, swallowed 2000 ripe *Ascaris* eggs and 6 days later developed pneumonia with dyspnoea, cyanosis, eosinophilia and pyrexia that lasted for 7 days. The sputum was profuse from day 11 to day 16 and contained *Ascaris* larvae, of which 202 were counted. By 50 days after infection, 667 *Ascaris* worms were voided in the faeces [33].

The passage of larvae through the lung is associated with an allergic reaction that was well studied in four Canadian students who developed pulmonary eosinophilia 10–14 days after eating a meal maliciously seasoned with *A. suum* ova [34]. Asthma occurred in all four students and urticaria was also a feature of the illness. Studies of immunoglobulin and eosinophil levels in the course of the illness showed that peak humoral antibody levels of IgM and IgE occurred before peak eosinophil levels, which were found in the recovery phase of the illness. The authors concluded from their observations that the high IgE levels were responsible, via a type I hypersensitivity reaction, for the asthma and urticaria and that the pulmonary infiltrates were due to a type III reaction following deposition of IgM–antigen complexes in the lung, perhaps facilitated by the changes in vasopermeability occasioned by release of mast cell mediators. It is of interest that high levels of IgE have been demonstrated in children infected with *A. lumbricoides* [35].

Other parasites implicated in this form of pulmonary eosinophilia include *Paragonimus westermani* [36] and *Ancylostoma braziliense* (see Chapter 22).

##### Pathology

Histopathological sections of lung from a patient dying from Loeffler's syndrome showed that the bronchi and bronchioles were dilated and filled with a neutrophil and eosinophil polymorphonuclear infiltrated exudate [37]. Charcot–Leyden crystals were seen in some areas. In some of the bronchioles one or more portions of nematode larvae were demonstrated. The pulmonary interstitium was also infiltrated with eosinophils and areas of atelectasis were seen.

##### Clinical features

Over 23% of Loeffler's original cases were detected during routine radiography and were asymptomatic. Symptoms when present are usually mild and may include cough, malaise, anorexia, rhinitis, night sweats, slight fever and

Table 38.1 Classification of pulmonary eosinophilias.

Loeffler's syndrome or simple pulmonary eosinophilia
Asthmatic pulmonary eosinophilia
Drug-induced pulmonary eosinophilia
Tropical pulmonary eosinophilia
Chronic or prolonged pulmonary eosinophilia
Churg–Strauss syndrome
Hypereosinophilic syndrome
Acute eosinophilic pneumonia

occasionally wheezing and dyspnoea [33,34]. Urticaria can occur. Sputum when present may contain eosinophils and, exceptionally, larvae. High fever may occur. Frequently there are no abnormal physical signs in the chest, although impairment of percussion note, a few crepitations or wheezes may be heard. Symptoms and physical signs usually disappear in a few days and almost always within a fortnight.

**Radiology**

The chest radiograph almost invariably shows bilateral involvement, with considerable variation in the extent and location of the pulmonary infiltrates [38]. These are usually scattered soft densities, a few centimetres in size, that tend to be discrete, without any clear-cut segmental distribution and often concentrated in the perihilar regions. In severe cases the densities may coalesce to create more extensive areas of consolidation. The opacities usually disappear within 6–12 days and almost always within a month.

**Investigations and diagnosis**

The white count is usually normal or high normal with a relatively low eosinophilia. Higher counts, with a total eosinophil count of greater than  $5 \times 10^9/L$  or even as high as  $16.5 \times 10^9/L$ , have been recorded. IgE and IgM levels are elevated in the acute phase of the illness but this is little aid to diagnosis [34].

Sputum should be examined for eosinophils and larvae and stools should be examined for parasites. Since the larvae of *Ascaris* only become adult some 6–8 weeks after infestation, eggs are unlikely to be found in the stools before this time. Stools should therefore be re-examined some 2–3 months after the onset of symptoms.

The main diagnostic problem arises from the radiographic abnormality, which needs to be differentiated from pneumonia, tuberculosis and pulmonary infarction. The transient nature of the shadows excludes tuberculosis; microbiology should help to exclude pneumonia; and pulmonary infarction, although it may cause similar pulmonary shadows, is not associated with eosinophilia unless there is a contemporaneous chronic parasitic infection.

**Treatment**

As the condition is usually mild, no specific therapy for the pulmonary eosinophilia is required. With severe manifestations oral corticosteroid therapy is extremely effective [34]. The *Ascaris* infestation may be treated with piperazine citrate 4 g in a single oral dose given after the larvae have developed into adult worms.

**Asthmatic pulmonary eosinophilia or allergic bronchopulmonary aspergillosis**

**Definition**

Asthmatic pulmonary eosinophilia is characterized by asthmatic symptoms, recurrent shadows on the chest radiograph and blood eosinophilia. The expectoration of inspissated mucus in the form of pellets or bronchial casts is relatively common.

**Aetiology**

This is by far the most common cause of pulmonary eosinophilia and it is seen worldwide. The paucity of cases in North America [39] has been attributed more to failure of recognition than to a true difference in prevalence [40]. The disease may be seen at any age, more commonly in women than men. Most cases are associated with type I hypersensitivity to *Aspergillus fumigatus*, hence the name [41–46]. Of 143 cases of pulmonary eosinophilia reported by McCarthy and Pepys [41], 111 had allergic bronchopulmonary aspergillosis; in a more recent series, 33 of 65 patients with pulmonary eosinophilia met the criteria for this condition [46]. The condition is now well recognized as a serious complication of cystic fibrosis [47,48]. The suggested criteria for a diagnosis of allergic bronchopulmonary aspergillosis are shown in Table 38.2. Other cases may be due to hypersensitivity to *Candida* antigens and individual cases due to hypersensitivity to *Pseudomonas aeruginosa*, *Aspergillus terreus*, *Helminthosporium* and *Curvularia lunata* have been reported [49–53].

The presence of high serum IgE levels in such patients, with marked elevations of IgE during acute episodes of pulmonary eosinophilia, suggests an important contribution from a type I hypersensitivity reaction and the acute rises may represent a response to an increased burden of *Aspergillus* antigen. The occurrence of late skin reactions to *Aspergillus* in many patients has also suggested that type III hypersensitivity mechanisms may be involved. However, it must be confessed that a complete understanding of the immunological mechanisms involved, which are surely more complex than those suggested above, is not yet available. A full account of the

**Table 38.2** Diagnostic criteria for allergic bronchopulmonary aspergillosis.

Asthma
Chest X-ray
Peripheral blood eosinophilia
Positive skin-prick test for <i>Aspergillus</i> antigen
Positive serum <i>Aspergillus</i> precipitins
Raised serum IgE levels

**Table 38.3** Drugs causing pulmonary eosinophilia.

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Ampicillin [54]
Beclometasone dipropionate (inhaled) [55]
Bleomycin [56]
Carbamazepine [57]
Chlorpromazine [58]
Chlorpropamide [59]
Clofibrate [60]
Cocaine (inhaled) [61]
Disodium cromoglicate (inhaled) [62]
Diclofenac [63]
Febarbamate [64]
Fenbufen [65]
Glafenine [66]
Granulocyte-macrophage colony-stimulating factor [67]
Heroin (inhaled) [68]
Ibuprofen [69]
Imipramine [70]
Interleukin 2 [71]
Interleukin 3 [72]
Iodinated contrast dye [73]
L-tryptophan [74,75]
Mephensin carbamate [76]
Methotrexate [77]
Methylphenidate [78]
Minocycline [79]
Naproxen [80]
Nickel [81]
Nitrofurantoin [82]
Para-aminosalicylic acid [83]
Penicillin [84]
Penicillamine [85]
Pentamidine (inhaled) [86]
Phenytoin [87]
Primethamine [88]
Rapeseed oil [89]
Sulfadimethoxine [90]
Sulfadoxine [91]
Sulfasalazine [92,93]
Sulindac [94]
Tetracycline [95]
Tolazamide [96]
Tolfenamic acid [97]
Vaginal sulfonamide cream [98]

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manifestations, diagnosis and treatment of allergic bronchopulmonary aspergillosis is given in Chapter 34.

### **Drugs and pulmonary eosinophilia** (see Chapter 55)

A large number of drugs have been associated with pulmonary eosinophilic episodes (Table 38.3). The pulmonary shadowing usually develops within several days of starting therapy with the drug and resolves within 1 week of stopping the drug, although occasionally episodes may persist for longer periods of time. Recurrence is only seen following rechallenge with the drug. The clinical and radiological features are similar to those of Loeffler's syndrome in the majority, although some cases more closely resemble the severe and prolonged

illness of chronic eosinophilic pneumonia. Some reactions are self-limiting but therapy with corticosteroids is often employed to hasten resolution.

### **Tropical pulmonary eosinophilia**

Weingarten [99] first described the condition of spasmodic bronchitis associated with leucocytosis, marked eosinophilia and a dramatic response to organic arsenicals in India.

### **Aetiology**

The condition has been reported in India, Sri Lanka, Burma, Malaysia, Indonesia, tropical Africa, South America and the southern Pacific [100,101] and may give rise to diagnostic difficulties when seen in immigrants in non-endemic countries [102]. There is little doubt that it represents a hypersensitivity reaction to filarial infestation because:

- 1 microfilariae have been demonstrated in the lung, liver and lymph nodes of typical cases [103];
- 2 high antifilarial antibody titres are found in patients and the titre diminishes after cure [104–106];
- 3 histamine release from basophils challenged with filarial antigen is much higher in patients with pulmonary eosinophilia than in patients with other manifestations of filarial infection [107];
- 4 the condition responds dramatically to antifilarial treatment.

### **Pathological features**

In the early weeks of the disease, histiocyte infiltrates in alveolar spaces give way to eosinophilic bronchopneumonia and eosinophilic abscesses [106,108]. After several months, eosinophils, histiocytes and lymphocytes often organize into nodular patterns, progressively evolving to predominantly histiocytic granulomatous responses marked by increasing fibrosis.

### **Clinical features**

Males comprise 80% of patients. The onset is often insidious with cough, sputum, wheeze, dyspnoea and chest pain [100,106,109]. Fever, weight loss and fatigue are common. These symptoms may continue for weeks or months with remissions and recurrences. Auscultation may reveal rhonchi and/or crepitations.

### **Radiographic abnormalities**

The chest film may be normal, although the typical appearance is of bilateral indefinite mottling uniformly distributed in both lung fields and involving the middle

and lower zones [100,106]. Increased bronchovascular markings may be noted and occasionally mottled shadows become confluent to produce a pneumonic appearance [110]. Cavitation and pleural effusion have also been recorded [111,112].

### Other investigations

There is nearly always an absolute eosinophil count of greater than  $3 \times 10^9/L$ , the usual range being  $5\text{--}60 \times 10^9/L$  [109]. The filarial complement test is positive. The sputum may contain predominantly eosinophils as does bronchoalveolar lavage fluid [113]. A marked increase in IgE concentration occurs, the IgE concentration appearing to be related to the degree of eosinophilia [105,114]. IgE levels are threefold higher in relapsing disease than in the primary disease [114].

Pulmonary function tests have shown an obstructive pattern in the early stages of the disease, progressing to a predominantly restrictive pattern with a decrease in DLCO in untreated long-standing cases [115–117].

### Treatment

Diethylcarbamazine in a dose of 6–8 mg/kg daily should be given orally in three divided doses for 10–14 days or for as long as 4 weeks [100]. Relief of symptoms occurs within a few days, and improvement of pulmonary function tests towards normal is detected in those who are treated early [100,115,116]. Clinical, haematological, radiological and physiological concomitants of the disease may still persist but continue to improve after the completion of 1 month of treatment with diethylcarbamazine [118]. Prolonged delay in treatment may result in irreversible pulmonary fibrosis.

### Chronic eosinophilic pneumonia or cryptogenic pulmonary eosinophilia

This category of pulmonary eosinophilia is characterized by more severe clinical manifestations and, in the absence of treatment, persistence of radiographic abnormalities.

### Aetiology

The aetiology is unknown. Some drugs, notably sulphonamides [119], nitrofurantoin [82] and chlorpropamide [59], have been implicated. In three patients the illness was associated with desensitization for allergic rhinitis [120]. In one case an associated immune complex vasculitis of skin was detected [121]; in others the pathological findings of microgranulomas and vasculitis with many degranulated eosinophils [122] has led to the suggestion that a cell-mediated reaction with release of lymphokines, which summon and activate eosinophils,

results in cellular damage largely mediated by the components of the eosinophil granules. The disease has been seen in association with an exacerbation of long-standing rheumatoid arthritis [123] and with coccidioidal infections [124].

### Pathology

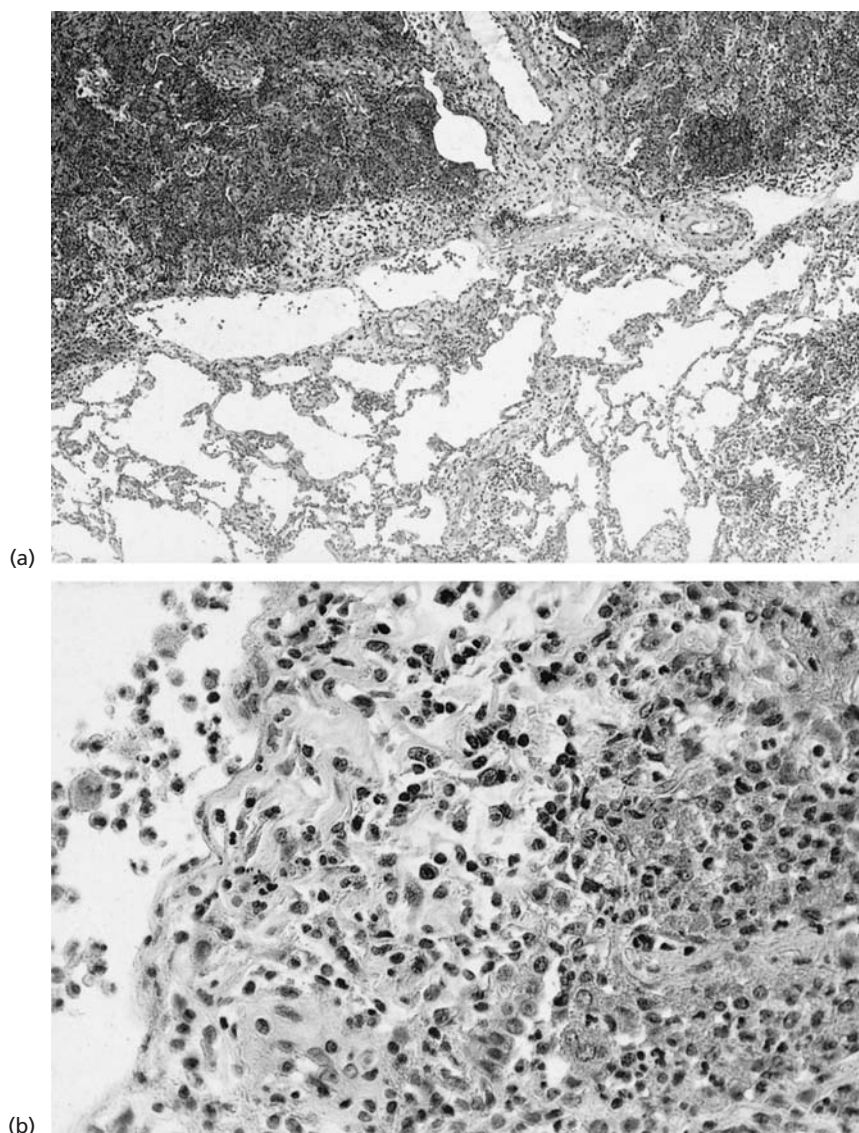
The histological findings are of interstitial and alveolar infiltration with eosinophils and histiocytes [125–127] (Fig. 38.3). The histiocytes contain eosinophil proteins and Charcot–Leyden crystals [128], and ECP is strikingly increased in bronchoalveolar lavage fluid [129]. Eosinophilic abscesses and multinucleated giant cells may be seen; mast cells, many partly degranulated, may be present. In some biopsy specimens, bronchiolitis obliterans, microgranuloma formation and vasculitis have been observed, indicating that the tissue response is not restricted to the alveoli [120–122]. Progression to lung fibrosis has been reported [130].

### Clinical features

The syndrome can occur at any age, although most patients are middle-aged women (female/male ratio, 2:1). Onset in pregnancy has been reported [131] and, although heredity is not considered a factor, the disease has been reported in identical twins [132]. The onset is usually insidious, with an average symptom duration of 7.7 months before diagnosis [133]. Patients may be moderately to severely ill, with cough and mucoid sputum, dyspnoea, malaise, weight loss, night sweats and high fever. Haemoptysis may be present and the clinical picture may mimic that of tuberculosis [125–127,133–136]. If asthma is present it is frequently of recent onset [120]. In the absence of treatment these symptoms may have persisted for weeks or months. Spontaneous remissions and recurrences have been recorded [120,137].

### Radiographic abnormalities

Radiographs typically show dense opacities, with ill-defined margins and without lobar or segmental distribution, arranged peripherally apposed to the pleura [1,120,125,126,133,137]. The opacities are usually axillary or apical but may be basal and mimic loculated pleural effusions. Opacities may disappear and recur in the same or different situations. Peculiar oblique or vertical lines without reference to the hilum or anatomical divisions may appear during resolution of the pneumonia. Gaensler and Carrington [120] described the changes as resembling the photographic negative of pulmonary oedema (Fig. 38.4), although this appearance may also occur in other conditions such as sarcoidosis [138] and bronchiolitis obliterans with organizing pneumonia [139]. Unilateral



**Fig. 38.3** Lung biopsy of patient with eosinophilic pneumonia: (a) intra-alveolar and interstitial infiltration with inflammatory cells (haematoxylin & eosin  $\times 25$ ); (b) bilobed eosinophils with granular cytoplasm, together with some histiocytes and lymphoid cells (haematoxylin & eosin  $\times 170$ ).

chest radiographic abnormalities have also been seen [135].

CT (Fig. 38.5) may show peripheral airspace disease, not always apparent on the chest radiograph [133,140]. Inapparent mediastinal adenopathy may also be detected by CT [140,141].

### Other investigations

In as many as one-third of cases, peripheral blood eosinophilia may not occur [120]. The white blood cell count may be increased and eosinophilia of over  $2.5 \times 10^9/L$  has been recorded [133]. Anaemia is not uncommon [137] and an erythrocyte sedimentation rate (ESR) as high as 100 mm in the first hour is a frequent finding [126,137,142]. Eosinophils may be seen in the sputum [126]. Bronchoalveolar lavage in one patient showed 42%

eosinophils and 48% macrophages prior to therapy, with a normal cell differential count 13 weeks after steroid therapy was instituted [143]. Dynamic lung volumes usually indicate a restrictive pattern and  $DLCO$  is decreased. Hypoxaemia, with an increased alveolar-arterial  $PO_2$  difference, may occur [125,144] and type II respiratory failure has been described [145]. IgE concentrations are normal or only slightly increased [126,135].

### Diagnosis

In most cases the radiographic and clinical appearances are so typical that a trial of corticosteroid therapy is indicated [120]. When there is doubt about the diagnosis, bronchoalveolar lavage or even open lung biopsy may be indicated to establish the diagnosis and exclude other possibilities.



**Fig. 38.4** Chest film of patient with chronic eosinophilic pneumonia before treatment with corticosteroids showing mainly peripheral areas of consolidation. His eosinophil count was  $2 \times 10^9/L$ .



(a)



(b)

**Fig. 38.5** (a) Chest radiograph of 50-year-old woman with patchy peripheral consolidation due to drug-induced chronic pulmonary eosinophilia. (b) High-resolution CT of the same patient showing patchy alveolitis and early fibrotic change. (Courtesy of Dr Lesley Gomersal.)

### Treatment

Typically, clinical improvement occurs rapidly within 2–3 days of instituting therapy with 30–40 mg of prednisolone daily. Radiographic clearing should be evident after 2–3 days and the chest film is usually normal within 10–14 days [120]. Occasionally higher doses of prednisolone are required. Decrease in the dose and withdrawal of steroids should be possible after recovery, although recurrences



requiring reinstitution of steroid therapy may occur. It is recommended that steroids should be continued in a maintenance dose of 5–20 mg daily for at least 6 months. The author usually tapers the dose slowly from the initial treatment dose over this period of time. A report of 12 cases followed for a mean interval of 10 years identified relapse (often multiple) in a majority when corticosteroids were discontinued or tapered; prompt resolution occurred with the reinstitution of therapy. A minority remained disease-free when treatment was discontinued [135]. Clearly, an attempt should be made to discontinue treatment, provided the possibility of recurrence is borne in mind.

### **Polyarteritis nodosa and allergic granulomatosis (Churg–Strauss syndrome)**

#### **Definition**

Classical polyarteritis nodosa is characterized by a necrotizing vasculitis of small and medium-sized muscular arteries with involvement of multiple organ systems. Eosinophilia and granulomas are not characteristic of this disease and the lung and spleen are usually not involved [146–149]. Allergic granulomatosis (Churg–Strauss syndrome [146–148]) strongly resembles classical polyarteritis nodosa but has some obvious distinguishing features. An allergic diathesis, particularly severe asthma, is usual and, unlike the classical disease, lung involvement is a *sine qua non* of this syndrome. Other features include peripheral blood eosinophilia, eosinophilic tissue infiltration and granulomatous reactivity. Histologically, in addition to involvement of small and medium-sized muscular arteries, small vessels such as capillaries and venules may be affected by the pathological process. To complicate matters further an ‘overlap syndrome’, with features of both classical polyarteritis nodosa and allergic granulomatosis, is now recognized.

#### **Aetiology**

In cases with pulmonary involvement the sex incidence is approximately equal. The disease is found at all ages, with a mean age at onset of 38 years [31]. The disease may prove to be an immune complex vasculitis due to type III hypersensitivity to an external or internal antigen. Immune complexes have certainly been demonstrated with vasculitis and hepatitis B antigenaemia [150,151]. When immune complexes are trapped on a vessel basement membrane, complement is activated leading to an accumulation of polymorphonuclear leucocytes that cause damage and necrosis of the vessel wall by release of lysosomal enzymes. An alternative cell-mediated mechanism, which would explain the granuloma formation, postulates that macrophages are recruited to the vessel wall by

lymphokines released from sensitized lymphocytes. The macrophages may be activated (possibly by immune complexes) to release lysosomal enzymes, with resultant vessel wall damage; at the same time the macrophages have the potential to transform into epithelioid cells with the formation of granulomas [146].

Studies using monoclonal antibodies have revealed large amounts of ECP and eosinophil protein X in the granulomas of Churg–Strauss syndrome. Activated and degranulating eosinophils are a feature of the pathological lesions and it would appear that these cytotoxic eosinophil proteins may play an active part in the development of the lesions [152].

In one large series [149] approximately one-quarter of the patients had received various drugs, most often sulphonamides, before the onset of their illness, and it has been suggested in the past that a real decrease in the incidence of polyarteritis was associated with a decline in the use of sulphonamides [153].

#### **Pathological features**

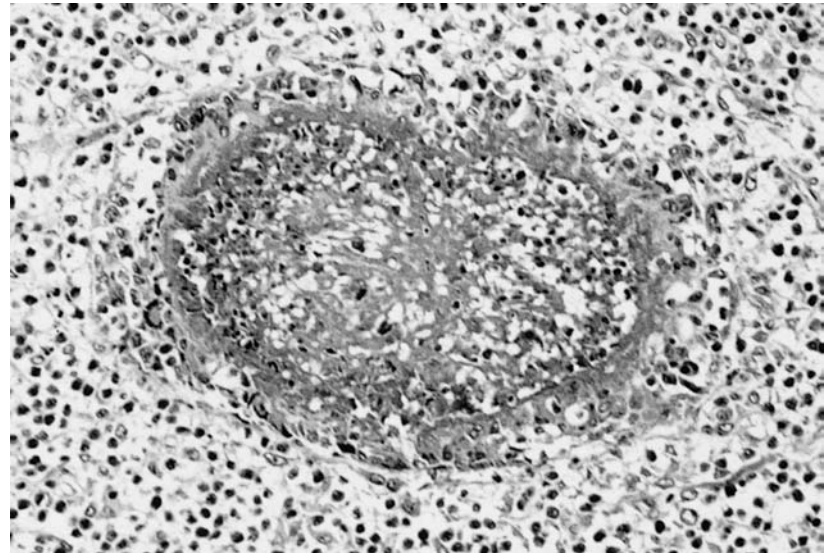
Macroscopically, necrotic lesions, infarcts and bronchiectasis may be found in the lungs [147–149]. The necrotic lesions may be nodular and cavitated and may give rise to areas of intra-alveolar haemorrhage. Microscopically, the necrotic areas are surrounded by giant cells, lymphocytes, plasma cells and neutrophils and there may be diffuse eosinophil infiltration. In the pulmonary arteries and veins, there is proliferation of intimal connective tissue and infiltration with eosinophils and neutrophils. The media particularly of the arteries often shows fibrinoid change, sometimes with giant cells, and granulomatous reactions are found in connective tissue and vessel walls (Fig. 38.6).

#### **Clinical features**

Patients with Churg–Strauss syndrome almost invariably have an illness presenting with respiratory symptoms [31,147,154]. These symptoms may precede other evidence of systemic involvement by a number of years. Asthma is the most common presenting symptom and is usually chronic and severe. Upper airway involvement may manifest as rhinitis, sinusitis or nasal polyps. In one series, asthma preceded the vasculitis in 80% of cases and the mean duration of this preceding asthma was 8 years [154]. Incidents of ‘pneumonia’ with cough and blood-stained sputum may occur and sputum may contain numerous eosinophils. There may be fever [154] and other systemic symptoms, including weakness, malaise, arthralgia, night sweats, myalgia and loss of weight. A diagnosis of tuberculosis may initially be considered (Fig. 38.7).

In patients with involvement of other systems, symptoms and signs referable to these systems may be noted.





**Fig. 38.6** Small artery from necropsy specimen in patient with Churg–Strauss syndrome showing a florid necrotizing vasculitis with thrombosis and inflammatory cells in the occluded lumen (haematoxylin & eosin  $\times 170$ ).

These include heart failure, pericarditis and hypertension [155,156]. The gastrointestinal tract may be involved, resulting in abdominal pain, diarrhoea or bleeding [31]. Skin lesions are found in 70% of patients and may include petechiae, purpura, nodules or urticaria. Mononeuritis multiplex occurs in 66% and central nervous system involvement in 29% [31]. Reversible exophthalmos and hearing loss have been reported [157].

### Radiographic features

In the chest film, patchy pneumonic consolidation often resembling chronic eosinophilic pneumonia is found and the shadows may have the same migratory characteristics [154,158,159]. Diffuse interstitial shadows may occur (Fig. 38.7) and nodules, which may cavitate, are frequently seen. Pleural effusion has been recorded. The clinical and radiographic presentation may be confused with tuberculosis.

### Other investigations

Anaemia and leucocytosis are common and eosinophilia occurs [31,147,154], with absolute counts higher than  $5 \times 10^9/L$  in one series [149]. The ESR is usually markedly elevated and a high plasma globulin fraction is found. IgE levels are elevated in most patients [160,161]. Anti-neutrophil cytoplasmic antibodies of the *P* type are commonly present [162,163]. Pulmonary function tests show obstructive defects. The diagnosis is established by biopsy of involved organs. Transbronchial lung biopsy is inadequate and open or thoracoscopic lung biopsy is preferred.

### Treatment

Without treatment the course of the disease is progressive,

with exacerbations and partial remissions. In one series [149], 70% of those beginning with a respiratory illness were dead within 1 year. The treatment of choice is corticosteroids and large doses, such as 40–60 mg of prednisolone daily, are often needed initially and should be continued for several weeks to ensure remission of the vasculitis [31]. With remission of symptoms and establishment of a normal ESR, the dose can be tapered to a maintenance level which, typically, is continued for at least 1 year. In the Mayo Clinic series of 30 cases treated with high-dose corticosteroids, 15 patients nevertheless died with a mean time to death of 4 years [154]. In cases resistant to corticosteroid therapy, remission may be induced by the addition of azathioprine [164] or cyclophosphamide [165]. Methylprednisolone pulse therapy has been used successfully in patients failing to respond to oral prednisolone [166,167].

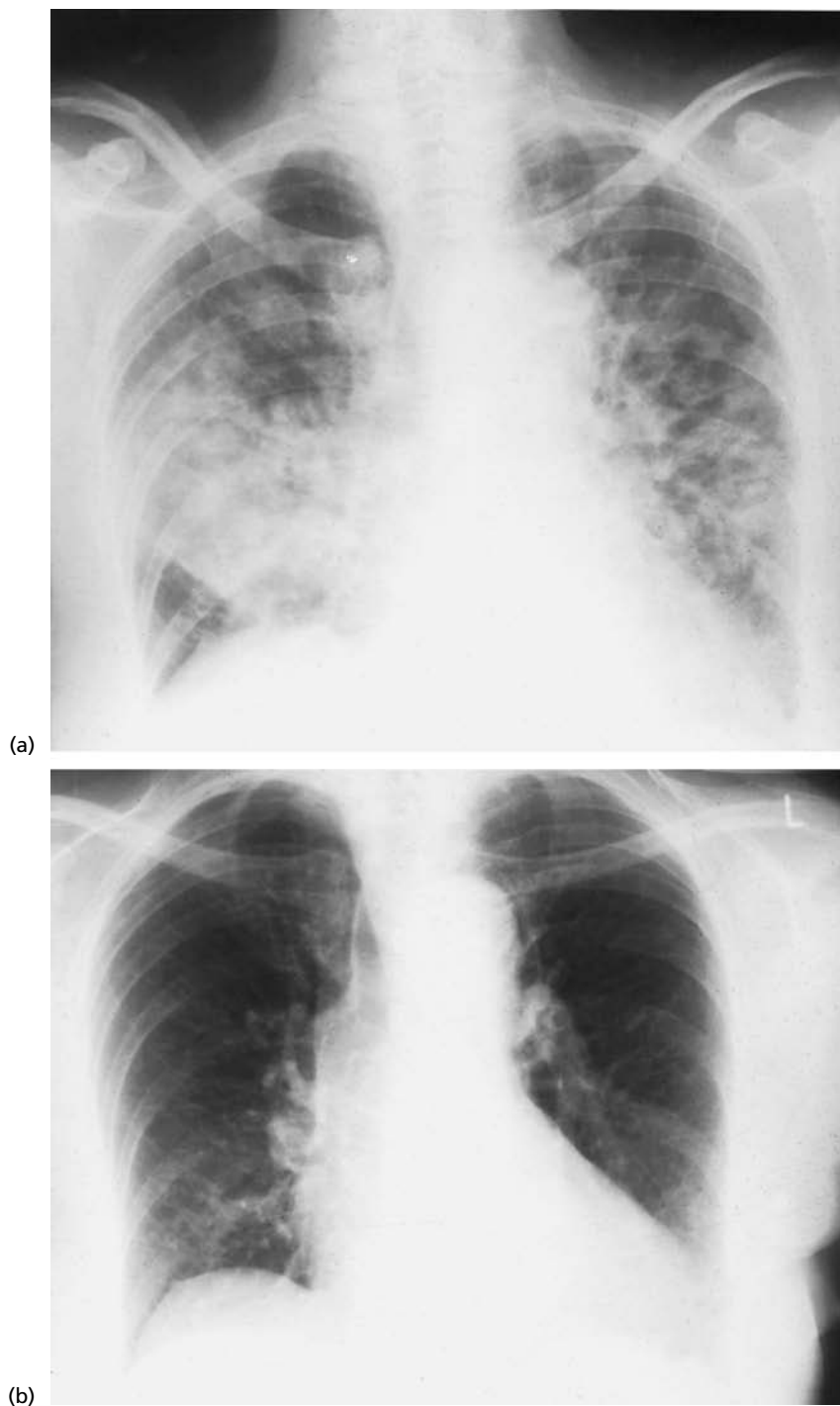
### Hypereosinophilic syndrome

This rare syndrome is characterized by marked peripheral blood eosinophilia and by eosinophilic infiltration of many organs in the absence of a known cause [168,169]. Suggested criteria for the diagnosis are:

- 1 persistent peripheral eosinophilia of greater than  $1.5 \times 10^9/L$  for longer than 6 months;
- 2 signs and symptoms of organ involvement;
- 3 no evidence of allergic, parasitic, vasculitic, neoplastic or other known cause of eosinophilia [168].

### Clinical features

The cause of the hypereosinophilic syndrome is unknown. Onset is usually in the third or fourth decade and males predominate [170]. The clinical presentation may



**Fig. 38.7** Churg–Strauss syndrome: the patient presented with fever, arthralgia, dyspnoea and haemoptysis. Chest film showed diffuse patchy consolidation (a) that responded rapidly to high-dose corticosteroids (b).

superficially resemble that of eosinophilic pneumonia, with systemic symptoms including fever, night sweats, anorexia, malaise, weight loss, pruritus and cough. However, a profound peripheral eosinophilia is usually present, with eosinophils comprising 30–70% of a normal or increased white count [168]. IgE levels are often high. Eosinophils are present in large numbers in the bone marrow, and eosinophilic metamyelocytes, myelocytes

and even myeloblasts may be found in the peripheral blood [168].

Pulmonary involvement, typically presenting as cough that is worse at night, may be seen in up to 40% of patients. Chest radiographs may show interstitial infiltrates and pleural effusions are common [168]. Bronchoalveolar lavage shows high percentages of eosinophils [171].

Cardiovascular involvement is the major cause of morbidity and mortality [172,173]. Endocardial fibrosis, restrictive cardiomyopathy, valvular damage and mural thrombus formation may occur. Arterial (and venous) thromboembolic disease is common. Splinter haemorrhages are frequent but infarction of the kidney, spleen, cerebrum and retina are also seen; deep vein thrombosis and other peripheral vascular occlusions such as femoral artery embolism have been recorded. Finally, eosinophil infiltration of the kidney, skin, gastrointestinal tract, joints and muscles may also give rise to symptoms.

Serum levels of interleukin-2 receptors appear to correlate with disease activity and severity [174].

### Treatment

About 50% of patients respond to extended initially high-dose oral corticosteroid therapy beginning with 60 mg of prednisolone daily [175]. It has been suggested [175] that treatment should be reserved for those with demonstrable end-organ damage due to the hypereosinophilia. Other drugs that have been used successfully include hydroxycarbamide (hydroxyurea), cyclophosphamide, azathioprine, interferon  $\alpha$ , cyclosporin, etoposide and vincristine [168,170,176–178].

## Acute eosinophilic pneumonia

### Diagnostic criteria

This relatively new entity was first described in 1989 [179,180]; the diagnostic criteria are given in Table 38.4 [31].

### Clinical features

Patients may be of any age or sex and typically present with an acute febrile illness of several days' duration with associated myalgia, pleurisy and hypoxaemia often requiring ventilatory support. There may be a history of allergic rhinitis [136]. Physical examination confirms fever, respiratory distress and diffuse inspiratory crepitations, usually without wheeze, on auscultation. There may be signs of pleural effusion.

**Table 38.4** Diagnostic criteria for acute eosinophilic pneumonia [31].

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Acute febrile illness of <5 days' duration
Hypoxaemic respiratory failure
Diffuse alveolar or mixed alveolar interstitial chest radiographic infiltrates
Bronchoalveolar lavage eosinophils >25%
Absence of parasitic, fungal or other infection
Prompt and complete response to corticosteroids
Failure to relapse after discontinuing steroids

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### Radiology

The chest radiograph typically shows diffuse alveolar or alveolar–interstitial infiltrates. Peripheral infiltrates (unlike chronic eosinophilic pneumonia) are unusual. Kerley B lines are common. Small to medium pleural effusions are often seen and, if tapped, show a high percentage of eosinophils [181].

### Other investigations

Peripheral blood eosinophilia is not usually found; in striking contrast, the eosinophil count in bronchoalveolar lavage fluid is high with an average of 42% in one early series [179]. Serum IgE levels have been elevated in some but not all patients. Pulmonary function studies show a restrictive pattern with a low diffusing capacity [181]. Lung biopsy confirms the presence of a non-vasculitic eosinophilic pneumonia [182].

### Treatment

Hypoxaemia may be severe enough to require ventilatory support. Treatment is with high-dose (60–125 mg daily) prednisolone or methylprednisolone until respiratory failure resolves. The lowest effective initial dose has yet to be determined, although it has been established that continuation therapy with 40–60 mg daily for 2–4 weeks with a subsequent tapering of dosage to zero over a further 2–4 weeks does not occasion relapse. The cause of this condition, if indeed it is a separate entity, remains to be determined. An acute hypersensitivity phenomenon has been suggested [179].

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# SARCOIDOSIS

A. GORDON LEITCH

## Definition

Until the precise cause of sarcoidosis is known, the following descriptive paragraph prepared by the Seventh International Conference on Sarcoidosis will continue to be useful in place of a definition:

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology most commonly affecting young adults and presenting most frequently with bilateral hilar lymphadenopathy, pulmonary infiltration and skin or eye lesions. The diagnosis is established most securely when clinicoradiographic findings are supported by histological evidence of widespread non-caseating epithelioid granulomas in more than one organ or a positive Kveim–Siltzbach skin test. Immunological features are depression of delayed-type hypersensitivity, suggesting impaired cell-mediated immunity, and raised or abnormal immunoglobulins. There may also be hypercalciuria with or without hypercalcaemia. The course and prognosis may correlate with the mode of onset: an acute onset with erythema nodosum heralds a self-limiting course and spontaneous resolution, while an insidious onset may be followed by relentless progressive fibrosis. Corticosteroids relieve symptoms and suppress inflammation and granuloma formation [1].

Since this description was published in 1976, substantial advances in the understanding of the immunology of sarcoidosis have resulted from the application of the technique of bronchoalveolar lavage (BAL) via the fiberoptic bronchoscope. These advances are described in detail later in the chapter and considerably enhance the outline of the immunological abnormalities given in the above description.

## Historical background

In 1936 Hunter [2] suggested that a case seen by Hutchinson in 1869 and reported in 1877 [3] may have been an example of the condition subsequently described by

Hutchinson in 1898 as Mortimer's malady. It now seems clear that Hutchinson did not himself identify the 1869 case as one of Mortimer's malady, making any claim to priority dubious [4]. In 1889 Besnier gave a detailed account of a patient with the clinical features of lupus pernio [5] and 3 years later Tenneson [6] described a similar case in which the histology was studied and the typical granulomatous lesion found.

Hutchinson in 1898 described skin lesions that principally affected the face, arms and hands and which were referred to for a long time as 'Mortimer's malady', a tribute to the lady who was the first of a series of patients with these manifestations. In his comment on four cases, Hutchinson showed remarkable foresight when he wrote 'the truth is probably that the various pathogenetic influences are capable of the most various combinations and that we have, on all sides, connecting links between maladies which have gained distinctive names'. Over the next few years, Boeck, Heerfordt and Jungling, unaware of the unitary nature of the disease, described clinical pictures that were regarded as disease entities and given eponymous designations [3,5,7–15] (Table 39.1). The term 'sarcoid' was introduced by Boeck because of a superficial resemblance of a skin lesion to sarcoma.

In 1914 Schaumann recognized the relation between the various recorded presentations and in an essay entitled 'Sur le lupus pernio' (for some reason not published until 1934) emphasized the systemic nature of the disease [13]. In 1917 he suggested the term 'lymphogranuloma benigna' [14]. This was something of a euphemism considering that Schaumann himself stated that 'the most usual course is that a classical tuberculosis manifests itself in the lungs, peritoneum, etc. causing death'. He clearly favoured a tuberculous aetiology. He felt that the benignity of the disease 'should be regarded as only relative and referred to the protracted course of the disease and, for a long time, its insignificant effect on general condition'. Apart from tuberculosis, death frequently occurred from 'debility, usually combined with severe dyspnoea and cardiac weakness'. It should, of course, be remembered



**Table 39.1** Historical background of sarcoidosis.

Date	Author	Description
1869	Hutchinson [3]	'Anomalous disease of skin of fingers' (papillary psoriasis)
1889	Besnier [5]	Lupus pernio
1898	Hutchinson [7]	Lupus vulgaris multiplex non-ulcerans (Mortimer's malady)
1899	Boeck [8]	Multiple benign sarcoid
1904	Kriebich [9]	Bone changes ('chronic osteomyelitis') in cases of lupus pernio
1905	Boeck [10]	Benign miliary lupoid
1906	Darier & Roussy [11]	Subcutaneous sarcoid
1909	Heerfordt [12]	Uveoparotid fever
1914	Schaumann [13]	'Sur le lupus pernio'
1917	Schaumann [14]	Benign lymphogranuloma
1920	Jungling [15]	Ostitis tuberculous multiplex cystica
1940+		Universal acceptance of term 'sarcoidosis'

that it was mainly the chronic form of the disease that was being recognized and that many cases were erroneously treated in tuberculosis sanatoria with inevitable exposure to infection.

With the introduction of mass miniature radiography during the Second World War, it soon became apparent that the hilar glands and lungs were affected, that many cases were asymptomatic and that spontaneous resolution was the rule in the vast majority of cases.

The relationship between erythema nodosum, bilateral hilar lymphadenopathy and sarcoidosis was first properly defined by Lofgren to give us the syndrome that bears his name [16,17]. In the 1940s the term 'sarcoidosis' was universally accepted as the name for this condition. It soon became obvious that many patients with sarcoidosis had previously been wrongly classified as tuberculosis, a situation that probably still exists in many developing countries today [18].

## Epidemiology

### Incidence and prevalence

There are considerable difficulties in obtaining reliable prevalence figures for sarcoidosis that allow valid comparisons between different geographical areas. The nature of the disease is such that many asymptomatic cases escape detection, particularly in countries where radiographic screening programmes are not available. Presentation may be to any one of a wide range of medical specialties, with all the resulting problems of collating medical records. Finally, there may be different degrees of awareness of the disease in different countries and probably also variation in diagnostic criteria.

### Mass radiography studies

The results of an international study of pulmonary sarcoidosis detected by mass radiography are shown in Table 39.2 [19]. There is considerable disparity in prevalence figures for the various countries, with a range from 0.2 per 100 000 in Poland and Brazil to 64 per 100 000 in Sweden. A more recent study from Sweden in which 64% of the population over 15 years were screened at 3-yearly intervals gave a prevalence of 19 per 100 000, which extrapolated to 24 per 100 000 assuming 100% screening [20,21]. A similar recent survey from Finland reported a prevalence of 15 per 100 000 in those over 15 years [22]. The wide range of reported prevalences may reflect a distinctive geographical pattern for the disease and suggest that sarcoidosis is an entity determined by a specific environmental factor or factors. Other factors that may contribute to geographical differences, other than the sources of error referred to in the introduction, are the age and sex structure of the population, ethnic groups and genetic factors, which are discussed later in this section.

### Data from diagnostic records

Where special efforts are made to identify all cases presenting to medical practitioners including general practitioners, the incidence is more likely to reflect the true state of affairs. A recent study of this kind in the Isle of Man [23] found a mean annual incidence of 15 per 100 000 over the years 1977–83 compared with 3.5 per 100 000 in the preceding 15 years when less intensive searching had been carried out.

A similar intensive study was conducted in four areas of the UK by the British Thoracic and Tuberculosis Association from 1961 to 1966 in predominantly Caucasian populations [24]. This found a range of annual incidences of 2.1–4.5 per 100 000 for men and 3.5–4.5 per 100 000 for women, with an increase in incidence from north to south. Peak incidence was in the age group 25–34 years. In the US Army, based on records of disability and death, the incidence of cases was found to be 11 per 100 000, with the peak incidence in the 25–29 age group [25]. The rates for Blacks were 16 times the rates for all other groups.

In developing countries, comparable figures are not easily obtained but where the disease has been sought, as in the Bantu, it has been found and is 10 times more common than in the white population [18]. In other countries where the incidence is believed to be low, such as China, South-East Asia and South America, it is still not clear whether this represents a real finding or is the result of a combination of confounding factors, such as misdiagnosis, inadequate diagnostic facilities and continuing confusion with tuberculosis [4].

Despite geographical variations in incidence of disease,

**Table 39.2** Prevalence of pulmonary sarcoidosis. (From Proceedings of the Third International Conference on Sarcoidosis 1963 [19].)

Country	Reporter	No. of cases examined (thousands)	No. of sarcoid cases			Prevalence per 100 000
			Total	Males	Females	
<i>Scandinavia</i>						
Finland	Patiala	1430	111			8.1
	Riska & Selroos	155	8			5.1
Norway	Riddervold	1448	387	181	206	26.7
Sweden	Bauer & Wijkstrom (I)	1873	1023	453	570	55*
	Bauer & Wijkstrom (II)	1351	867	396	471	64
<i>UK and Eire</i>						
London	James	868	160	87	73	19
Scotland	Douglas	1709	141	59	82	8.2
						(6.5–18)
N. Ireland	Milliken	1448	149	60	89	10.3
Eire	Logan	383				33.3
<i>Europe</i>						
Czechoslovakia	Levinsky & Altmann	3436	118	53	65	3.4
France	Turiaf	207	20			c. 10
Germany						
W. Berlin	Fried	(2200 <sup>†</sup> )	319	114	205	14.5
Leipzig	Lindig	1017	134	48	86	13.3
Hungary	Mandi & Kelemen	c. 91	5			5
Italy	Muratore	17	2			(11.6)
The Netherlands	Orie & Brugge	4591	994	370	624	21.6
Poland	Jaroszewicz	93	10			10.7
Portugal	Villar	c. 3500	6			0.2
Switzerland	Sommer	3161	515			16.3
Yugoslavia	LaGrasta	277	33	6	27	11.9
<i>America</i>						
Canada	Pollak	c. 77	>8			>10.5
Argentina	Rey	340 <sup>‡</sup>	17			5.0
	Castells	695	7			1.0
Brazil	Certain & de Paula	1810	4			0.2
Uruguay	Purriel	1839	8			0.4
<i>Asia</i>						
Israel	Rakower	422	7	6	1	1.6
Japan	Hosoda & Nobechi	193	11			5.6
<i>Australia and New Zealand</i>						
Australia	Marshall	1571	145	66	79	9.2
New Zealand	Reid	1081	171	88	83	16
						(6.1–24.3)

\*I, II, two surveys.

<sup>†</sup>Population.<sup>‡</sup>University students.

the pattern of disease in different countries is remarkably similar [26] (Table 39.3), with a few important exceptions. Patients most commonly present with respiratory symptoms, ocular or skin disease or because of a routine chest radiograph.

### Age and sex incidence

Most studies have shown the highest incidence in the third and fourth decades [24–30], with a variable female predominance [27,31,32]. Children and the aged are not immune but the disease is uncommon at the extremes of life. It is of interest that in Japan, where children over

**Table 39.3** Involvement of various tissue systems (%) in 3676 patients with sarcoidosis. (From James *et al.* [26].)

City	Intrathoracic	Reticuloendothelial*	Eyes	Skin	Erythema nodosum	Parotid	Nervous system	Bone
London	84	40	27	25	31	6	7	4
New York	92	55	20	19	11	8	4	9
Paris	94	32	11	12	7	6	4	4
Los Angeles	93	46	11	27	9	6	2	4
Tokyo	87	24	32	12	4	5	4	2
Reading	89	30	16	13	32	5	9	1
Lisbon	88	29	6	18	12	2	4	13
Edinburgh	94	39	11	7	33	5	3	1
Novi Sad	90	14	15	4	11	3	1	11
Naples	99	0	0	0.4	6	0	0	0
Geneva	97	17	12	6	11	2	1	3
Total	87	28	15	9	17	4	4	3

\*Reticuloendothelial, spleen and peripheral lymph nodes.

8 years of age are included in a comprehensive mass radiography programme, the prevalence rates for school-children have ranged from 1 to 2 per 100 000 [33].

**Ethnic factors**

As already mentioned, sarcoidosis is 16 times more common in Black compared with non-Black US soldiers and is also much commoner in the Bantu compared with the white South African population [18,25]. In London, the annual incidence of sarcoidosis was shown to be 20 per 100 000 in Black people per 100 000 in Asians and 1.5 per 100 000 in Caucasians [34]. As reported previously from London and the USA, erythema nodosum is relatively uncommon in Black people, who tend to have more extrathoracic and severe disease requiring steroid therapy [35,36]. The clinical picture in Asians and Puerto Ricans more closely resembles that in West Indians and Black people than in Caucasians [34,36].

**Familial factors**

A British Thoracic Society Research Committee investigation reported 59 families in Britain with more than one case of sarcoidosis [37]. There were three families with more than two cases, giving a total of 62 instances made up of five twins (four monozygotic and one dizygotic), 28 siblings, 22 parent–child and seven husband–wife. The total number of patients was 121, comprising 46 males and 75 females. A review of 160 published instances of familial sarcoidosis also showed a marked excess of monozygotic over dizygotic twins (13:1), supporting a genetic influence. The most striking features of these were the significantly larger proportions of like sex over unlike sex pairs among both siblings and parent–child instances and the excess of mother–child over father–child associations. The conclusions were valid even when account was taken of

the known higher incidence of sarcoidosis in females [24]. Other published reports also show a marked excess of mother–child over father–child relationships but only a slight excess of like sex over unlike sex pairs [38,39]. An Irish study described 114 index cases of sarcoidosis with a total sibling pool of 534 [40]. Of the index cases, 11 had siblings with a diagnosis of sarcoidosis giving a prevalence of sarcoidosis among siblings of 2.2%. This may suggest that genetic influences are determinants for the development of sarcoidosis. Nevertheless, the demonstration in the Isle of Man of space–time clustering of the disease is also consistent with sarcoidosis being a communicable disease [41,42].

**Human leucocyte antigens**

A number of studies of human leucocyte antigens (HLA) in sarcoidosis have been undertaken and the evidence that HLA type does not influence susceptibility to sarcoidosis is reviewed by Scadding and Mitchell [4].

There is evidence that HLA type does influence the pattern of disease. A high incidence of HLA-B8 has been found in London patients with arthropathy or erythema nodosum [43]. Two other studies have confirmed this association [44,45]: of 107 white patients with sarcoidosis, 40% had HLA-B8, while the percentages among those with arthropathy and erythema nodosum were 62% and 89% respectively. In 19 Swedish patients with acute-onset sarcoidosis (all having bilateral hilar lymphadenopathy and arthropathy and seven erythema nodosum), HLA-B8 was present in 67% and HLA-DR3 in 90% compared with frequencies of 24% and 26% in the Swedish population [46]. These authors noted that HLA-B1, -B8 and -DR3 occur in linkage disequilibrium and that this haplotype has been associated with abnormal immune responsiveness [46]. A more recent study in English Caucasians and Black West Indians with sarcoidosis has found an

increased frequency of HLA-Cw7 in the Caucasians and that HLA-DR3 and the B8/Cw7/DR3 haplotype were associated with a good prognosis in the Caucasians. No significant associated good prognostic indices were found in the West Indians [47]. In Japan, increased frequencies of HLA-DRw52 and -DR5J have been found in sarcoidosis patients, the latter being especially significant in unresolved cases [48–50].

It would appear from studies to date that HLA-B8, -Cw7 and -DR3 are associated with the hilar lymphadenopathy/erythema nodosum/arthopathy form of the disease, which carries a good prognosis. This association may explain the correlation between the frequencies of HLA-B8 and sarcoidosis with erythema nodosum in different populations, for example the frequency of HLA-B8 is 29% in London, 16% in New York and 2% in Tokyo and the percentage of patients with sarcoidosis and erythema nodosum in these cities is 31%, 11% and 4%, respectively [45].

## Aetiology

The cause of sarcoidosis is unknown. A number of aetiologies, including exposure to pine pollen or beryllium and infection with *Mycobacterium*, viruses and fungi, have been suggested and rejected as reviewed by Scadding and Mitchell [4]. Animal inoculation studies have suggested the possibility of an unidentified transmissible agent [51], as have the Isle of Man studies [41,42].

### Possible role of an unidentified transmissible agent

In 1969 Mitchell and Rees [51] reported the results of a controlled experiment in which an attempt was made to demonstrate a transmissible agent from sarcoid material. Sarcoid and non-sarcoid lymph node homogenates were inoculated into the footpads of normal and immunologically deficient mice. The early and late changes in the footpads were assessed microscopically. A substantial proportion of the mice receiving sarcoid homogenate showed the histological characteristics typical of sarcoidosis in humans, which evolved fully after a period of 6–8 months following inoculation. Kveim tests were carried out and positive results were confined to a proportion of those mice given sarcoid homogenates and were all associated with sarcoid granulomas in the footpad. Conversely, the inflammatory lesions seen in the footpads of mice inoculated with non-sarcoid homogenates were negative. The authors concluded from this preliminary work that an agent, as yet unidentified, may have been transmitted to the mice from human sarcoid tissue; however, an alternative explanation might be that they were demonstrating the reactivity of mice to a factor, or factors, common to granulomatous reactions in general. They obtained

similar results with tissues from Crohn's disease [52]; normal human lymph node extracts used as controls did not give rise to footpad granulomas or positive Kveim tests.

The work on induction of granulomas in mice by injection of human sarcoid and ileitis homogenates has been confirmed and extended by other workers and allows the speculation that the affected lymph nodes of sarcoidosis and regional ileitis and ileitis bowel may harbour transmissible agents that play a role in granuloma formation [53–56].

Later work by Mitchell and Rees [55] found that granulomas could be produced in normal or immunologically deficient mice by footpad, intraperitoneal or intravenous injections with fresh whole sarcoid homogenates, fresh supernatants or fresh 0.22- $\mu$ m filtered supernatants. In contrast, no granulomas were seen in response to identically prepared non-sarcoid tissue homogenates. Successful passage was also achieved following the inoculation of both filtered and unfiltered 'sarcoid' mouse tissue homogenates into secondary hosts [56]. The agent could be inactivated by autoclaving or by irradiation with cobalt-60 [57].

In 1983 Mitchell and Rees [58] reported that although the human tissues used had been negative microscopically and culturally for *Mycobacterium*, acid-fast bacilli had been seen in granulomatous tissues of mice passaged from sarcoid tissues of six patients. These were found in mouse lungs and spleen 17 months or more after the injection of homogenate or supernatant filtrate of mouse granulomatous tissue on first to third passage from the original injection of human sarcoid tissue 3–9 years before. *Mycobacterium tuberculosis* was grown from pooled homogenates of lungs and spleen from mice in two of these serial passages. This has fuelled interest in the suggestion originally made by Burnet in 1959 [59] that a protoplast or L form of the tubercle bacillus may be a cause of sarcoidosis.

The implication that *M. tuberculosis* might have a pathogenic role in sarcoidosis has been further explored by sophisticated and very sensitive molecular biological techniques, including polymerase chain reaction (PCR) for the mycobacterial DNA sequence known as IS6110 [60–62]. In one UK study, *M. tuberculosis* DNA was found by PCR in half the patients with sarcoidosis, one-third of the patients with inactive tuberculosis and in 60% of patients with active tuberculosis [61]. In contrast, a meticulously controlled North American study found DNA from *M. tuberculosis* in only a minority of patients with sarcoidosis [62]. An accompanying editorial [63] emphasizes that for most patients with sarcoidosis PCR analysis of their cells or tissues is unable to detect any DNA from *M. tuberculosis* at a level of sensitivity of 15 organisms per million human cells. The sensitivity of PCR for *M. tuberculosis* is fraught with hazard, particularly with regard to

contamination [63]. At present, the jury does not have enough evidence to implicate mycobacteria in sarcoidosis. It may be that detected DNA simply represents previous mycobacterial infection. Studies in patients with sarcoidosis from countries with dramatically differing prevalences of tuberculosis may resolve this issue.

### Transplantation and sarcoidosis

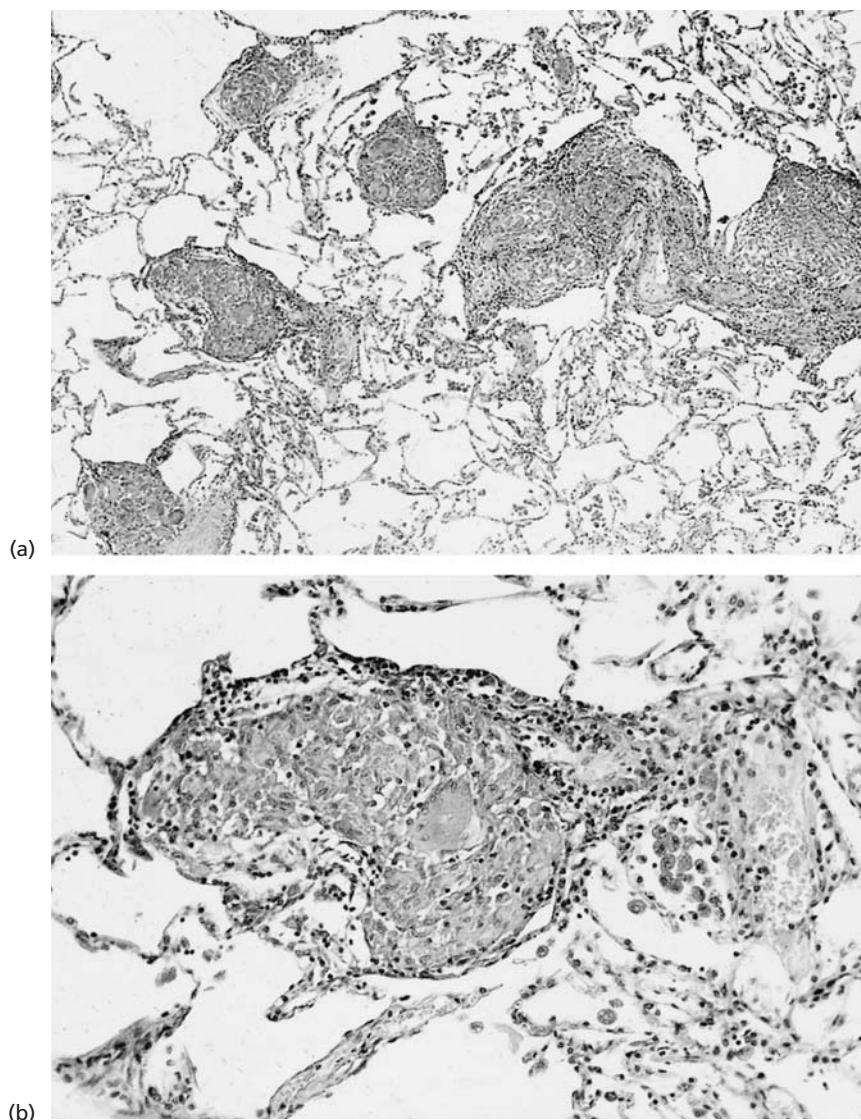
Recurrence of disease in the pulmonary allografts of patients treated for end-stage pulmonary sarcoidosis by lung transplantation has been recorded [64,65] and is consistent with current thinking about the immunopathogenesis of the disease (see below). Recurrence was limited to transbronchial biopsy evidence of granulomas within months of transplantation in one report [64] and to radiological and biopsy evidence of sarcoid infiltrates 13 months after transplantation in the other [65]. Disease

recurred despite immunosuppression and responded to an increased dose of oral prednisolone [65].

### Pathology

The histological reaction in active sarcoidosis (Figs 39.1 and 39.2) consists essentially of nodular collections of large closely packed, pale-staining histiocytes (epithelioid cells). In early lesions the nodules are all characteristically at the same stage of development. A few multinucleated giant cells are usually seen among the histiocytes and some lymphocytes are often present at the periphery of the nodule. Three different types of inclusion bodies may be found in the cytoplasm of the epithelioid and giant cells.

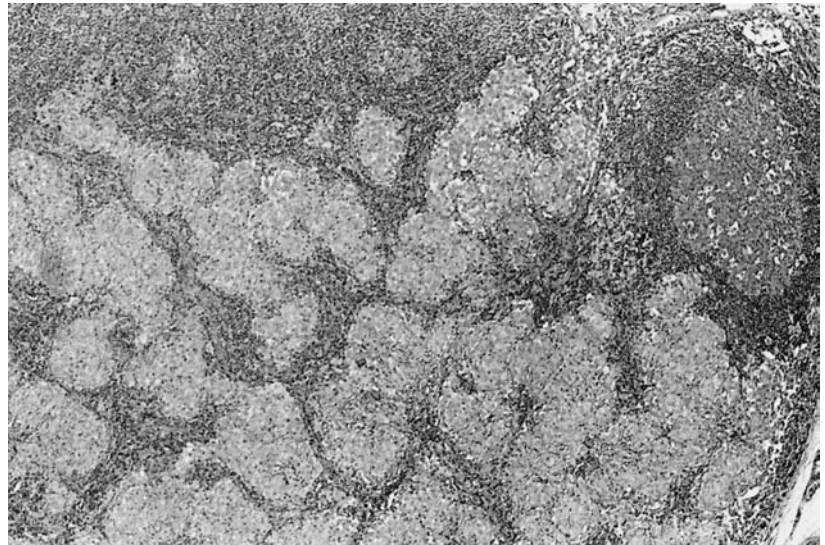
1 Schaumann bodies, which are round or oval and vary in size from that of a leucocyte to about 100  $\mu\text{m}$  in diameter. The larger of these bodies (sometimes referred to as con-



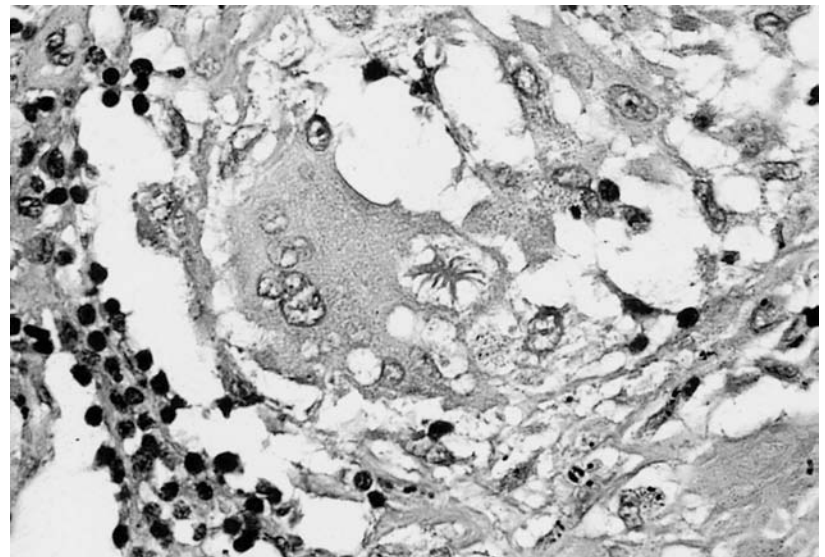
**Fig. 39.1** Resected lung from patient with sarcoidosis: (a) small, compact epithelioid and giant cell interstitial granulomas (haematoxylin & eosin  $\times 15$ ); (b) epithelioid and giant cells in the granuloma (haematoxylin & eosin  $\times 35$ ).



**Fig. 39.2** Lymph node from same patient as in Fig. 39.1 showing multiple non-caseating granulomas (haematoxylin & eosin  $\times 35$ ).



**Fig. 39.3** Multinucleate giant cell from a sarcoid granuloma containing a typical asteroid body (haematoxylin & eosin  $\times 350$ ).



choid bodies) seem to be formed of basophilic concentric lamellae that appear to contain calcium and iron.

2 Doubly refractile crystalline inclusion bodies are 1–20  $\mu\text{m}$  in diameter and may take up stains for calcium and iron.

3 Asteroid bodies consist of a central mass 2.3–3  $\mu\text{m}$  in diameter with radiating straight or centred spinous projections, the whole being 5–25  $\mu\text{m}$  in diameter (Fig. 39.3).

Necrosis does not occur in the sarcoid nodule, or is only minimal. In consequence the reticulin between the histiocytes and around the nodules remains intact. Where present, this is an important point of distinction from the tuberculous follicular reaction. No acid-fast bacilli are found in the sections or can be cultured from them, with rare exceptions that may be explained by pre-existing, coexisting or consequential independent infection.

The epithelioid cells are large mononuclear cells about 20  $\mu\text{m}$  in diameter with round or oval nuclei and are derived from macrophages. They are poorly phagocytic but highly secretory, producing acid phosphatase, cathepsin,  $\beta$ -glucuronidase, collagenase, elastase, cytolytic factors, lysozyme and angiotensin-converting enzyme [66–71]. Giant cells are up to 300  $\mu\text{m}$  in diameter, containing as many as 30 nuclei usually arranged peripherally. Giant cells occur by the fusion of macrophages, which are constantly arriving, dividing and ageing. Spector [72] points out that the macrophages in sarcoid granulomas are not only metabolically active but are turning over rapidly, in contrast to macrophages in granulomas produced by relatively inert materials such as carbon. Soler and colleagues [73] have studied serial sections of a pulmonary sarcoid granuloma by electron microscopy and noted that epithelioid cells tend to be central and

macrophages peripheral. This supports Spector's concept of the constant arrival of macrophages into a granuloma pool of mixed young and old macrophages, epithelioid and giant cells. The inclusion bodies are all non-specific end-products of the active metabolism and secretion that has taken place. As the lesion ages, reticulin fibres ramify between epithelioid cells, gradually thicken and eventually become converted into collagen. It loses its outline and becomes a solid amorphous eosinophilic mass of hyaline material.

The lymphocytes associated with the granulomas are larger than usual and morphologically appear activated [73]. Lymphocyte accumulations are more common in active lesions, when they are predominantly CD4 T-helper cells. As activity declines CD8 T-suppressor cells become more common [74]. Relatively large numbers of B cells and plasma cells are also present, suggesting that immunoglobulin production is also occurring at sites of granuloma formation [75].

Sarcoid follicles may resolve completely. When healing occurs in long-standing cases, the cellular nodules become replaced by fibrous tissue. In chronic sarcoidosis, follicles with the characteristic appearance may exist among masses of avascular fibrous tissue. Sclerosis of a follicle usually begins at the periphery with the formation of discrete hyaline clumps, which fuse to girdle the nodule; hyalinosis proceeds in a centripetal fashion until the follicle is wholly involved [76].

Several electron microscope studies have been made of Kveim and sarcoid lesions [77–82]. The epithelioid cells are seen by the electron microscope to be closely packed. At their margin, there is much plication and interdigitation of the various cells [78]. All the cells have large numbers of mitochondria indicating high metabolic activity. Certain cells show small dark bodies that are some kind of granule and may include large, pale vacuole-like bodies which probably contain protein. Very dark fibrillar material between the cells has the appearance of collagen. The giant cells show irregular peripheral nuclei and have numerous mitochondria, consistent with high metabolic activity.

The histological features of the sarcoid lesion are not specific and may occur in tuberculosis as well as leprosy, tertiary syphilis, brucellosis, primary biliary cirrhosis, hypogammaglobulinaemia, fungal infection and berylliosis [83–86]. A localized sarcoid reaction of the same histological pattern is sometimes observed in the vicinity of lesions due to carcinoma (especially in regional lymph nodes), lymphomas, fungal infections [87], trauma and chemical injury. Zirconium, a constituent of deodorant sticks, has been shown to cause a chronic axillary dermatosis via the development of a specific hypersensitivity reaction. These local tissue sarcoid reactions can usually be distinguished from systemic sarcoidosis by the absence of depressed or negative delayed-type hypersensitivity

reactions and a negative Kveim test [88]. Lack of evidence of sarcoid lesions in other tissues or organs is another distinguishing feature.

## Immunology

The granulomas of pulmonary sarcoidosis are now thought to be the consequence of activation of lymphocytes and macrophages within the lung, with resultant release of potent mediators that play a critical part in the pathogenesis of the disease [89–92] (Fig. 39.4). The stimulus for activation is unknown, although the state of activation of lung mononuclear cells is characteristic of that due to antigen stimulation and it may be that an unknown antigen is involved. In support of an unknown antigen is the finding of circulating immune complexes, particularly in the early stages of the disease [93–97]. Major advances in understanding the pathogenesis of sarcoidosis have come from studies on cells obtained by BAL using the fiberoptic bronchoscope [98]. Studies that have compared lavage with biopsy cell populations, including typing of T cells, suggest that cells obtained by lavage are representative of those found in biopsies from the same patient [99–101]. The total number of cells recovered at BAL is increased, with striking increases in the absolute numbers of macrophages and lymphocytes, although the percentage of macrophages decreases while the lymphocyte percentage increases (Fig. 39.5).

## Lung lymphocytes

In active sarcoidosis the vast majority of lavage lymphocytes are T lymphocytes and of these most are CD4 T-helper cells, these cells outnumbering T-suppressor cells by 10 to 1. The T cells are activated, as demonstrated by increased rosetting with sheep erythrocytes at 37°C, and have been shown to release a number of lymphokines [101–105]. These include interleukin (IL)-2, a 15-kDa glycoprotein known to induce T-cell activation and replication [106]. Such activated T cells release other lymphokines that produce polyclonal B-cell activation and increased immunoglobulin production resulting in hyperglobulinaemia [106–108]. In addition, activated T cells release monocyte chemotactic factor and migration inhibition factor that act together to attract, immobilize and activate monocytes, the building blocks of granuloma formation [109].

## Lung macrophages

The macrophage population in the lung is increased in active sarcoidosis and consists of alveolar macrophages and young macrophages that are probably freshly recruited monocytes [90]. The macrophages are activated, as shown by increased uptake of gallium-67 [110] and the



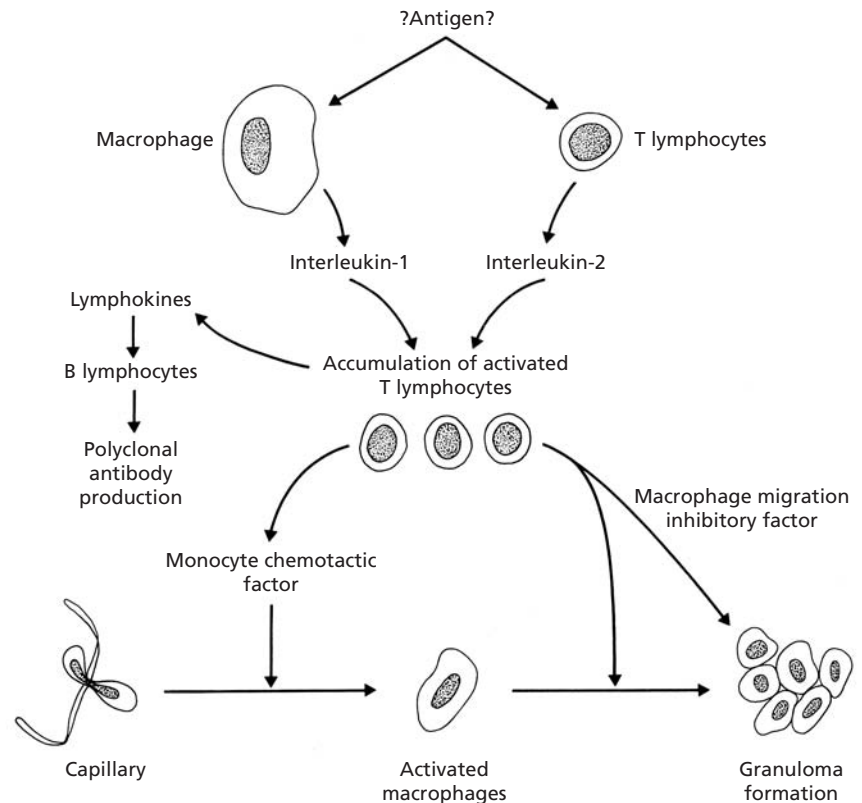


Fig. 39.4 Pathogenesis of granuloma formation (see text for explanation).

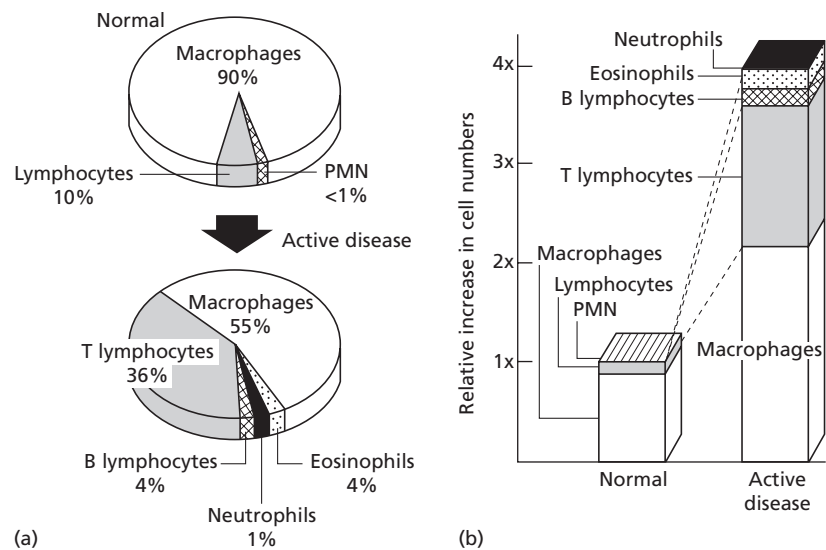


Fig. 39.5 Proportions (a) and total numbers (b) of cells obtained by bronchoalveolar lavage in normal subjects and in active sarcoidosis. (From Crystal *et al.* [90].)

release of mediators. IL-1 is released and leads to T-cell activation [111,112]. In addition, the release of interferon  $\gamma$ , fibronectin and alveolar macrophage-derived growth factor may promote fibroblast recruitment, attachment and proliferation and lead to fibrosis [89,113]. Transforming growth factor  $\beta_1$  can also be demonstrated in the sarcoid granuloma [114].

## Blood

In striking contrast to the findings in the lung, peripheral blood in sarcoidosis usually shows a lymphopenia with a lower than normal ratio of T-helper to T-suppressor cells [115–117]. Where the ratio of T-helper to T-suppressor cells is low, blood lymphocytes show diminished phytohaemagglutinin responsiveness [116]. These findings may explain the depression of delayed-type hypersensitivity

that has long been noted as a feature of sarcoidosis. Thus, reactions to tuberculin, mumps virus antigen, *Candida albicans* antigen and trichophytin have all been shown to be depressed in patients with sarcoidosis [118–122]. The hyperglobulinaemia that is a feature of chronic active sarcoidosis is largely due to overproduction of predominantly IgG and IgA at sites of disease activity [95,108].

### Modes of presentation

The diversity of the possible clinical manifestations is such that a practitioner in almost any branch of medicine may be called upon to make the diagnosis. All kinds of combinations of organ involvement are possible [123] (Table 39.4). With the exception of the pleura, the serous membranes are rarely involved but only the adrenals appear to be sacrosanct. No authenticated adrenal involvement has been reported apart from a suggested but unproven case in one series [124].

Sarcoidosis would be relatively unimportant if not for the fact that it can affect vital organs in a chronic fashion, with the development of irreversible fibrosis resulting in functional impairment. Involvement of the eyes can lead to blindness and death can occur from cardiac, respiratory or renal failure.

### Thoracic sarcoidosis

#### Clinical features

The hilar glands and the lungs are the organs most commonly affected in sarcoidosis and intrathoracic involvement is the most frequent accompaniment of sarcoidosis affecting other organs (see Table 39.3). By convention thoracic sarcoidosis is classified in four stages on the basis of the appearances of the chest radiograph. Stage I represents hilar lymphadenopathy (Fig. 39.6), stage II hilar adenopathy plus pulmonary opacities (Fig. 39.7) and stage III pulmonary opacities only. Stage IV represents the development of irreversible pulmonary fibrosis.

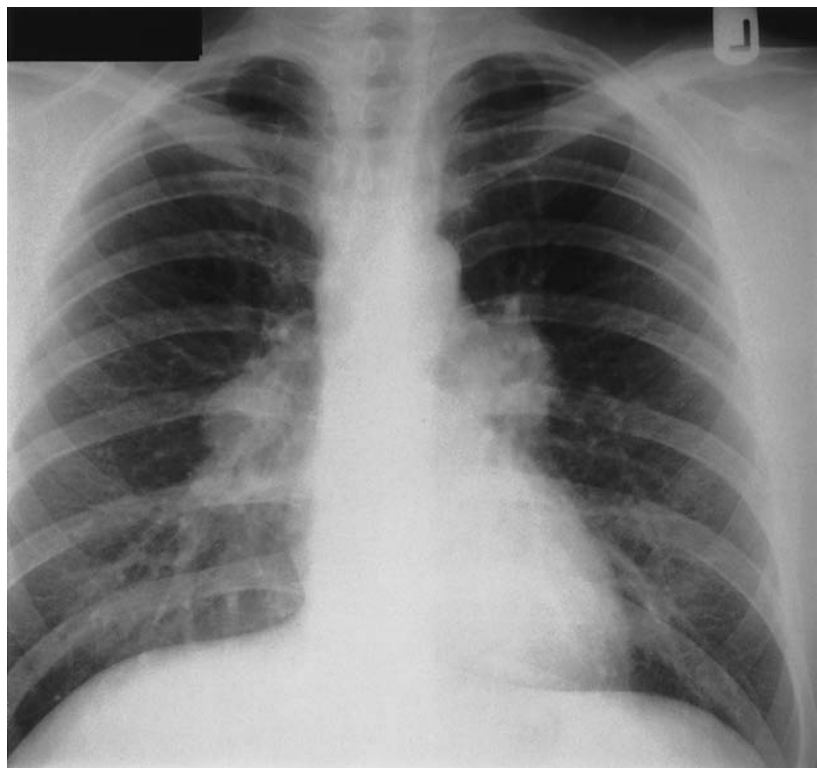
#### Hilar lymphadenopathy

Enlargement of hilar lymph glands with or without paratracheal lymphadenopathy is the commonest manifestation of sarcoidosis (Fig. 39.6). Usually, the glands are bilaterally and symmetrically involved, although rarely hilar enlargement may appear unilateral [125,126]. Many cases of hilar lymphadenopathy due to sarcoidosis undoubtedly go unrecognized because of the absence of symptoms.

In the UK, the most common association that may suggest the diagnosis is erythema nodosum [127]. Sarcoidosis is now the most likely cause of erythema

**Table 39.4** Possible presentations of sarcoidosis.

<i>Chest physician</i>
Hilar glands
Diffuse pulmonary opacities
Breathlessness
<i>Ophthalmologist</i>
Uveitis: anterior and posterior
Conjunctivitis
Non-specific
Phlyctenular
Keratoconjunctivitis
Enlarged lacrimal glands
Sjögren-like syndrome (when salivary glands involved)
Glaucoma
<i>Neurologist</i>
Peripheral neuropathy
Eye change
Meningitis
Isolated cranial nerve lesions
Space-occupying lesions
Pituitary involvement (usually posterior)
Transverse myelitis
<i>Rheumatologist</i>
Subcutaneous tissue swellings
Polyarthralgia
Bone cysts
<i>Gastroenterologist</i>
Hepatomegaly
Splenomegaly
<i>Dermatologist</i>
Erythema nodosum
Plaques
Papules
Nodules
Lupus pernio
Scars
<i>Cardiologist</i>
Pulmonary heart disease
Myocarditis and congestive cardiac failure
Conduction disorders
<i>Surgeon</i>
Diagnostic lymph node biopsy
<i>ENT surgeon</i>
Nasal granuloma
Laryngeal granuloma
<i>General physician</i>
All above, for 'sorting out'
Atypical mumps
Hypercalcaemia
Renal calculi
Impaired renal function



**Fig. 39.6** Extensive bilateral hilar lymphadenopathy in a 31-year-old man with biopsy-proven sarcoidosis.

nodosum in the 20–40 age group in this country and its occurrence should always prompt further investigation by chest radiography. The association of erythema nodosum with sarcoidosis varies throughout the world. It is common in Scandinavia [128] and the UK but is an unusual manifestation in the USA in the white as well as the black population. In North America a generation ago erythema nodosum was apparently equally uncommon as a complication of primary tuberculosis [129]. In a worldwide study of sarcoidosis, erythema nodosum was more commonly the mode of onset in the three British series than elsewhere, with a frequency of about one-third of all presentations compared with about 10% elsewhere [26]. At the extremes, the incidence in Edinburgh was 33% and in Tokyo zero.

Polyarthralgia affecting principally the knees, ankles, wrists and elbows is a frequent accompaniment of erythema nodosum and may precede the skin rash. The joint symptoms commonly subside in 3–6 weeks and joint effusions are unusual. Other presenting symptoms may include cough, dyspnoea, chest pains [130], loss of weight, malaise or excessive fatigue.

The differential diagnosis of bilateral hilar adenopathy includes tuberculosis (usually unilateral with high tuberculin sensitivity), coccidioidomycosis and histoplasmosis (USA), lymphoma (may be pain and usually systemic upset), leukaemia (blood count diagnostic), beryllium disease (occupational history), hypogammaglobulinaemia (recurrent infections) and enlarged

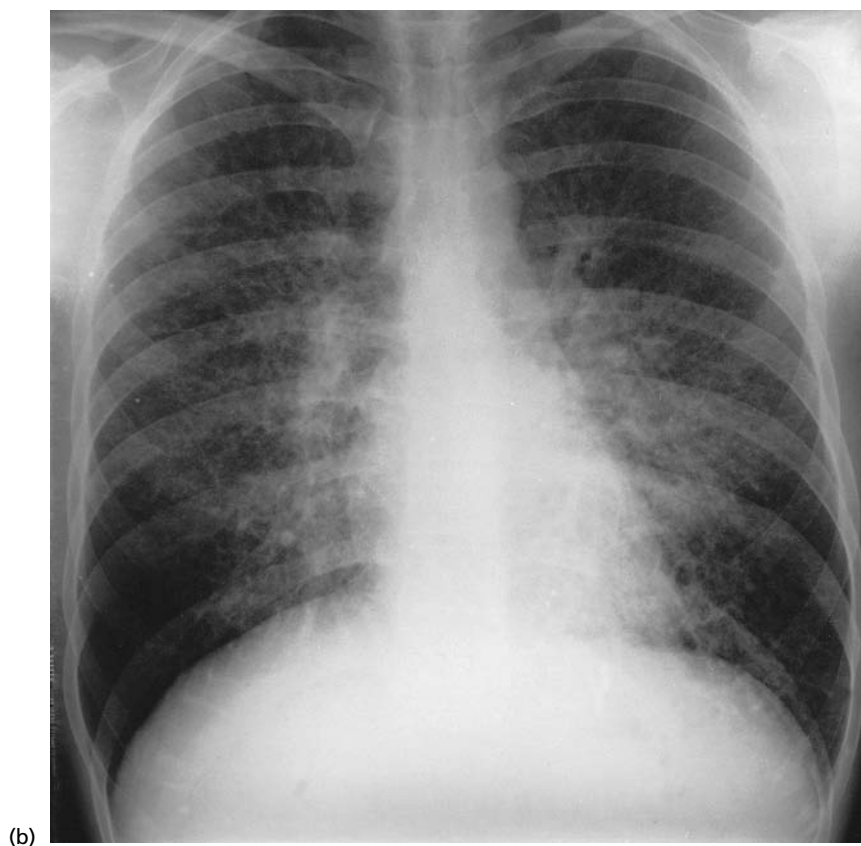
pulmonary arteries (characteristic appearances on CT scans).

The hilar lymphadenopathy syndrome with or without erythema nodosum is most commonly a benign manifestation. In the Edinburgh series of 230 cases of stage I disease, 80% resolved spontaneously in the first year and a further 10% showed spontaneous resolution in the second year [26]. In the worldwide study of 1865 cases of stage I disease, resolution ranged from 46 to 90% with an overall average of 65% [26]. The average time for the chest film to become normal is about 8 months [31]. About 1 in 10 cases of hilar lymphadenopathy develop chronic sarcoidosis with or without the development of further manifestations such as pulmonary opacities. In general, the older the age at onset, the greater the chance of chronicity. In a few of the cases that resolve spontaneously, transient pulmonary opacities may develop when the glands begin to regress and clear spontaneously thereafter [31]. Plaque-like or eggshell calcification may develop in persistently enlarged hilar and mediastinal glands [131,132] (Fig. 39.8).

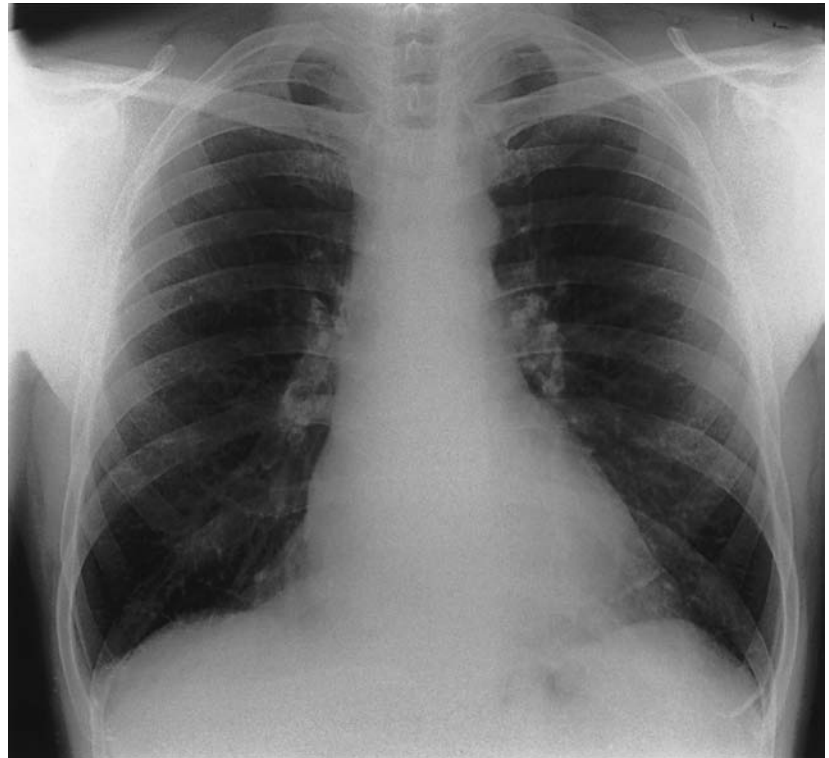
### *Pulmonary disease*

#### *Pulmonary opacities*

Most patients with pulmonary opacities present with stage II or stage III disease, although occasionally a patient presents with chronic progressive dyspnoea due to stage



**Fig. 39.7** (a) Chest radiograph of a 25-year-old man showing bilateral hilar and paratracheal lymph node enlargement (stage I sarcoidosis). (b) The same patient 18 months later showing the development of marked pulmonary shadowing (stage II sarcoidosis).



**Fig. 39.8** Calcified hilar nodes in a patient with previous sarcoid hilar lymphadenopathy. (Courtesy of Dr James Choo-Kang.)

IV disease. There are often no symptoms but there may be those already outlined for hilar adenopathy. Many types of abnormality may be seen on the chest film and these may be classified as follows:

- 1 disseminated miliary lesions (Fig. 39.9);
- 2 disseminated nodular lesions (Fig. 39.10);
- 3 linear type of infiltration extending fan-wise from the hilum;
- 4 diffuse and confluent patchy shadows;
- 5 diffuse fibrosis (Fig. 39.11);
- 6 diffuse fibrosis with cavitation [133];
- 7 diffuse ground-glass shadowing [134];
- 8 changes similar to chronic tuberculosis as regards location and distribution;
- 9 bilateral confluent massive opacities resembling areas of pneumonia;
- 10 atelectasis.

Of the varieties of pulmonary change, cavitation and atelectasis are the least common. Aspergillomas may rarely develop in cavities, apparently more commonly in men [135].

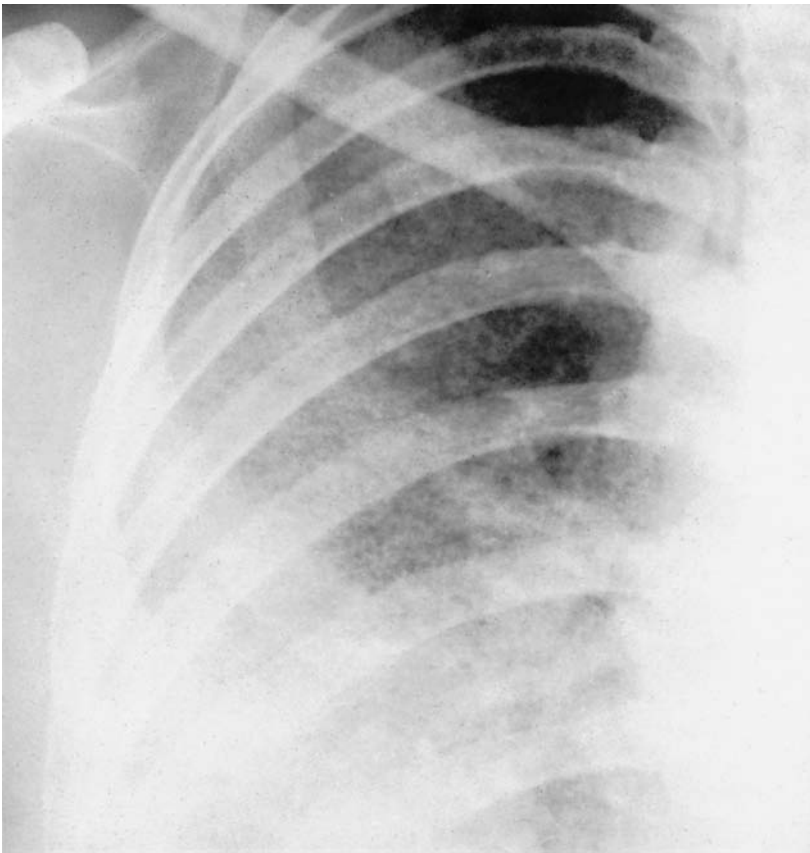
The differential diagnosis of sarcoidosis with pulmonary opacities (in which there is usually a disparity between the minimal symptoms and signs and the marked radiographic abnormalities) includes extrinsic allergic alveolitis, fibrosing alveolitis and carcinomatous infiltration (in which dyspnoea may be disproportionate to the radiographic abnormality), pneumoconiosis (occupational history), miliary tuberculosis (fever, systemic

symptoms, choroidal tubercles), metastatic malignancy (primary source may be evident), alveolar cell carcinoma (usually associated with dyspnoea if bilateral), eosinophilic granuloma (may be bone cysts on radiograph), honeycomb lung (in which evidence of mesodermal dysplasia or eosinophilic granuloma may be found) and talc granulomatosis [136].

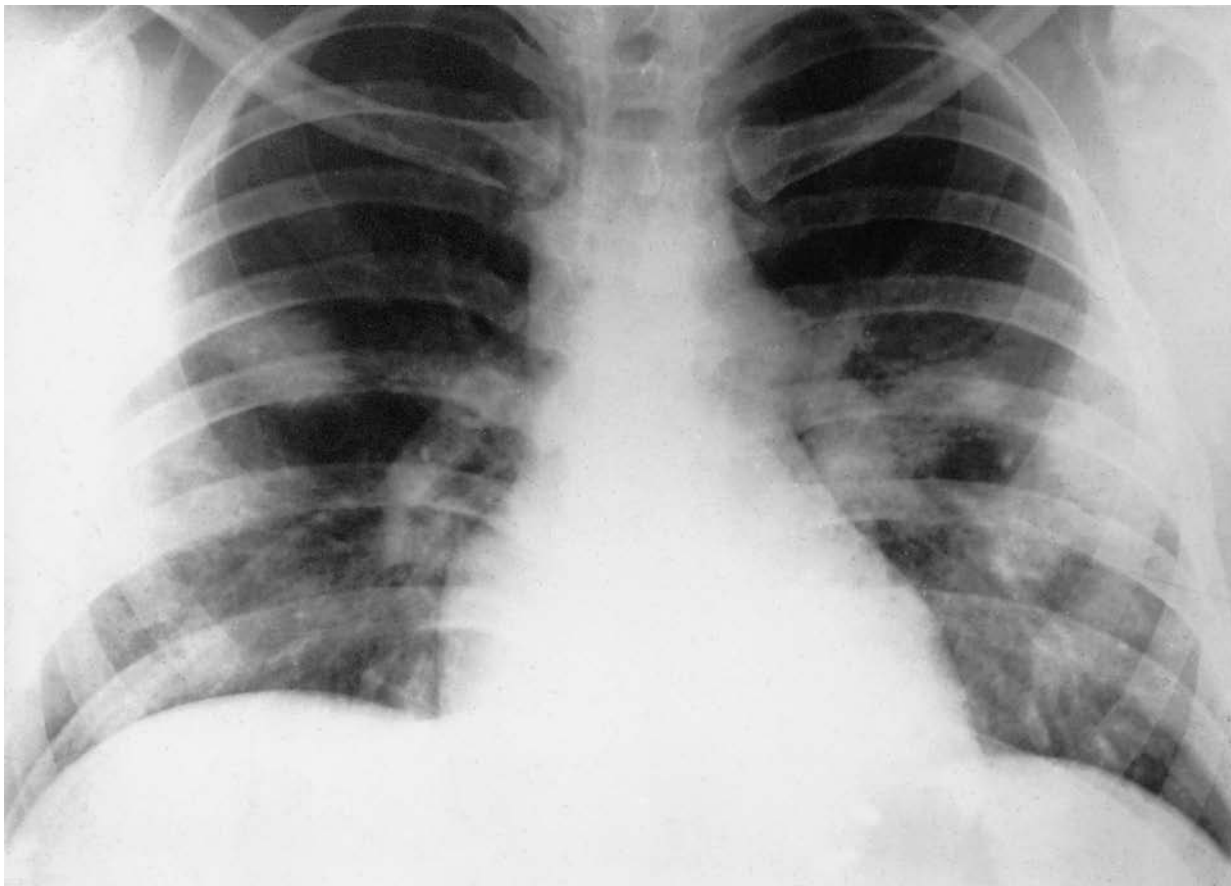
In the Edinburgh series, 60% of pulmonary opacities showed spontaneous clearing. Half of these had cleared within 1 year, 80% within 2 years and the remaining 20% in periods from 3 to 7 years. Excluding those cases taking more than 2 years to clear, the average time for spontaneous resolution of pulmonary opacities was around 11 months.

Of patients with pulmonary opacities for whom corticosteroid therapy was considered necessary, some 50% showed clearing without any rebound phenomena after the withdrawal of treatment so that overall 80% of pulmonary opacities cleared either spontaneously or with corticosteroids and did not recur. These patients obviously belonged to a transient group of sarcoidosis and the duration of corticosteroid therapy must have coincided with the period of waning of the disease. A few patients who, for a variety of reasons, were not treated with corticosteroids early in the disease progressed to serious respiratory disability as a result of pulmonary fibrosis and many have developed the features of chronic bronchitis and airflow obstruction over the years.

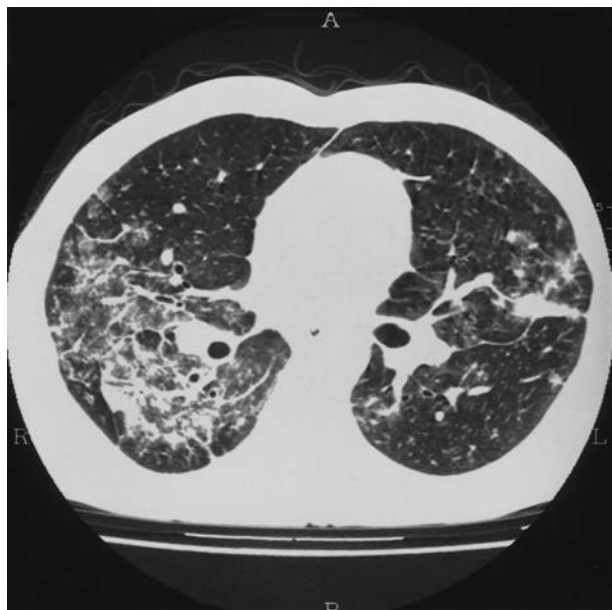
In the Edinburgh series, about 1 in 10 patients with



**Fig. 39.9** Miliary shadowing on the chest radiograph of a 21-year-old woman with sarcoidosis.



**Fig. 39.10** Bilateral coarse nodular shadows in a 40-year-old man with sarcoidosis.



**Fig. 39.11** High-resolution CT of a patient with chronic sarcoidosis showing irregular diffuse fibrosis. The patient showed no response to corticosteroids.

pulmonary involvement proved to have chronic disease, as in the hilar gland group. Males fared worse than females as far as the tendency to chronicity was concerned; fortunately, the use of long-term corticosteroid therapy would seem to have prevented major disability in the majority [137]. Of the 130 patients with stage II disease and 62 with stage III disease reported from Edinburgh, radiographic resolution, spontaneous or after treatment, occurred in 79% and 42% respectively. In the worldwide study, the percentage resolution varied quite markedly from centre to centre, with overall figures of 49% for stage II and 20% for stage III disease [26].

#### *Bronchial sarcoidosis*

The bronchi may be involved in sarcoidosis through external compression by glands, resulting in atelectasis in a very few cases [138]. Sarcoid lesions may actually be present in the bronchi and it would seem that the more often bronchial lesions are sought the more commonly they are found [139,140]. Stenosis of major airways may result [141]. Bronchial hyperreactivity to methacholine may be demonstrated but not usually in patients with normal spirometric values [142,143].

#### *Pleural sarcoidosis*

Pleural sarcoidosis is uncommon but has been reported [144–146]. In one review of the literature, pleural involvement was found in 0.8% of 2410 patients from 10 large series [147]. In contrast, in a review of 227 biopsy-proven

cases of sarcoidosis, Wilen and colleagues [145] described pleural effusion and/or thickening in 23 (10%). Pleural effusions were noted in 15 and in all of these the disease progressed to stage II or beyond. However, 87% of the patients in this series were Black and such patients are well recognized to have more florid expressions of the disease.

The effusion may be a transudate or an exudate and may appear early or late in the course of the disease. It may be blood-stained and the predominant cell is usually the lymphocyte, although eosinophilic effusion has been reported [148]. Pleural biopsy may show thickened fibrous pleura interspersed with non-caseating granuloma. Rarely, presentation may occur with acute pleuritic pain [149].

#### *Rare thoracic manifestations of sarcoidosis*

Superior vena cava obstruction has been reported in sarcoidosis due to enlarged nodes compressing the superior vena cava [150]. There has been one report of a young woman who died with progressive pulmonary hypertension and was found to have non-caseating granulomas obliterating the pulmonary veins as well as granulomas in the hilar lymph nodes and liver [151]. The author has seen a similar patient.

### **Extrathoracic sarcoidosis**

#### **Clinical features**

##### *Lymphatic system*

The lymph nodes most frequently affected in sarcoidosis are those of the hilar and paratracheal groups. Of the superficial nodes, those of the right scalene group are most commonly affected but enlargement of any of the superficial nodes may be found. The involvement of superficial lymph nodes provides readily accessible tissue for biopsy.

##### *Eyes*

Ocular manifestations have been reported in as many as 25% of patients with sarcoidosis [32,152–155]. The eyes should be examined routinely, preferably with a slit lamp, in all cases since mild asymptomatic eye involvement may be commoner than is suspected. Uveitis is the most frequent manifestation of eye involvement causing symptoms. It develops acutely with pain in the eyes and misty vision in about one-third of patients, while the remainder show the chronic form that develops insidiously. Anterior uveitis is usual in self-limiting sarcoidosis, while posterior uveitis is typical of the chronic form of the disease. Acute conjunctivitis, sometimes of the phlyctenular type, may



occur particularly in early sarcoidosis and conjunctival biopsy may provide proof of the diagnosis. Keratoconjunctivitis sicca results in dryness of the eyes; a Sjögren-like syndrome may be encountered if the salivary glands are also involved. The lacrimal glands may also be enlarged.

### *Skin*

The most common skin manifestation in sarcoidosis is erythema nodosum, which in severe cases may be associated with prolonged fever [156]. Recurrent episodes of erythema nodosum may occur sometimes over many years [157]. Maculopapular eruptions, subcutaneous nodules, plaques and lupus pernio are other lesions that may be found. Occasionally old scars, including tattoos, may become infiltrated with sarcoid tissue (Fig. 39.12). The clinical examination of a case of suspected sarcoidosis should include inspection of previous traumatic, operation and vaccination scars for the development of lividity, which suggests infiltration. Women appear to be more prone to chronic skin lesions. Rarely the site of a previous Mantoux test may become infiltrated with sarcoid tissue.

Sarcoidosis of the upper respiratory tract carries a 50% risk of the development of lupus pernio within 2–3 years [158]. The early use of corticosteroid therapy may prevent this complication.

### *Upper respiratory tract*

Sarcoidosis of the upper respiratory tract is an uncommon but disabling manifestation of the disease affecting the nose, nasopharyngeal mucosa and the larynx [158–160]. Disease of the nasal mucosa results in crusting, obstruc-

tion and discharge in varying degrees. The septum and inferior turbinates are most commonly involved, although sometimes the lesions are more widespread. The mucosa is erythematous and granular, with associated polypoid hypertrophy causing nasal obstruction that is aggravated when stagnation and crusting leads to suppuration, purulent discharge and rarely epistaxis.

Disease of the laryngeal and pharyngeal mucosa may coexist with, or be independent of, nasal lesions. Hoarseness, cough, dysphagia and dyspnoea secondary to upper airway obstruction may occur [160]. Inspection reveals erythema and oedema with or without punctate nodules and mass lesions.

A patient presenting with sarcoidosis of the upper respiratory tract has a 50% chance of developing lupus pernio, although one feature may be present without the other. Sarcoidosis of the upper respiratory tract and lupus pernio are nearly six times more common in women in the child-bearing years of life. Both are indicators of chronic fibrotic sarcoidosis, developing insidiously and progressing indolently over the years with associated chronic lesions of the lungs, skin or bone.

Nasal septal or palatal perforations may complicate untreated sarcoidosis of the upper respiratory tract. Misguided submucous resection in this condition almost certainly results in septal perforation. The Kveim test is almost always positive, and this assists in the differential diagnosis of granulomas in the upper respiratory tract, which includes Wegener's granulomatosis, tuberculosis and leprosy.

### *Alimentary system*

Involvement of the salivary glands and liver is common, while affection of the pancreas and gastrointestinal tract is



**Fig. 39.12** Subcutaneous nodules and infiltration of biopsy scar with sarcoid tissue in a Black patient.

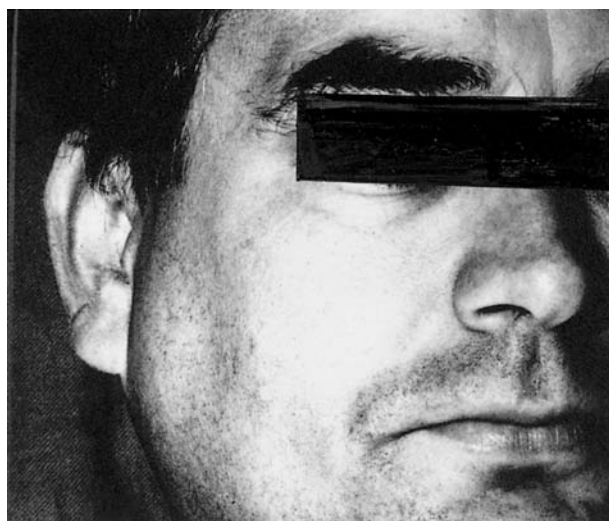
rare. Pancreatitis has been reported [161,162], and bloody ascites secondary to granulomatous involvement of the peritoneum has been described in two cases [163]. There is no evidence that Crohn's disease is a manifestation of sarcoidosis and the Kveim test has been shown to be negative in such cases [164–168]. Liver involvement, though frequent as judged by the results of biopsy, does not usually cause symptoms unless there is gross enlargement, when discomfort may occur.

#### *Uveoparotid fever*

Uveoparotid fever was first described by Heerfordt in 1909 [12] as a febrile illness characterized by uveitis and swelling of the parotids, accompanied frequently by facial palsy. At first thought to be a mild form of tuberculosis, it is now recognized as one of the curious combinations of organ involvement that can occur in sarcoidosis. Parotid enlargement is bilateral in more than half the cases and may be mistaken for mumps [169]. Unlike mumps, however, the swollen parotids are not painful (Fig. 39.13). Enlargement of the lacrimal and other salivary glands may sometimes accompany the uveoparotid syndrome.

#### *Haemopoietic system*

Enlargement of the spleen is relatively common in sarcoidosis and is usually symptomless, although gross enlargement may give rise to abdominal discomfort. Spontaneous rupture of the spleen has been recorded [170]. Hypersplenism is rare but, like haemolytic anaemia, has been described [170,171].



**Fig. 39.13** Enlarged parotid glands as a presenting feature in sarcoidosis.

#### *Nervous and endocrine systems*

Sarcoidosis affecting the nervous system by infiltration or sarcoid deposits may result in a variety of clinical pictures [172–190]:

- 1 peripheral neuropathy or mononeuritis multiplex;
- 2 cranial neuropathy, most commonly of the seventh cranial nerve (sarcoidosis is the commonest cause of bilateral facial nerve palsy);
- 3 lymphocytic meningitis, in which the cerebrospinal fluid shows pleocytosis, increased protein and decreased glucose levels;
- 4 meningoencephalitis;
- 5 space-occupying lesions;
- 6 epilepsy;
- 7 brainstem and spinal syndromes are rare but may masquerade as multiple sclerosis, amyotrophic lateral sclerosis or spinal tumour.

Left recurrent laryngeal nerve palsy due to compression of the nerve by enlarged mediastinal nodes has been reported as the presenting symptom of sarcoidosis [189,190].

In most series, the majority of patients have presented with the neurological abnormalities; in only a minority did neurological signs develop in patients with an established diagnosis of sarcoidosis. The reported series illustrate the infinite variety of the clinical expression of central nervous system (CNS) sarcoidosis (and the difficulty in making the diagnosis in the absence of evidence of sarcoidosis in other systems), the chronicity of this form of the disease in most instances, and its variable and often poor prognosis even when corticosteroid therapy is employed [177,191,192].

The affinity of sarcoid granulomas for cerebral vessels has been stressed by many authors and may offer one explanation for the variable response to corticosteroid therapy. Areas of cerebral ischaemia and infarction have been described in relation to granulomatous angiitis. The development of meningeal fibrosis is another feature that may determine progression of neurological phenomena and limit response to corticosteroid therapy and may sometimes compel surgical intervention for relief of hydrocephalus or intractable epilepsy.

Sarcoid invasion of the posterior pituitary or hypothalamus may result in diabetes insipidus. It is rare for sarcoidosis to involve the anterior pituitary or other endocrine glands sufficiently to disturb function. Hypothalamic hypothyroidism has been described and it is important to be aware of this possible complication of CNS sarcoidosis because of the therapeutic implications [173]. In addition to diabetes insipidus and hypopituitarism, hypothalamic involvement can result in other diverse manifestations, including marked somnolence, hypothermia, personality changes, central alveolar hypoventilation, loss of libido, amenorrhoea and cessation

of normal sexual development. These hypothalamic syndromes have been reviewed extensively [193–195].

### *Musculoskeletal system*

Bone involvement in sarcoidosis most commonly affects the terminal phalanges of the hands and feet, although the proximal limb bones are occasionally involved in severe cases. Radiologically, the punched-out bone cysts initially noted by Kriebich [9] and later studied in detail by Jungling [15] are the most typical of the skeletal changes, although diffuse infiltration of the phalangeal shaft and destruction of cortical and medullary bone are occasionally seen. It is not uncommon for a single digit to be wholly spared while others on the same hand or foot are severely involved. The bone lesions are not affected by treatment with corticosteroids [196]. They were present in only 3% of the Edinburgh series [26].

Subcutaneous tissue swellings affecting several of the fingers or toes are frequently associated with bone involvement and add to the disability resulting from progressive disorganization of the terminal phalanges. It is unusual to find radiographic bone changes without clinical evidence of abnormality in the digits. Unlike the bone lesions, the subcutaneous swellings are usually improved by corticosteroid therapy. Skin sarcoids commonly coexist.

In one series of 29 patients with sarcoidosis of bone observed for up to 43 years, the hands and/or feet were affected in 26 patients, the nasal bone in three and in one each the hard palate and temporal bones were involved [197]. There were three types of bone lesion: lytic in 25 patients, permeative in nine and destructive in three. Lytic lesions are minute defects of the cortex, or larger defects of both cortex and medulla, and are usually rounded. With the passage of time, the larger defects may form the characteristic appearances of cysts. Permeative lesions show 'tunnelling' of the cortex of the shaft of the phalanx, leading to distortion of the normal cortical and trabecular pattern, which is replaced by a fine or coarse reticular pattern. Destructive lesions are rapidly progressive, with multiple fractures of devitalized cortex, sequestrum formation and local deformity. In this series, soft tissue swelling preceded the radiographic abnormality for up to 4 years in 10 patients, accompanied it twice, followed it once and was absent in 16 (55%). Bone involvement was usually an incidental finding when sarcoidosis presented elsewhere. Other features included intrathoracic sarcoid (86%), lupus pernio (48%), skin plaques (41%), ocular lesions (48%), nasal mucosal disease (24%), hepatomegaly (13%), splenomegaly (10%) and parotid enlargement (10%). Pulmonary infiltration with or without lymphadenopathy was present in three-fifths and hilar adenopathy alone in one-third of patients. Abnormalities in the chest radiographs of patients with bone sarcoid resolved in only 20%, underlining the chronicity of the sarcoid process in these patients.

Sarcoid granulomas may occur in skeletal muscle, most commonly affecting the pectoral, shoulder, arm and calf muscles [198–204]. The muscle foci are usually symptomless, but exceptionally there may be pain, weakness, atrophy or even pseudohypertrophy [205]. Only very rarely can nodules be palpated in muscles; they can be more often detected in tendon sheaths. Respiratory muscle weakness due to sarcoid involvement has been reported [206,207]. Serum creatine phosphokinase may be elevated [208].

Sarcoid arthritis independent of erythema nodosum has been described [209]. In the vast majority of cases, however, the polyarthralgia of sarcoidosis is simply a feature of the erythema nodosum syndrome.

### *Genitourinary system*

Sarcoidosis may affect the kidneys in two ways, both of which can cause varying degrees of functional impairment [210–213]. There may be either invasion of the organ by sarcoid granulomas or deposition of calcium in and around the renal tubules (nephrocalcinosis) secondary to hypercalcaemia or, more commonly, hypercalciuria [214]. The reported incidence of hypercalcaemia has varied greatly. One large series found persistent hypercalcaemia in only 8 of 364 patients (2.2%) and only in association with severe and widespread sarcoidosis [215]. The disturbance in calcium metabolism in sarcoidosis is due to an unexplained increase in sensitivity to vitamin D, which results in increased absorption of calcium from the gut. The value of corticosteroid drugs in reversing this effect is well established; they are thought to act by accelerating the already delayed clearance of 1,25-dihydroxyvitamin D<sub>3</sub> from the blood [216]. It has been shown that exposure to sunlight increases the degree of hypercalcaemia, and there is an impression that hypercalcaemia in sarcoidosis is commoner in sunny climes [217]. The symptoms include tiredness, muscular weakness, thirst, polyuria, vomiting and constipation. There may be deposition of calcium in the kidneys, cornea and subcutaneous tissues [217]. When direct sarcoid involvement of the kidney is suspected renal biopsy is justified [218].

Renal calculi are a rare but not unknown presenting feature of sarcoidosis; in an Italian series 1% of patients presented with renal calculi [219]. Glomerulonephritis may also rarely occur in sarcoidosis [220]. Sarcoidosis of the epididymis has been reported [221].

### *Cardiovascular system*

The cardiovascular system may be affected by sarcoidosis in two ways. Extensive pulmonary fibrosis can lead to cor pulmonale, while actual involvement of the myocardium may result in dysrhythmias, conduction disorders, heart failure or sudden death [222–225]. Pericarditis has been recorded [224,226]. ECG abnormality in the absence of

cardiac symptoms is a frequent finding during the course of sarcoidosis [227,228].

There is good reason for believing that involvement of the heart in sarcoidosis is more frequent than was once thought [226]. A clinicopathological study of 84 unselected patients demonstrated myocardial involvement in 25% [229]. Most often only a small part of the myocardium is involved, explaining the absence of clinical features. Occasionally angina may result from granulomatous myocardial disease [230,231]. In a UK series of 163 patients with cardiac involvement, 70 had died at an average age of 47 years [224]; 45 deaths were sudden and in 26 of these sarcoidosis was previously undiagnosed. Other principal manifestations were ventricular extrasystoles or tachycardia in 64, complete heart block in 31, lesser heart block in 56, supraventricular tachycardia in 35 and myocardial disease in 34. If suspected, a 24-h ECG, echocardiogram, exercise ECG and thallium imaging should be performed and treatment with corticosteroids and antiarrhythmics initiated for any significant dysrhythmia [224,225]. Cyclophosphamide therapy may be effective in steroid-unresponsive disease [232]. Combined heart and lung transplantation is the ultimate effective therapy [233] for life-threatening cardiac sarcoidosis and lives may be saved in the waiting period by employing implantable pacemakers or automatic cardiac defibrillators [234]. Endomyocardial biopsy has been successfully used to establish the diagnosis [235].

## Investigations

### Pulmonary function tests

There have been numerous studies of abnormalities of pulmonary function associated with the various stages of intrathoracic sarcoidosis [236–243]. Functional impairment cannot be predicted from the radiographic appearances [242]. A patient whose chest film has become normal may still have significant pulmonary sarcoidosis as judged by reduction in static lung volumes, decreased pulmonary compliance and a reduction in carbon monoxide diffusing capacity [243]. Conversely, extensive shadowing may sometimes be associated with little impairment of function. The most subtle indication of lung function abnormality appears to be a decrease in *DLCO*, which may only be evident on exercise studies. Reduced *DLCO* has been demonstrated in patients whose radiograph only shows hilar adenopathy.

Evidence of airflow obstruction is common in patients with sarcoidosis; two separate studies of black North American and British white patients found airflow obstruction in over 60% [244], indicating that this is the commonest physiological abnormality in pulmonary sarcoidosis. Airflow obstruction was found at all stages of disease, was unrelated to smoking history and was not reversible with bronchodilators [244,245]. It seems likely

that this finding reflects the common occurrence of airway involvement in sarcoidosis [246] and is consistent with the presence of bronchial hyperreactivity [142,247].

Abnormal oxygen uptake responses to exercise in patients with mild pulmonary sarcoidosis have been reported and have been attributed to possible subclinical impairment of right-sided cardiac function [248].

### Kveim test

It is now well established that particulate saline suspensions of sarcoid tissue contain, in varying amounts, some component that when injected intradermally in a patient with active sarcoidosis can provoke the slow development of an epithelioid cell granuloma of sarcoid type. This is the basis of the Kveim test [249–252] and for over two decades a steady accumulation of data has resulted in a wide acceptance of the test as a reliable and clinically useful aid to diagnosis. Unfortunately, shortage of suitable tissue and fears of transmission of viral infection have caused the test to be abandoned in most centres.

### Value of the test

False-positive reactions are rare, only 1–2% [168,249], and a positive test can be regarded as virtual proof of active sarcoidosis. The more active the disease, the greater the likelihood of the test being positive. Its highly specific nature makes it an invaluable tool in the elucidation of atypical cases and often obviates the need for more traumatic forms of biopsy. Unfortunately, even with the best test substances presently available, positive results are obtained in only 75% of patients with clinical evidence of the disease [32,253].

### Nature of the test substance

Sarcoid tissue suitable for preparation of Kveim test substance must meet the following criteria [254]:

- 1 it must have a sufficiently high concentration of the active principle;
- 2 it must have a sufficiently low concentration of substances giving non-specific, inflammatory responses;
- 3 it must be free from agents of transmissible disease;
- 4 there must be sufficient tissue to provide adequate supplies to prove these points and to be available for general diagnostic use.

The details of the preparation of Kveim test substance are of prime importance in relation to both the activity and specificity of the material; monitoring of bulk test material for activity and specificity should be a continuous process [166,255,256]. Douglas and colleagues [250] have described in detail a technique used in Edinburgh for the preparation of two test suspensions that have satisfied all the criteria when subjected to worldwide validation.

The Kveim test substance is remarkably stable; its activity is only destroyed by autoclaving or exposure to alkali. It can stand boiling for 30 min [257]. Freeze-dried test material kept for several months at room temperature retains its potency and specificity [253,258]. The active principle is particulate [259]. It is not water soluble and is not contained in the nucleoprotein or the lipid fraction of the material [260,261], and its precise nature is still unknown. Similar skin reactions can be induced in patients with sarcoidosis by the injection of non-viable autologous BAL cell preparations [262]. Other substances can produce local sarcoid reactions in systemic sarcoidosis (e.g. killed tubercle bacilli) but none so reliably as sarcoid tissue.

Studies with subcellular fractions (nuclear, mitochondrial, microsomal and submicrosomal) prepared by homogenization and differential ultracentrifugation have shown that results equal to those of the whole homogenate can be obtained by all fractions except the submicrosomal. These results tend to support the view that the active principle in sarcoid tissue that evokes the epithelioid granulomatous response is of particle form and is concentrated in the membrane-containing elements [250,251].

#### Method of testing

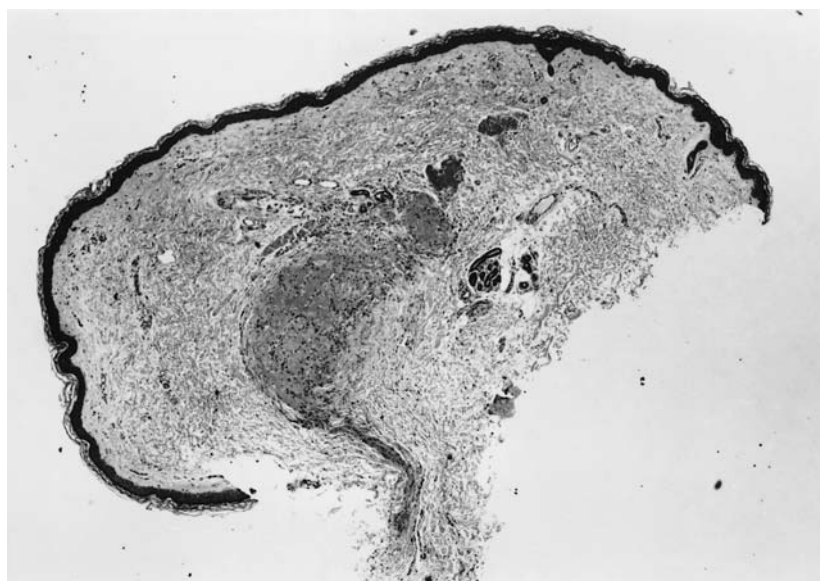
The test is performed by injecting intradermally 0.1–0.2 mL of a suspension of human sarcoid tissue, usually obtained from a cervical gland. Rarely, splenectomy for splenomegaly due to sarcoidosis allows the preparation of large quantities of test substance. Within 2–3 weeks a positive test shows a purplish-red nodule at the site of injection. Biopsy at 4–6 weeks reveals sarcoid tissue on histological examination (Fig. 39.14).

The forearm is usually used as the site of injection but, for cosmetic reasons, the upper and outer thigh may be used in females. Biopsy is made with a Hayes–Martin drill, which can remove a small core of skin without leaving a significant scar.

Coincident corticosteroid therapy depresses the reaction and, if at all possible, treatment should not be given until the test is read.

#### Nature of the Kveim reaction

The epithelioid granuloma of the Kveim reaction shares the histological, histochemical, immunofluorescent and ultrastructural features of the granuloma found within affected organs in sarcoidosis, and it has been supposed that the substances and mechanisms involved in the development of both granulomas are the same [249,252,263]. Two theories, which are not mutually exclusive, have been proposed. On the one hand, some believe that the Kveim test detects a specific aetiological agent, some component of which is present in the sarcoid tissue from which the test substance is made. Others have felt that it simply demonstrates a specific form of tissue reactivity common to sarcoid patients. Despite the increasing sophistication of immunological studies, it is still not known which of these two theories, if either, is correct. Siltzbach has supported the unitarian concept of sarcoidosis, using as evidence the fact that the spleen of a single sarcoid patient has provided a test substance that has been shown to produce specific reactions in sarcoid patients all over the world, suggesting that 'a primary inciting agent may be at work' [254]. The uniformity of response to Kveim testing in all geographical areas has been taken to support the concept of a single disease rather than a syn-



**Fig. 39.14** Kveim biopsy showing typical sarcoid granuloma.

drome, and a single aetiology rather than a multiple one. It might equally mean that the test is detecting a specific form of reactivity. The Kveim 'reaction' remains an immunological puzzle [252].

### Tissue biopsy procedures

Tissue biopsy is often crucial to the diagnosis of sarcoidosis. Strictly speaking, an absolute diagnosis of sarcoidosis cannot be made on suggestive clinical and radiographic findings alone because of the similarity between sarcoidosis and other conditions such as tuberculosis and reticulosis. Similarly, a biopsy report describing sarcoid tissue is of itself insufficient for absolute diagnosis since this might simply represent a local sarcoid tissue reaction. When typical clinical and radiographic findings are supported by histological proof of the sarcoid granulomatous process and tuberculosis has been excluded by the tuberculin test and by bacteriology, the diagnosis of sarcoidosis can be confidently made.

The desirability of histological confirmation of the disease in every case was undoubted in the years when the patterns of disease were being evaluated. However, we have now reached the stage when the quest for demonstrable sarcoid tissue must be tempered by the knowledge concerning the presentation and behaviour of sarcoidosis that has accrued over the last three decades. In the UK, a young woman with erythema nodosum, bilateral hilar lymphadenopathy and a negative tuberculin test has sarcoidosis for all practical purposes and physicians would hesitate to employ any biopsy procedure in these circumstances. On the other hand, obscure bilateral pulmonary changes may justify biopsy, including scalene node biopsy, mediastinoscopy or preferably transbronchial lung biopsy via the fiberoptic bronchoscope. If potent Kveim reagent is not available, the decision whether to perform diagnostic biopsy exercises the physician's judgement.

The tissues found to be useful for biopsy in sarcoidosis have increased in number with the years (Table 39.5) and now include superficial lymph nodes, mediastinal glands, skin, palate, bronchus, lung, liver, conjunctiva, gastrocnemius muscle, bone marrow and old scars with evidence of infiltration. The wide range of positivity for scalene fat-pad biopsy is probably explained by failure to distinguish between biopsy of palpable nodes and 'blind' biopsy.

Transbronchial biopsy of lung and bronchial wall via the flexible fiberoptic bronchoscope is the procedure of choice in the diagnosis of diffuse pulmonary abnormality of probable sarcoid aetiology and is employed especially if there are cogent reasons for securing a diagnosis earlier than can be expected from the Kveim test [264,265]. A minimum of four lung biopsies by this method optimizes the chances of securing a diagnosis.

**Table 39.5** Results of biopsy in sarcoidosis (several authors). Figures in parentheses indicate percentage positive.

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<i>Readily accessible abnormalities</i>
Epitrochlear lymph nodes (100)
Enlarged parotid glands (100)
Nasal mucosal lesions (100)
Subcutaneous nodules (100)
Cutaneous lesions (including livid scars) (90)
Palpable scalene lymph nodes (90)
Inguinal lymph nodes (90)
Axillary lymph nodes (80)
Enlarged tonsils (80)
Bronchial mucosa (visible abnormality) (80)
Conjunctival lesions (75)
 <i>Less readily accessible abnormalities</i>
Mediastinal lymph nodes (100)
Lung (open biopsy) (100)
Lung (transbronchial biopsy) (80)
Liver (80)
Scalene fat pad (40–75)
Gastrocnemius muscle (70)
Palate (40)
Bronchial mucosa (no visible abnormality) (30–40)
Bone marrow (30)

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### Tuberculin testing

Numerous studies have shown that about two-thirds of patients with active sarcoidosis fail to react to 100 TU; about one-quarter react to 100 TU, less than one-tenth to 10 TU and less than 1 in 20 to 1 TU.

### Serum angiotensin-converting enzyme

Lieberman was the first to report that serum angiotensin-converting enzyme (ACE) was elevated in patients with sarcoidosis compared with controls, giving rise to the hope of a relatively simple method for confirming the diagnosis [266]. Serum ACE has been reported to be elevated in 75% of patients with active sarcoidosis, with higher levels in Blacks than whites [267]. The enzyme probably originates from active epithelioid and giant cells and is elevated in BAL fluid of patients with active sarcoidosis compared with that of controls and patients with inactive sarcoidosis [268–270]. Serum ACE may be elevated in conditions other than sarcoidosis, such as Gaucher's disease, leprosy and atypical mycobacterial infection [267]. In other conditions, the combined false-positive rate for non-sarcoid patients has been reported to be as high as 20% in one series [271].

A number of studies have reported falls in serum ACE levels following steroid therapy and also in association with clinical improvement in the natural course of the disease [267,272–275]. Nevertheless, clinical or radiographic deterioration may occur without an associated

rise in serum ACE, and clinical or radiographic improvement may occur without any fall in elevated serum ACE levels [274–276].

In summary, there is evidence that serum ACE is elevated in a majority of patients with sarcoidosis and that its measurement may therefore be of value in substantiating a diagnosis in a difficult case. Elevated serum ACE is neither sensitive nor specific for sarcoidosis. Serial measurements do not necessarily predict activity of disease or outcome as assessed clinically, radiographically or in terms of respiratory function and are therefore unnecessary in routine clinical management, although possibly of interest in research studies [274].

### **Gallium-67 scanning**

Gallium-67 is concentrated in metabolically and mitotically active tissues, where it binds to granulocytes and macrophages [110,277]. Sarcoid and other inflammatory tissue avidly accumulate gallium and gallium scanning may be used to delineate it. Following an intravenous injection of  $11 \times 10^7$  Bq of gallium-67 citrate, simultaneous anterior and posterior scans of the thorax are performed 3 days later [278]. The pattern of uptake is generally diffuse and involved nodes may be well defined. In one study, 65% of patients with sarcoidosis had increased uptake of gallium-67 with little correlation between degree of uptake and clinical, physiological and radiographic findings [279]. Close correlations between gallium uptake and the total number of lymphocytes, or T lymphocytes recovered by BAL and serum ACE levels, have been reported [279,280]. Gallium uptake diminishes with spontaneous or steroid-induced improvement in sarcoidosis but, as with serum ACE, abnormal values may be found even in the presence of a normal chest film and pulmonary function [273,274,279]; positivity of the initial gallium scan appeared to have no predictive value for outcome in one prospective study [274].

In summary, increased gallium-67 uptake by the lungs is found in the majority of patients with pulmonary sarcoidosis but is not specific for this condition. It is an expensive investigation involving a substantial radiation dose to the patient and cannot at present be justified in the routine investigation of this disease. A possible role in the diagnosis of atypical cases of sarcoidosis has been suggested [281] but awaits further evaluation.

### **Bronchoalveolar lavage**

As already mentioned, BAL fluid from patients with pulmonary sarcoidosis contains increased numbers of T lymphocytes, with a high ratio of CD4 to CD8 T cells, and increased macrophages in comparison with control fluid. This finding may be used to support but not prove a diagnosis of sarcoidosis [90,98]. The first 20 mL of the BAL

specimen should be discarded and cell counts made on subsequent specimens [282,283].

### **Measurements in blood, urine and sputum**

Serum calcium should be measured as well as 24-h urinary calcium. Serum globulins may be elevated, although this finding is of little diagnostic or prognostic significance. Routine examination of the peripheral blood is of no value in diagnosis. If sputum production is a feature, acid-fast bacilli should be sought by direct smear or culture.

### **CT of the thorax**

CT of the thorax is usually unnecessary in sarcoidosis. It may be of value, when used with contrast, in differentiating hilar enlargement due to lymphadenopathy from enlargement of the pulmonary vessels. Hilar and mediastinal lymphadenopathy are usually found to be more extensive than the plain chest radiograph indicates. Pulmonary abnormalities may include irregular linear opacities, ground-glass shadowing (particularly related to bronchovascular bundles, interlobar septa and in subpleural areas) and nodular or ill-defined shadows with a similar distribution. CT is frequently abnormal in the presence of apparently normal lungs on the chest radiograph [284–286].

### **Strategy for investigation of suspected sarcoidosis**

As already mentioned, where bilateral hilar lymphadenopathy and erythema nodosum occur together in a tuberculin-negative young woman it is probably excessive to pursue a tissue diagnosis. However, in the case of obscure pulmonary infiltrates where sarcoid is suspected, initial investigations should include a baseline measurement of lung volumes and *DLco* and tuberculin testing. If corticosteroid therapy is not obviously imminently indicated, a Kveim test may establish the diagnosis within 6 weeks. If early therapeutic intervention seems likely to be necessary or if Kveim test reagent is unavailable, the diagnosis is most likely to be established at fiberoptic bronchoscopy, when at least four transbronchial lung biopsies (with or without endobronchial mucosal biopsies) should be taken to search for epithelioid granulomas. Serum and 24-h urinary calcium should be measured.

The role of BAL has been investigated in two careful studies. Keogh and colleagues [287] reported 19 patients with pulmonary sarcoidosis, of whom 80% were initially classified as having 'low-intensity alveolitis' (BAL T cells <28% of total and/or gallium scan negative) and 20% as having 'high-intensity alveolitis' (BAL T cells >28% of total and gallium scan positive). Clinical, radiological and physiological assessment did not predict the intensity of



the alveolitis. With serial assessments of these parameters they showed that 75% of patients with high-intensity alveolitis reverted to low-intensity alveolitis spontaneously, whereas the reverse phenomenon occurred in 12% of patients with low-intensity alveolitis. An episode of high-intensity alveolitis was associated with deterioration in pulmonary function in 87%. They suggested that staging the intensity of alveolitis in these patients might aid therapeutic decision-making. Turner-Warwick and colleagues [274] have repeatedly staged 32 patients with gallium scans, BAL and serum ACE while withholding the information from the clinicians who managed the individual patients on the basis of clinical, radiological and functional parameters. Initial values for gallium uptake, BAL lymphocyte count and serum ACE were not predictive of the outcome in individual patients. Although these parameters tended to normalize with clinical improvement in disease, poor concordance with clinical, radiological and functional parameters was observed. This would suggest that in the routine investigation of pulmonary sarcoidosis, measurement of serum ACE, gallium uptake and BAL lymphocyte count are of little help in planning the future management of the patient.

In extrapulmonary sarcoidosis, attention should be directed to obtaining biopsy material from the most accessible involved site (see Table 39.5).

## Treatment

In nearly every case, corticosteroid therapy can suppress the manifestations of active sarcoidosis, a possible exception being CNS sarcoidosis. Although there is considerable debate about the indications for corticosteroid therapy in thoracic sarcoidosis, most are agreed that steroid therapy is indicated when vital organs are involved or if there are significant symptoms.

### Thoracic sarcoidosis

Bilateral hilar lymphadenopathy alone is not an indication for corticosteroid therapy since the vast majority resolve spontaneously with the passage of time. The associated arthralgia may necessitate treatment with non-steroidal anti-inflammatory drugs; exceptionally, when systemic upset is severe with persisting or recurring erythema nodosum, a few weeks of corticosteroid therapy may be required to suppress symptoms.

There is no universal agreement about the indications for corticosteroid therapy in stage II and stage III thoracic sarcoidosis [288]. One extreme view would be that in a disease which may have a mortality of 5–10% and significant disability due to fibrosis in 3–20% if left untreated [288], it is mandatory to treat all patients with pulmonary shadowing due to sarcoidosis. At the other extreme, it can be argued that corticosteroids are unnecessary in the man-

agement of stage II and III sarcoidosis since controlled trials show that although there may be early (e.g. at 6 months) significant differences in chest radiography or lung function in the treated versus the control group, in the longer term (1–15 years) there are no significant differences between the treated and control groups [289–295]. By the nature of their design, however, these trials of necessity exclude patients for whom corticosteroid therapy was considered clinically indicated and the patients studied therefore presumably had a relatively good prognosis. There is no doubt that if all patients with stage II and stage III sarcoidosis were treated with corticosteroids many would be unnecessarily exposed to the risk of side-effects.

Our own policy is to treat patients with significant symptomatology, most commonly dyspnoea. In asymptomatic patients, baseline assessment of lung volumes and DLCO is undertaken and the patient then observed with repeated radiographic and functional assessment at regular intervals for 6–12 months. Treatment may be initiated if significant symptoms develop, if there is significant radiographic or functional deterioration or if at the end of the observation period there has been no significant improvement. There is evidence to suggest that serial assessment of gallium uptake, serum ACE or BAL lymphocyte counts does not contribute any additional advantage to such a management plan [273]. A recent report from the USA of the management of 98 patients endorses the view that the use of simple clinical criteria augmented by simple radiographic and pulmonary function tests minimizes the number of patients exposed to corticosteroid therapy and results in no adverse outcomes [296]. Treatment, when required, is initiated with prednisolone 20–40 mg in daily or alternate-day regimens and is continued for 3–6 months, when a slow and graduated reduction in dosage may be attempted while clinical, radiographic and functional status is monitored. If relapse is to occur, it is commonly seen when the prednisolone dose is reduced below 7.5–15 mg; this necessitates a return to a higher dose and a further period (6–12 months) on a continuing maintenance dose, commonly 10 mg daily, before further reduction in dosage is attempted. In the Edinburgh series, corticosteroid therapy was given to 260 patients; this was discontinued in 80% in 2 years and their follow-up was uneventful [137]. This experience contrasts with that found in a predominantly black American population where relapses occurred in the majority on reduction of prednisolone dosage below 10–15 mg and the majority required more than 2 years of treatment, perhaps reflecting the greater severity and chronicity of the disease in this population [297]. Although most patients respond satisfactorily to the dosage regimen outlined above, individual relatively unresponsive patients may require higher doses of prednisolone initially to suppress activity, and a small proportion of patients are found to require

long-term treatment with corticosteroids. Despite this, some progress remorselessly to chronic pulmonary fibrosis.

Anecdotal experiences and accounts, including our own, of the benefits of high-dose inhaled corticosteroids in the management of pulmonary sarcoidosis, often in patients who reject systemic corticosteroid therapy, are beginning to be addressed by controlled trials [298]. At present the precise role of this intervention in replacing, or reducing the dose of, systemic corticosteroids remains to be determined [299,300].

There has been a report of successful treatment of pulmonary sarcoidosis with cyclosporin in three patients, two of whom were unresponsive to steroids and one in whom corticosteroids were contraindicated [301]. Cyclosporin was a logical choice since it acts by suppressing T-helper lymphocytes and there may be a case for further studies of its use in different clinical situations. Chlorambucil has

also been used successfully in corticosteroid-resistant sarcoidosis [302].

### Extrathoracic sarcoidosis

Treatment with the same dosage schedule of oral corticosteroids is also indicated in the management of eye involvement uncontrolled by topical steroids and in persistent hypercalcaemia or hypercalciuria to prevent the development of nephrocalcinosis and renal failure. CNS, symptomatic muscle and myocardial sarcoidosis are all indications for corticosteroid therapy, although CNS sarcoidosis may be unresponsive even to high doses of prednisolone. In one such case of unresponsive sarcoid meningitis, improvement was recorded following whole brain irradiation [303]. Disfiguring skin lesions may justify treatment, as may parotid and lacrimal gland enlargement and symptomatic splenic involvement.

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# PULMONARY LYMPHOCYTIC ANGIITIS AND GRANULOMATOSIS

ANTHONY SEATON

A number of conditions, originally grouped together because they share the common factors of a lymphocytic angiitis or vasculitis with a tendency to granuloma formation, may cause disease of the respiratory tract [1–9]. It is now recognized that despite their similar histological appearances they differ in clinical characteristics, natural history and aetiology, and several represent low-grade lymphocytic neoplasms. Nevertheless, their names have become familiar to chest physicians and since they all cause similar diagnostic problems they are considered together in this chapter. These conditions are:

- 1 classical Wegener's granulomatosis;
- 2 limited Wegener's granulomatosis;
- 3 midline granuloma;
- 4 lymphomatoid granulomatosis;
- 5 benign lymphocytic angiitis and granulomatosis;
- 6 necrotizing sarcoid granulomatosis;
- 7 bronchocentric granulomatosis.

Two other conditions characterized by eosinophilic granulomas, polyarteritis nodosa and allergic granulomatosis (Churg–Strauss syndrome), have been considered separately in Chapter 38.

## Classical Wegener's granulomatosis

In 1931 Klinger [10] described a patient with destructive sinusitis, nephritis and disseminated vasculitis but it was not until 1936 that Wegener [11] clearly defined the triad as a distinct clinical and pathological entity. In 1954 a review by Godman and Churg [12] led to the establishment of firm criteria for the diagnosis. Classical generalized Wegener's granulomatosis is characterized by (i) necrotizing granulomas in the respiratory tract, (ii) generalized focal necrotizing vasculitis and (iii) focal necrotizing glomerulonephritis. In practical terms the demonstration of one or more of these in combination with positive serological evidence is now generally accepted as fulfilling the criteria. When one element of the triad is absent it is usually the renal or the upper respiratory tract component.

## Frequency

Wegener's granulomatosis is more common than was once thought. Up to 1967 approximately 200 cases had been reported, although two series published in the 1980s matched this total number of cases [13–15]. Since then, the description of the antineutrophil cytoplasmic autoantibody as a marker of the disease, and the attention drawn to it at the International Symposium at the Mayo Clinic in 1986, have increased the rate at which it has been diagnosed, and it is now estimated to occur at a rate of about 5–12 new cases per million population per annum [16].

There is a slight male preponderance (male/female ratio 3:2) and most patients reported have been of Caucasian extraction. The condition may be found at any age including childhood, although the peak incidence is in the fourth and fifth decades [15,17]. There is a suggestion that, at least in England, the disease may present more frequently in the winter months [16].

## Pathogenesis and antineutrophil cytoplasmic antibodies

The pathogenesis of Wegener's granulomatosis remains unclear. The finding of a significant increase in HLA-DR2 frequencies suggests that in some cases there may be a genetic predisposition to this disease [18], and the increased incidence in winter is consistent with Wegener's original hypothesis that infection may play an aetiological role. There are indications that deposition of circulating immune complexes in vessel walls initiates the vasculitis. The antibodies are usually of the IgG or IgM class. Following deposition, the immune complexes trigger the complement cascade thus generating potent chemotactic factors for polymorphonuclear leucocytes such as C5a [19]. Once attracted to the site, neutrophils release lysosomal enzymes, such as elastase and collagenase, with resultant necrosis of vessel walls [20]. In support of this concept is the finding of circulating immune complexes in patients



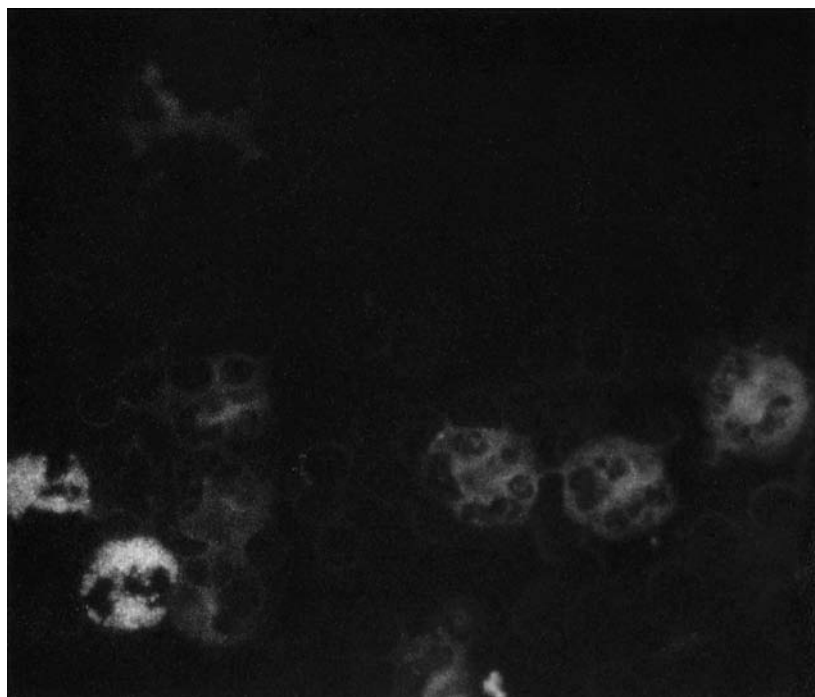
with Wegener's granulomatosis, their correlation with disease activity or relapse and the probable beneficial therapeutic effect of plasmapheresis [13,21–25]. In addition IgG, IgM and complement deposition have been demonstrated in tissue from kidney, lung and the maxillary sinus of patients with Wegener's granulomatosis [23,24,26]. However, the failure to demonstrate deposition of immunoglobulins and complement in involved tissue [26–28] or the presence of circulating immune complexes in all patients [13] suggests that the phenomenon may be relatively transient or, alternatively, that the immune complex concept of pathogenesis may not be the whole story [29].

There is also evidence that cellular as well as humoral immune mechanisms play a part in pathogenesis. Immune complexes can cause granuloma formation [30]. Lymphocytes, mainly T cells, and monocytes are seen infiltrating vessels [27]. In addition, it is suggested that T lymphocytes can be sensitized to antigen and on contact with it release lymphokines, resulting in cellular infiltration, giant cell formation and tissue destruction [9]. After ingestion of immune complexes, macrophages may also release tissue-damaging lysosomal enzymes or transform into epithelioid cells and form granulomas.

In 1985 van der Woude and colleagues reported an association between Wegener's granulomatosis and the presence in the blood of antineutrophil cytoplasm antibodies (ANCA), and this finding has been replicated by a number of other investigators [31–33]. ANCA react with cytoplasmic granules in neutrophils and demonstrate one of two staining patterns: diffusely cytoplasmic (cANCA) or per-

inuclear (pANCA) (Fig. 40.1). The main target of cANCA appears to be proteinase C and that of pANCA myeloperoxidase [34,35]. Initial use of ANCA in an indirect immunofluorescence test suggested that they had a very high specificity and sensitivity for the diagnosis of Wegener's granulomatosis, based on studies from large specialized units. However, ANCA have been shown to occur in other diseases, including such common conditions as tuberculosis, lung cancer and human immunodeficiency virus (HIV) infection, and a recent audit of the results of the use of the test in a regional diagnostic service has shown a sensitivity of 65% and a specificity of 77% in patients with respiratory symptoms, cANCA being somewhat more sensitive [36]. False-positive results were found in other autoimmune diseases, cancer, pulmonary emboli and pulmonary fibroses. Since Wegener's granulomatosis is relatively rare, the positive predictive value of the test is quite low, at around 45%.

The role, if any, of ANCA in pathogenesis remains the subject of speculation, and it is debated whether they are a cause or consequence of some of the pathological features. In support of a pathogenic role, ANCA have been shown to cause neutrophils to release free radicals and to injure endothelial cells, while T lymphocytes have been demonstrated to become sensitized to ANCA [37–39]. It has been proposed on the basis of *in vitro* studies that viral or other illnesses that lead to the release of cytokines, such as tumour necrosis factor, cause neutrophil enzymes to migrate to the surface of the cell from the primary granule and that presentation of these antigens at the cell surface leads to the development of the ANCA [37]. This in turn



**Fig. 40.1** Neutrophil leucocytes from a patient with Wegener's granulomatosis stained by immunofluorescent technique to show cytoplasmic antibodies.

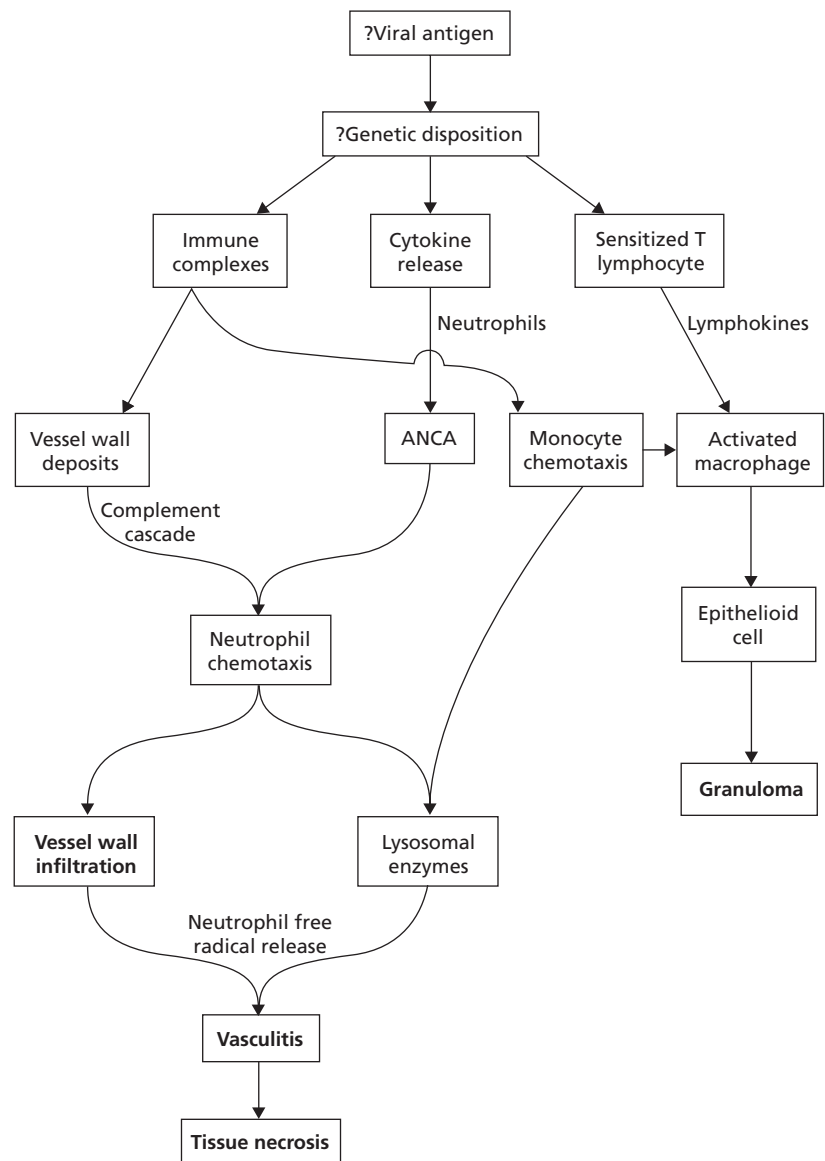
may cause release of free radicals, damage vascular endothelium and recruit more neutrophils. On balance it seems likely that a condition characterized by granulomatous inflammation of lungs, nasal passages and kidneys is likely to have an environmental cause, the pathological changes being a consequence of inflammation resulting from secondary disturbances of the immune defences. This is in keeping with Wegener's original suggestion that the disease is an altered response to an infective organism. An outline of a proposed pathogenesis is shown in Fig. 40.2 [9].

### Pathology

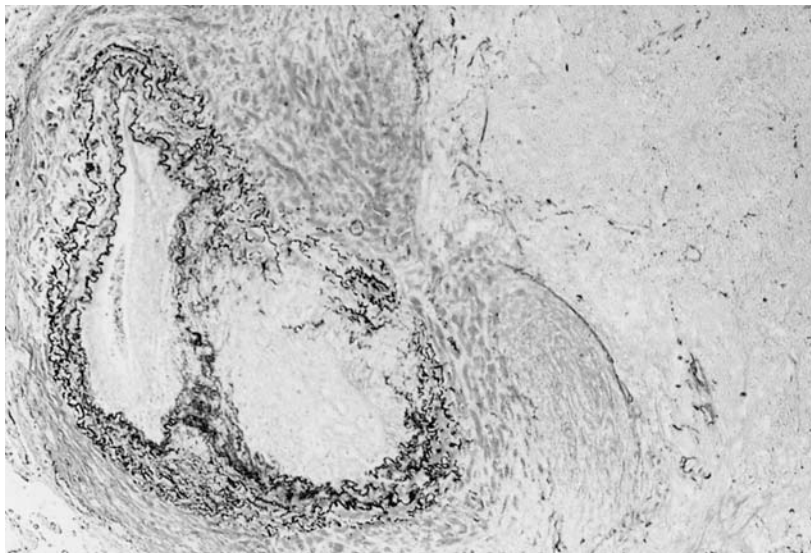
The pulmonary lesions are characterized by the presence of confluent or isolated areas of basophilic necrosis that frequently display cavities or crevices [40,41]. Communi-

cation with a sizeable bronchus may occur, resulting in evacuation of the necrotic material. The lesion may look distinctly suppurative, resembling an abscess or a septic infarct. Eosinophils are present throughout the lesion and are more numerous within the necrotic core where destructive angiitis of muscular arteries and veins can be seen (Fig. 40.3). The tissue around the foci of necrosis consists of fibroblastic and histiocytic proliferation with variable numbers of giant cells (Fig. 40.4). Scanty lymphocytes and plasma cells are also seen in the tissue surrounding the necrotic areas. Similar pathology may be seen in other affected organs.

The renal lesion is a focal necrotizing glomerulonephritis [26,28]. Fibrinoid necrosis with destruction of one or more glomerular capillary loops, along with a neutrophil infiltrate, is characteristic. Granulomatous change may be seen around affected glomeruli, as may necrotizing



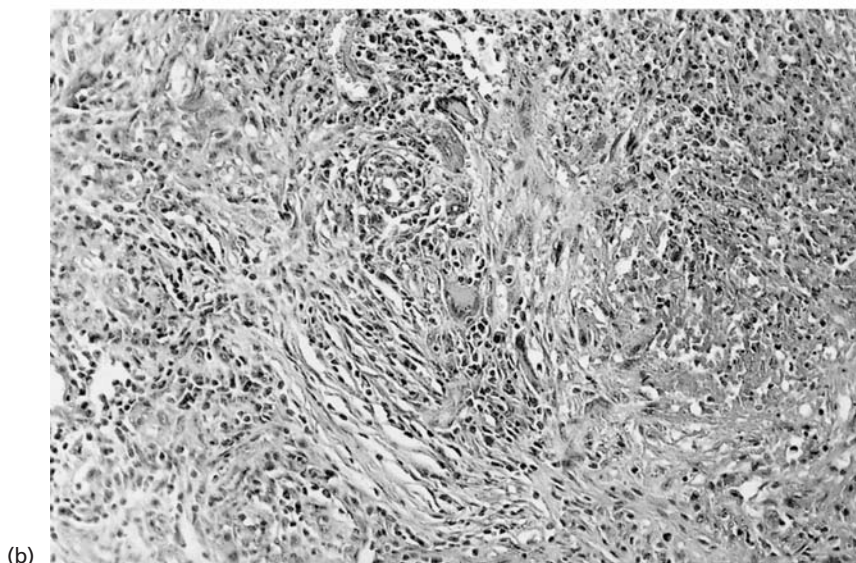
**Fig. 40.2** Proposed pathogenesis of Wegener's granulomatosis. (Adapted from Leavitt & Fauci [9].)



**Fig. 40.3** Lung biopsy from Wegener's lesion stained for elastic tissue showing destruction and loss of elastic laminae and partial obliteration of lumen in artery adjacent to area of necrosis (elastic van Gieson  $\times 35$ )



(a)



(b)

**Fig. 40.4** (a) Open lung biopsy specimen from patient with Wegener's granulomatosis showing darkly stained area of necrosis with involvement of small airway (haematoxylin & eosin  $\times 25$ ). (b) Higher-power view of same lesion showing poorly formed granuloma with giant cells and chronic inflammatory cells (haematoxylin & eosin  $\times 110$ )

vasculitis of small and medium-sized vessels. When healing occurs following treatment, the changes seen are hyalinization of affected areas, capsular adhesions and epithelial crescent formation in Bowman's capsule. With suitable immunofluorescent stains it is often possible to demonstrate immunoglobulin or complement deposition in the glomerular capillary membrane and/or mesangium.

### Clinical features

The clinical expressions of Wegener's granulomatosis are diverse and the patient may present initially to practitioners from almost any branch of medicine [42,43]. Neither sex predominates. The course varies from a very acute systemic illness with dramatic pulmonary and renal manifestations to a much more chronic, often nasal, inflammatory condition, although acute presentations are more usual. Chronic courses are more frequent in those without renal involvement. In the large National Institutes of Health (NIH) series, most patients at presentation had evidence of upper airways involvement and fewer than half had lung involvement, although this developed in almost all eventually. Renal disease at presentation was relatively uncommon but developed in almost 80% within 2 years; similarly, eye involvement increased from 15 to 50% over the same period [43]. The main nasal symptoms are rhinorrhoea, nasal mucosal ulceration or sinusitis. To these may be added respiratory symptoms such as cough and haemoptysis. Alternative presentations are with systemic symptoms, such as anorexia, malaise, fever, weight loss and arthralgia, or with involvement of other organs such as the skin, eye or ear. When the diagnosis is suspected haematuria and proteinuria should always be sought as evidence of renal involvement. The most common systems involved are discussed below.

### Upper respiratory tract

Nasopharyngeal lesions can include mucosal ulceration with crusting, perforation of the nasal septum and varying degrees of sinusitis. In chronic cases, saddle nose deformity may occur but erosion of skin or palate as seen in midline granuloma does not [15]. 'Strawberry gums' or hyperplastic gingivae that are red to purple in colour with many petechiae may be seen [44,45]. Radiographs of the nasal sinuses may show obliteration due to chronic bacterial infection, resulting in sinus wall thickening and new bone formation [46]. Biopsies usually show either acute or chronic inflammation, with granulomas or vasculitis in only 50% of cases [15].

### Lower respiratory tract

Respiratory tract symptoms may lead to the finding of an abnormal chest film [47]. The most common finding is of

solitary or multiple nodules 1–10 cm or more in diameter and these may cavitate (Fig. 40.5). Rarely, rupture of a cavitated nodule may result in pneumothorax; even more rarely a cavitated nodule may be colonized by an aspergilloma [48–50]. The radiological appearances are very variable [47,51]. Nodular and alveolar infiltrates are commonly seen on chest radiographs and may appear relatively insignificant. Such findings should not lull one into a false sense of security if other clinical features are present to suggest the diagnosis. Alveolar infiltrates may be due to intrapulmonary haemorrhage, which is more common than was once thought and may be detected by increases in diffusing capacity for carbon monoxide [52,53]. Small pleural effusions may occur. Endobronchial involvement is not uncommon and may result in large airway stenosis or lobar collapse [54,55]. CT may be helpful in providing evidence of vascular involvement, showing vessels leading into nodules and small peripheral densities suggestive of microinfarcts [56].

Functionally, patients with Wegener's granulomatosis frequently have decreased lung volumes and diffusing capacity, although airways obstruction is even more common and presumably reflects endobronchial disease [57]. The defects in pulmonary function improve with therapy but a persistent decrease in diffusing capacity is often found.

### Urogenital

There may be no renal tract manifestations at the time of presentation. More commonly, microscopic or macroscopic haematuria with proteinuria is found. If renal failure is not established at presentation, it may develop rapidly and progressively and is the principal reason for seeking an urgent pathological diagnosis and initiating chemotherapy as soon as possible. Renal failure carries a poor prognosis but, even when established, recovery is possible with present-day therapy [25,58–60]. Other, uncommon urogenital manifestations include involvement of prostate, testes, ureter and penis [61].

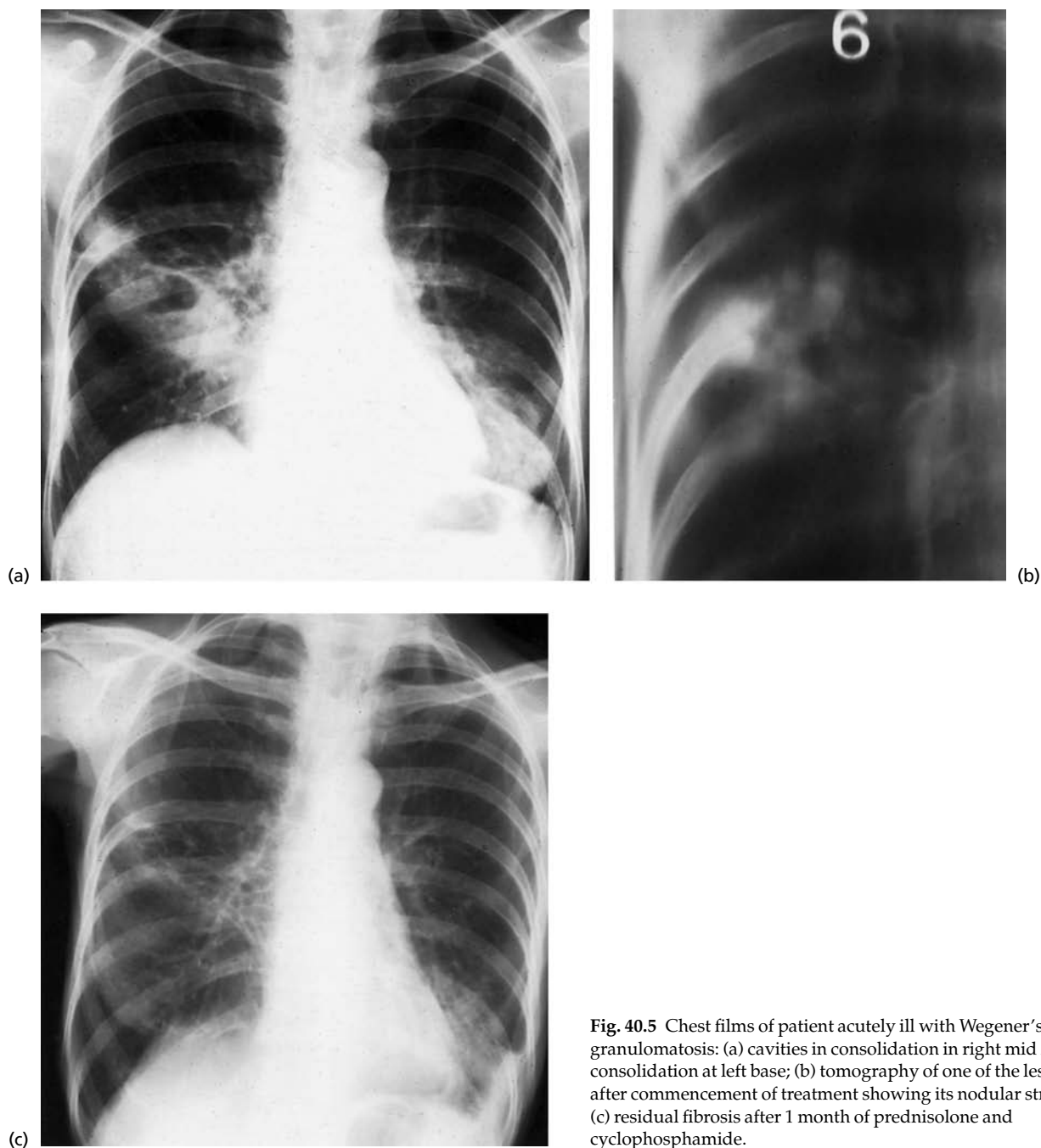
### Eyes

Eye manifestations are found eventually in some 60% of patients [15,43], including corneal/scleral ulceration, granulomatous keratitis or uveitis, conjunctivitis, proptosis, orbital pseudotumour, dry eyes, retinal vein occlusion and retinal artery thrombosis [62,63].

### Ears

The ear is also involved in about 60% of patients [15]. The patient may present with serous or purulent otitis media, usually secondary to nasopharyngeal ulceration and obstruction of the eustachian tube [64,65]. The middle ear





**Fig. 40.5** Chest films of patient acutely ill with Wegener's granulomatosis: (a) cavities in consolidation in right mid zone and consolidation at left base; (b) tomography of one of the lesions just after commencement of treatment showing its nodular structure; (c) residual fibrosis after 1 month of prednisolone and cyclophosphamide.

and mastoid may be destroyed by granulomatous tissue, with associated lesions of cranial nerves, most commonly the fifth, seventh, ninth and twelfth [65,66]. Sensorineural hearing loss may occur due to cochlear inflammation [65].

### Skin

Skin and mucosal involvement occurs in up to 50% of cases [15]. In one review of 75 patients with dermatological manifestations, the most frequent findings were palpable purpura and oral ulcers, with skin nodules, skin

ulcers and necrotic papules occurring less commonly [67]. Other manifestations included gum hyperplasia, pustules, digital necrosis and livedo reticularis. In general the purpuric lesions were associated with vasculitic histopathology and the non-purpuric with granulomas.

### Joints

Polyarthralgia is common and is seen in about 50% of cases [15]. In most series, true arthritis has been less common, although it was present in the majority of

patients in one report, presumably representing selection bias [68].

### Heart

Cardiac disease as a presenting manifestation of Wegener's granulomatosis must be very rare indeed, although subtle cardiac involvement in established cases is probably less so. The most frequent manifestations are pericarditis, myocarditis and dysrhythmias due to coronary vasculitis [15,69,70]. Aortitis and aortic valvulitis with sterile endocarditis have been reported [70,71]. The availability of ANCA allows the diagnosis to be made more readily than previously and the condition should be considered in cardiac disease of obscure aetiology.

### Nervous system

Central nervous system involvement can occur with direct invasion by granulomatous tissue from ear or sinus, with resultant cranial nerve involvement. Remote granulomatous involvement of the brain is also recognized [72]. Vasculitic lesions of the peripheral nervous system may give rise to mononeuritis multiplex, while central nervous system vasculitis may result in thrombosis or haemorrhage in brain tissue.

### Gastrointestinal system

Gastrointestinal involvement is not common but patients have been described presenting with features more typical of inflammatory bowel disease, and severe haemorrhage has been recorded in patients with vasculitis of bowel [73–75].

### Investigations

Most patients have a normochromic, normocytic anaemia with a raised erythrocyte sedimentation rate, leucocytosis and hyperglobulinaemia. Plasma levels of C-reactive protein are raised and, although not specific for this disease, have been used as an index of activity [76]. As discussed above, a positive test for ANCA, especially those of the diffuse type (cANCA), in conjunction with consistent clinical features is as close as there is to a diagnostic test [31,77] (see Fig. 40.1).

### Differential diagnosis

Where the clinical findings are suggestive, no time should be wasted before obtaining biopsies of the involved organs, most commonly the upper respiratory tract and the lungs. Renal biopsy should be considered even in the absence of renal manifestations, since early renal disease may be detected and confirm the diagnosis.

The differential diagnosis is wide-ranging and includes conditions as diverse as polychondritis and Behçet's disease. Other vasculitic diseases may need to be considered, such as polyarteritis, systemic lupus erythematosus and Churg–Strauss syndrome, other granulomatous diseases such as sarcoidosis and the infectious granulomatoses and neoplastic diseases such as nasopharyngeal lymphoma or pulmonary Hodgkin's disease. Finally, the other principal pulmonary–renal condition, Goodpasture's syndrome, frequently enters into the differential diagnosis. In children, diagnostic confusion with Henoch–Schönlein purpura has been recorded [17].

### Treatment

The management of the condition may be tailored to the presenting clinical course. It has to be said that as the condition is rare, guidance on treatment at present is based on the results of case series rather than on controlled trials, and these are largely (and almost inevitably) derived from highly specialized centres where selection bias ensures that the case mix is atypical. There is therefore an important need for exercising good clinical judgement in interpreting the literature in relation to one's individual patient. Having said this, there is no real dispute about the management of ill patients with progressive lung or renal disease, who require to be treated vigorously with corticosteroids and cyclophosphamide in high dose in order to induce remission. The problem of how to treat arises mainly in those less ill patients in whom the course is slowly progressive and the diagnosis made early, the disease being primarily granulomatous and confined to lungs and upper airways. In such patients, co-trimoxazole may be effective in a dose of 960 mg twice daily [78,79]. If this does not bring about improvement within 6–8 weeks, prednisolone 40 mg on alternate days should be added, reserving the further addition of cyclophosphamide 2 mg/kg daily for those who still fail to respond [77].

In most cases the presentation warrants treatment with corticosteroids and cyclophosphamide. The NIH group originally reported 93% complete remission in 85 patients using an induction regimen of cyclophosphamide 2 mg/kg and prednisolone 1 mg/kg [15]. More recently they have reported improvement in 91% and complete remission in 75% of 180 patients, mostly treated with the same regimen though including some less severely affected patients treated with cyclophosphamide, other cytotoxic drugs or steroids alone or in combination [43]. However, 50% of remitting patients suffered relapse, although half of all remissions lasted at least 5 years. There was a 13% mortality, either from the disease itself or from side-effects of treatment, and almost all patients suffered some side-effects. Even after a 10-year remission, some 20% of patients relapse.

The usual starting dose of prednisolone of 1 mg/kg daily may be increased in severely ill patients. Once complete remission has been achieved, usually within about 4 weeks, the prednisolone is changed to an alternate-day regimen; if remission is maintained, the prednisolone is tapered to zero over about 1 year depending on the clinical response. Cyclophosphamide is usually started at 2 mg/kg daily or more in severe cases and continued for a year after complete remission has been achieved, when a slow but graduated reduction in dosage (25 mg every 2–3 months) can be made to zero if no relapse occurs. If relapse occurs, therapy has to be restarted or increased. Cyclophosphamide causes serious side-effects; cystitis occurred in 43% of the NIH series, bladder cancer in 3% and myelodysplasia in 2%. The dose may have to be reduced to ensure a leucocyte count of greater than  $3 \times 10^9/L$ , with a neutrophil count of  $1 \times 10^9/L$ . Other side-effects of cyclophosphamide include hair-thinning, an increased incidence of herpes zoster, gonadal dysfunction and rarely, but significantly, the later development of leukaemia or lymphoma [80–83]. The side-effects of the steroids are as expected and include a much increased risk of infections, though this can be reduced by alternate-day therapy.

The major challenge in treating Wegener's granulomatosis relates to prevention and management of side-effects. If these are unacceptable, therapy with methotrexate may be effective [84]. Azathioprine has also proved successful in occasional cases [85], but neither of these drugs has become established as first-line treatment. Other experimental therapies have included plasmapheresis and transfusion of pooled gamma globulin [22,25,76,86–88]. If renal failure develops, dialysis and even renal transplantation may be necessary [15].

There has been much discussion of the value of serial ANCA titres in monitoring response and detecting early relapse. There is a general relationship between level of antibodies, severity of disease and risk of relapse, and concentrations fall with successful treatment. However, the finding of high or rising ANCA in a patient on treatment is not a sure indication that relapse is imminent and should probably only be taken as a guide to more careful follow-up rather than as an indication for increasing the therapy [89,90]. As always, good clinical judgement should be used in a patient on treatment who shows rising ANCA, in balancing the risks of increasing the dose against those of side-effects; the patient's clinical status should generally be the main determinant of change in therapy.

Finally, the occasional mechanical complication may persist in large airways despite standard treatment. Such endobronchial obstruction has been shown to respond to radiotherapy and bougienage or to stenting [55,91].

## Prognosis

The condition, when recognized, was uniformly fatal prior to the introduction of corticosteroids; these drugs alone made little long-term difference, with a mean survival of 5 months and 90% of patients dead within 2 years [92]. Better recognition of the condition allows diagnosis in a relatively benign category with a much better prognosis than that of the more common progressive disease, though one suspects that many of these, treated initially with co-trimoxazole, relapse later. Of those requiring standard cyclophosphamide and corticosteroid treatment, more than 80% can be expected to be alive at 5 years [43,93]. However, as noted above, there is a large cost in terms of therapeutic side-effects, including late development of lymphomas and bladder cancer. The patient is probably never free of the risk of relapse, even when complete and prolonged remission appears to have occurred, and life-long outpatient supervision is advisable [85].

## Limited Wegener's granulomatosis

In 1966 Carrington and Liebow identified a group of 16 patients with otherwise typical Wegener's granulomatosis in whom renal disease was not present [94–96]. A positive ANCA test is less frequent than in the classical form of the disease. There may be involvement of other tissues such as the skin and eye [1,62,63]. The pulmonary lesions in this condition predominate in the lower lobes and the most common form is a discrete lesion greater than 1 cm in diameter. In two-thirds of cases the lesions are multiple and bilateral and in one-third cavitation occurs.

The patients usually present with lower respiratory tract symptoms with variable degrees of systemic upset, although a lesion may be discovered at routine radiographic examination of an asymptomatic patient. The disease appears to follow a less aggressive course than classical Wegener's granulomatosis, although relapse after treatment is not infrequent and may be in a more aggressive form with renal involvement [85]. A 20% 5-year mortality was reported prior to modern treatment [95]. Death has occurred from progressive involvement of the lung or massive haemorrhage from a cavitating lesion but is more likely now as a result of relapse to a more aggressive form.

This condition responds to steroids and should be treated with both cyclophosphamide or azathioprine and corticosteroids as for the classical form of the disease [1].

## Midline granuloma (nasal T-cell lymphoma)

Midline granuloma is a localized process characterized by



a pansinusitis and destructive lesions of the nasal septum and soft and hard palate. The process is localized to the upper airway, although ulceration can occur through skin [97]. If left untreated, death eventually ensues from cachexia, haemorrhage, meningitis or infection [98]. Biopsies of involved tissue reveal acute and chronic inflammation with necrosis and it is unusual to see granulomas or vasculitis [99,100]. There is no associated systemic disease. It must be differentiated from Wegener's granulomatosis, nasal carcinoma and infectious diseases [100]. Recent evidence indicates that it is a locally invasive lymphoma of T-cell variety [101,102]. There are interesting geographical variations in its incidence and it is more common in the Orient. In many cases, Epstein-Barr virus has been demonstrated in the malignant T lymphocytes and may be causative [103-105]. Radiation therapy has proved successful in arresting the process, although management should be discussed with appropriate lymphoma specialists if possible [87,98,100].

## Lymphomatoid granulomatosis

### Pathology

Histologically, lymphomatoid granulomatosis is a necrotizing angiocentric and angiodestructive infiltrative process composed of small lymphocytes, plasma cells, histiocytes and atypical lymphoreticular cells. It predominantly involves the lungs, although infiltration of skin, kidney and the nervous system is not uncommon [1,106]. Upper airway lesions are unusual [106]. Recent evidence suggests that the pulmonary manifestation of this condition, in contrast to cutaneous and head and neck manifestations, may be predominantly an Epstein-Barr virus-associated B-cell lymphoma with a marked T-cell reaction leading to the vasculitis [107]. However, this hypothesis is based on study of small numbers of cases and it would not be surprising if other series showed different results in the future.

### Clinical features

In a study of 152 patients there was a male/female ratio of 1.7:1 [106]. Most patients present with chest and/or systemic symptoms such as fever or malaise. Neurological signs, including peripheral neuropathy, are not uncommon. Laboratory investigations are generally unhelpful. The chest film shows a similar frequency and distribution of nodular masses, cavitation and migratory lesions as are seen in Wegener's granulomatosis [108]. However, reticulonodular changes are seen in lymphomatoid granulomatosis and not in Wegener's granulomatosis. A skin rash, most commonly raised and erythematous, and neurological signs are the most common extrapulmonary findings and renal involvement may occur.

### Treatment and prognosis

The median survival of the 152 patients in the original series of Katzenstein and colleagues [106] was 14 months and 94% were dead by 3 years; 12% of all patients developed generalized evidence of lymphoma. The outcome appeared to be independent of any therapy employed, including steroid and cytotoxic drugs. Before the lymphomatous nature of the condition was recognized there were reports of response of localized disease to radiotherapy [109], and in one study 7 of 15 patients achieved complete remission for a mean of 5.2 years with cyclophosphamide 2mg/kg and prednisolone 1mg/kg [110]. Current advice would be to regard the condition as a low-grade lymphoma *ab initio* and treat it accordingly, bearing in mind the toxic effects of antineoplastic drugs and the relatively benign course of low-grade lymphomas [111].

## Benign lymphocytic angiitis and granulomatosis

### Pathology

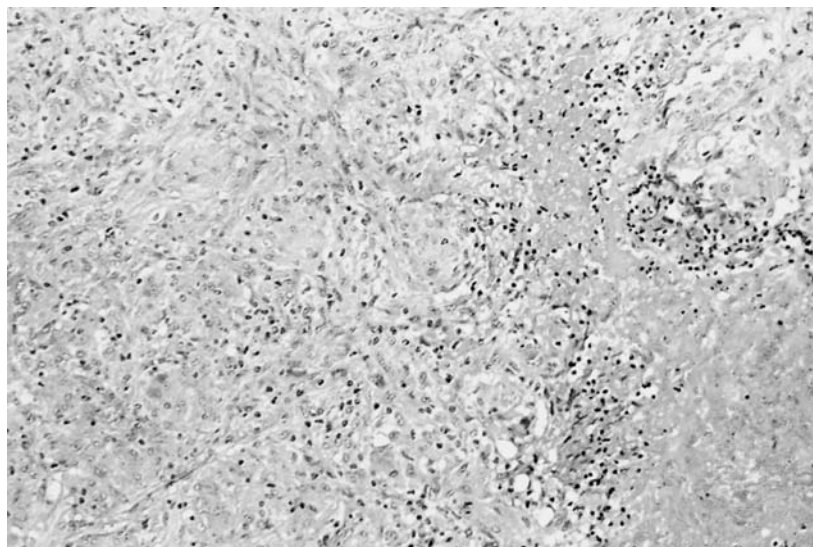
This very rare clinical entity is characterized by pulmonary infiltrates consisting of lymphocytes, plasma cells and histiocytes, with lymphocytic infiltration of arteries and veins [41,112,113]. Compression or infiltration of the walls of the bronchioles that resembles bronchiolitis obliterans is commonly seen. The chest radiographic appearances are most frequently of a single nodule but may show other features similar to Wegener's granulomatosis. It is now regarded as a T-cell lymphoproliferative disease but is probably not a malignant lymphoma [114].

### Clinical features

The condition may present with symptoms suggesting respiratory tract infection or be discovered incidentally on routine chest radiography. It is one of the lung conditions that may appear in HIV infection [115]. Extrapulmonary involvement is uncommon but skin and eye lesions have been reported.

### Treatment and prognosis

It is frequent for the lung lesions to wax and wane and for opacities to clear spontaneously with minimal residual fibrosis, only to be followed by the development of fresh lesions elsewhere. Development into lymphomatoid granulomatosis has been described [5]. Corticosteroid therapy is ineffective, although cytotoxic drugs, particularly chlorambucil, have been reported to be effective in producing remission [40,41].



**Fig. 40.6** Lung biopsy from patient with necrotizing sarcoid granulomatosis showing irregular necrosis to the right of a zone of confluent epithelioid granulomas (haematoxylin & eosin  $\times 120$ ).

## Necrotizing sarcoid granulomatosis

### Pathology

First described by Liebow in 1973 [1], this condition is characterized by pulmonary lesions with granulomatous vasculitis and pneumonitis against a background of sarcoid-like granulomas and parenchymal necrosis of variable extent (Fig. 40.6). Muscular pulmonary arteries and veins are infiltrated by histiocytes, spindled mononuclear cells, lymphocytes and giant cells, with a tendency towards marked involvement of the subintima [116,117].

### Clinical features

The disease is three to five times more common in women than men and the average age at presentation is 50 years. Patients may be entirely asymptomatic or may present with chest pain, cough or dyspnoea with or without systemic features such as malaise, fever, night sweats, weight loss and lethargy [116–119]. Extrapulmonary involvement is unusual but granulomatous disease of the nervous system has been described.

The chest film most commonly shows bilateral nodules or nodular infiltrates, although solitary nodules have been seen (Fig. 40.7). Miliary shadowing, hilar lymphadenopathy and pleural effusions have been recorded.

### Treatment and prognosis

The condition may resolve spontaneously [116] though in most cases resolution has been achieved either with corticosteroid therapy or surgical resection of a single lesion. It remains possible that this pathological entity is simply a variant of sarcoidosis since there are many immunological parallels [5,120]. The author has reviewed one case that

progressed to a fatal conclusion, with widespread pulmonary arteritis and pulmonary hypertension, owing to a foolish medicolegal misdiagnosis of asbestosis.

## Bronchocentric granulomatosis

### Pathology

The characteristic feature of bronchocentric granulomatosis is a necrotizing granulomatous reaction centred around airways (Fig. 40.8). Large and small airways are involved but the most marked changes are in the periphery, where irregular necrotic lesions lie within collapsed consolidated lung tissue. The necrotic lesions consist of airways with ulceration of the surface epithelium and cellular debris within the lumen, often with irregular masses of eosinophils. Occasional true epithelioid granulomas are present in the tissues surrounding the necrotic lesions. There is a variable but often marked peribronchial inflammatory infiltrate in which eosinophils may be prominent. Proximal bronchi may show plugging by inspissated material and there may be chondritis and cartilage destruction within their walls. Pulmonary arteritis is not a major feature and when it occurs is secondary to the bronchial and parenchymal infiltration [1,121,122].

### Clinical features

Patients with bronchocentric granulomatosis divide into two groups: those with and those without asthma [121,123]. The asthmatic patients present with chest-related symptoms such as cough, haemoptysis, dyspnoea, wheeze and chest pain, whereas the non-asthmatics tend to present with non-specific symptoms such as malaise, fever or fatigue.



(a)

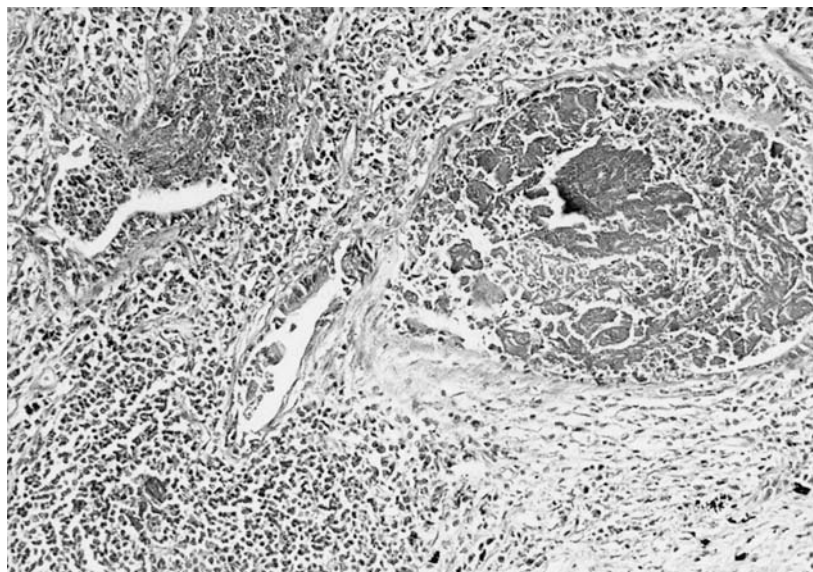


(b)

**Fig. 40.7** Chest films of patient with necrotizing sarcoid granulomatosis: (a) nodular lesions in right lung, originally thought to be metastases; (b) 2 weeks later, showing increasing consolidation also at right base.

The radiological appearance is commonly that of a solitary mass lesion, most often in the upper lobe, although alveolar and reticulonodular infiltrates have also been described [124]. Adenopathy and cavitation are uncom-

mon. Asthmatic patients tend to be younger and have peripheral blood eosinophilia, positive skin tests, and precipitins and elevated IgE levels to *Aspergillus fumigatus*. This organism may be present in sputum or lung biopsy



**Fig. 40.8** Section of lung resected from patient with bronchocentric granulomatosis. Small bronchi are seen with walls partly destroyed by a florid infiltrate with lymphocytes and eosinophils and intraluminal cellular and granular debris (haematoxylin & eosin  $\times 85$ ).

specimens [121,122], and pathological appearances of bronchocentric granulomatosis are frequently present in lung specimens resected from patients with typical bronchopulmonary aspergillosis [125]. The asthmatics have an eosinophil pulmonary infiltrate, whereas the non-asthmatics have a predominance of neutrophils. It has been postulated that the main requirement for the development of bronchocentric granulomatosis is a sustained inflammatory insult within the lumen, often associated with proximal bronchial obstruction and distension of distal airways by retained secretions and cellular debris [122]. In the asthmatic, the allergic response to *Aspergillus* (or other fungus) provides the insult [121]. In the non-asthmatics the insult is usually unidentified though inter-

esting case reports of bronchocentric granulomatosis in association with tuberculosis, echinococcosis, ankylosing spondylitis and seropositive arthritis suggest that it may be varied [126–130].

### Treatment and prognosis

Most patients with this disease are diagnosed after thoracotomy and resection of the diseased lung effects a cure; some patients require corticosteroids for some time post-operatively [121,123,131]. For those with residual or recurrent disease, corticosteroid therapy is recommended with an initial dosage of 40 mg of prednisolone daily, tapering once remission is achieved.

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# LUNG CANCER

RONALD J. FERGUSON

## Epidemiology

### Size of the problem

During the twentieth century lung cancer has emerged as the most common form of malignant disease in the western world. In the UK after the Second World War there was a dramatic rise in the numbers of patients dying from lung cancer (Fig. 41.1) and for some time it has been the most common cause of cancer death in men. Around 40 000 new patients are now seen each year, accounting for more than 8% of all male deaths and 4% of all female deaths [1]. In the European Community, almost 160 000 new patients are registered each year as having lung cancer and in 1992 the Surgeon General reported 133 700 deaths from the disease in the USA [2].

The disease is more common in men than women, although this difference has become smaller; in the USA and the UK, the male/female ratio was approximately 5:1 in 1970 but fell to around 2.5:1 in 1982 [3]. Recently, mortality rates have been falling in men of all ages. In contrast, lung cancer is the most rapidly increasing cause of cancer death in women. Since 1984, deaths from lung cancer have exceeded those due to breast cancer among women in Scotland and in some parts of northern England, and lung cancer looks set to be the major cancer killer of women in other areas. Encouragingly, mortality rates have recently begun to decline in younger women in England and Wales (Fig. 41.1), although the incidence of the disease continues to climb in the older age groups.

### Aetiological factors

#### Tobacco smoking

It has been known for many years that the smoking of tobacco cigarettes is by far the most common cause of lung cancer [4,5]. In England, Wales and the USA, it is estimated that 92–94% of lung cancer deaths are attributable to tobacco smoking in males, the figures in females being

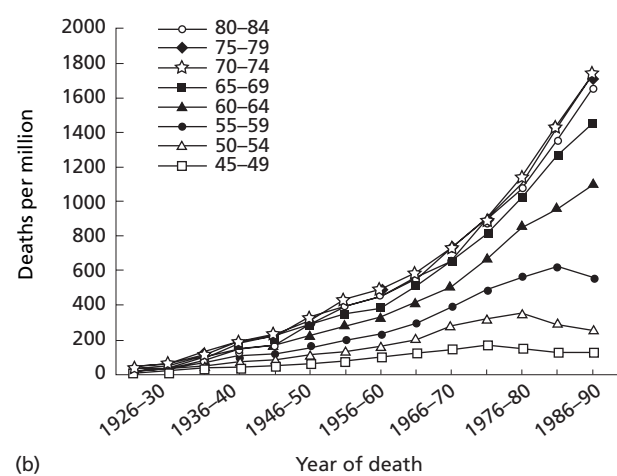
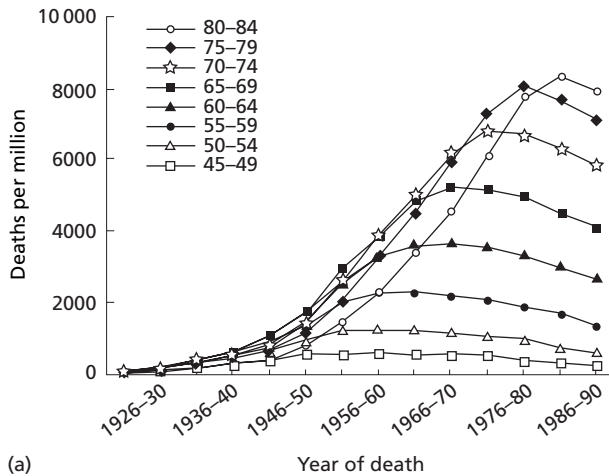
78–80% [6]. The evidence for this association is derived from epidemiological studies, the earliest of which were retrospective. Doll and Hill [7] compared over 1300 lung cancer patients in hospital with a matched group of controls. It was found that there were very few non-smokers in the cancer group and this group contained many more heavy smokers than were found in the control group. Further support for the hypothesis that smoking causes lung cancer was provided by prospective studies. Doll and Peto [8] correlated the smoking habits of over 34 000 British doctors with lung cancer mortality over a period of 20 years and found a significant decline in both cigarette smoking and lung cancer mortality in this group. This was in contrast to the general male population in whom neither mortality rate from the disease nor tobacco consumption fell. These data were subsequently supported by studies of a large group of American physicians [9] and of British women doctors [10].

It has been estimated that cigarette smokers are 8–20 times more likely to develop lung cancer than lifelong non-smokers and that the extent of this risk correlates closely with the number of cigarettes smoked [11]. There is some evidence to suggest that the risk of lung cancer may be reduced by the use of filter tips and by lower tar yields [6,12]. Following cessation of smoking, the risk of developing carcinoma of the lung has been shown to decline progressively with time. However, even by 10–20 years the risk is still about 2.5 times that of non-smokers [13].

Unfortunately, smokers do not only increase their own risk of developing lung cancer, since there is evidence that the inhalation of other people's tobacco smoke (passive smoking) on a long-term basis is linked with an increased incidence of the disease. This risk was first noted in a study of non-smoking wives of heavy smokers in Japan [14]. It has now been shown that people who have been exposed to environmental tobacco smoke in their homes, both as children and adults, have an increased risk of lung cancer [15].

Pipe and cigar smokers have a slightly reduced risk of developing lung cancer compared with cigarette smokers,





**Fig. 41.1** Mortality from lung cancer by age and year of death, England and Wales 1921–90: (a) males, (b) females. (From Lung and Asthma Information Agency Factsheet 93/1, with permission of Professor Ross Anderson.)

probably because less smoke is inhaled [13]. It is also clear that of the principal histological types of lung cancer, squamous cell carcinoma and small-cell carcinoma have the clearest association with cigarette smoking, while adenocarcinoma is the commonest histological type in non-smokers who develop the disease [6].

#### Trends in smoking and lung cancer

In the UK, the consumption of cigarettes by men rose steadily throughout the first half of this century: the average annual consumption of cigarettes per man in 1905 was 800, rising to 4420 by 1945 [16]. Since then, and particularly in the last 20 years, consumption has fallen, reaching 2380 by 1985. The pattern of annual consumption in women has lagged behind that of men, starting with 13 in 1921, reaching 1250 in 1945 and peaking at 2630 in 1974. Since then consumption has fallen, but more slowly than that of men, reaching 1930 in 1985. The prevalence of cigarette smoking shows a similar trend, decreasing from 52% of men in 1972 to 31% in 1990; prevalence among women has fallen from 41% to 29% over the same time span [17]. If the current trends in the UK continue, smoking will soon be more common in women than in men. The clear link between tobacco consumption and lung cancer means that trends in the disease closely follow changes in cigarette consumption but with a lag period of approximately 20 years. Two important statistics concerning cigarette smoking will be reflected in the future pattern of lung cancer cases: (i) smoking problems among young women have increased in recent years; and (ii) most cigarette smokers are now in the less affluent socioeconomic groups in society [2]. At present the risk of an unskilled working

**Table 41.1** World age-standardized rates per 100 000 (WASR) for selected cancer registries, cancer of the trachea, bronchus and lung (ICD-9 162), 1983–87.

Males		Females	
Country/registry	WASR	Country/registry	WASR
Scotland	88.1	Scotland	30.5
Netherlands, Eindhoven	87.2	USA, Connecticut, whites	29.9
Italy, Varese	82.3	Canada	23.9
Poland, Cracow	73.1	Denmark	23.1
Canada	68.5	England and Wales	20.5
England and Wales	65.4	China, Shanghai	18.1
USA, Connecticut, whites	62.5	Poland, Cracow	13.2
Denmark	58.5	Japan, Osaka	11.7
China, Shanghai	53.0	Italy, Varese	8.2
Spain, Zaragoza	42.2	Netherlands, Eindhoven	7.9
Japan, Osaka	41.5	Spain, Zaragoza	3.6
India, Bangalore	10.1	India, Bangalore	1.9

man dying of lung cancer is three times that of a professional man and it is likely that smoking habits are the major contributor to this difference. Table 41.1 shows the marked geographical variation in lung cancer mortality in different developed countries. The precise reasons for this variation are unclear; although socioeconomic, genetic and cultural differences exist, cigarette consumption must be important. While cigarette consumption is decreasing in all industrial societies it is extremely worrying that smoking is increasing in less developed countries, especially Africa and South America. Of the 10 nations with the highest smoking rates among males, eight are regarded as developing countries and of the top 30 only nine are industrialized [18]. If the current trends in tobacco consumption continue, it has been estimated that by the year 2025 80% of the projected 3.5 million cases of lung cancer per year will be in developing countries.

### Atmospheric pollution

The role of environmental air pollution in the production of lung cancer is controversial and has certainly been far less important than the part played by cigarette smoking. Studies carried out to investigate the effect of environmental pollution and which have allowed for tobacco consumption show that urban dwellers have a risk of lung cancer that is 1.26–2.33 times greater than people living in the countryside [19,20]. Atmospheric pollution has also been used to explain the differences of incidence in lung cancer between two countries with similar cigarette consumption (Table 41.1). Recently there has been a lot of interest in the influence of residential radon exposure in the development of lung cancer. It is known that underground miners exposed to high levels of the radon progeny that decay from uranium have an increased risk of lung cancer [21]. Residential radon is the principal source of exposure to ionizing radiation in most countries. Studies from Sweden have suggested that residential exposure to radon is an important factor in the development of lung cancer in the general population, the interaction between radon exposure and smoking being almost a multiplicative effect [22,23].

### Occupational factors

Certain occupations are associated with a higher than expected incidence of lung cancer. Table 41.2 lists a number of known causative agents and it is predictable that the list will grow with the ever-increasing complexity of industrial processes. In many instances the carcinogenic effect of the individual exposure is added to or multiplied by the effect of cigarette smoking, making the apportion-

ment of blame difficult in individual cases. Asbestos is particularly notable for its association with lung cancer. There is often a considerable latent period between exposure to asbestos and the onset of lung cancer. The risk rises until at least 30 years after first exposure, with an approximately linear relationship between the dose of asbestos and mortality and no detectable threshold dose below which there is no increased risk of lung cancer. The interaction between asbestos exposure and smoking appears important [24], all longitudinal studies having shown that the interaction between these two risk factors is close to multiplicative [25].

The precise importance of asbestos exposure in the development of lung cancer in the general population is unknown. De Vos Irvine and colleagues [26] estimated that 5.7% of cases of lung cancer in the west of Scotland were asbestos-related. Extrapolating these figures to the whole of the UK would suggest that in excess of 2000 cases a year may be related to asbestos; however, this projection may not be appropriate since the west of Scotland has been an area with classically high exposures in shipyards and construction. Data from the SWORD surveillance scheme [27] suggest that comparatively few such cases are recognized, possibly because once the patient is identified as a tobacco smoker the physician does not enquire further into asbestos exposure. Also this exposure may appear trivial and have occurred many years before the presentation with lung cancer. Other aspects of asbestos-related disease are discussed in Chapters 43 and 54.

The increased risk of lung cancer described in workers extracting metal ores from deep mines is thought to be caused mostly by radioactivity rather than the metal being mined. This radioactivity emanates from radon gas, high concentrations of which can build up in poorly ventilated mines. Groups of workers in whom lung cancer has been described include uranium miners in various American states [28], fluorspar miners in Canada [29], iron ore miners in Sweden [30] and tin miners in Cornwall, England [31]. Other occupational exposures associated with lung cancer include nickel [32], the extraction and production of chromium salts [33], the use of arsenicals in the metal refining and chemical industries [34], the use of chloroethers in production of ion exchange resins [35] and coke oven work in the steel industry [36]. It is suspected that printing ink used in the newspaper industry may have been associated with lung cancer [37].

### Pulmonary scarring

There have been reports of lung cancer occurring in close spatial relation to localized areas of pulmonary scarring and in patients with more diffuse lung fibrosis. The pathogenesis of these small numbers of 'scar cancers' is not established and in many cases the subject's tobacco smoking history may be highly relevant. This is particu-

**Table 41.2** Occupational causes of lung cancer.

Cause	Occupation
Asbestos	Mining, processing, usage
Radioactivity (radon daughters)	Metal ore mining Uranium mining Fluorspar mining
Nickel	Refining
Chromium salts	Extraction, production, usage
Arsenic	Metal refining Chemical industry Insecticides
Chloroethers	Organic chemical industry
Mustard gas	Manufacture
Volatile coal products (?)	Coke oven workers
Printing ink (?)	Printing industry

larly true in patients with asbestos exposure, as mentioned above. It used to be believed that lung cancer only occurred in asbestos-exposed individuals secondary to the lung fibrosis of asbestosis, and in the UK and several other countries compensation for asbestos-related disease recognized lung cancer as work-related only if there was radiological or pathological evidence of lung fibrosis [38,39]. However, Wilkinson and colleagues [40] studied the occupational histories of 271 patients with lung cancer and a suitable control group and showed that the risk of lung cancer from asbestos exposure was independent of radiologically apparent pulmonary fibrosis.

Cryptogenic fibrosing alveolitis (see Chapter 31) is also associated with cancer of the lung and, like asbestosis, an increased incidence of adenocarcinoma has also been noted in this group [26,41]. The incidence of lung cancer has also been found to be three times higher than anticipated in over 3500 patients with sarcoidosis [42]. It is not clear whether this was due to pulmonary fibrosis, although the histological distribution was no different from that in the general population upper lobe fibrosis due to tuberculosis may be associated with neoplastic change [43], adenocarcinoma being the usual cell type. A high proportion of cases of bronchioloalveolar carcinoma (a subtype of adenocarcinoma) occurs in areas of scarring [44] and this cell type has also been described in relation to congenital cystic lung disease [45].

## Laboratory studies

Lung cancer is not a single entity but a generic term applied to a heterogeneous group of epithelial lung tumours that show varying degrees of malignancy in their different rates of progression and patterns of behaviour. Current laboratory evidence suggests that lung cancer starts with a single cell capable of developing into various pathological forms, including mixed tumours (Fig. 41.2). Clinicians recognize four major groups, namely squamous carcinoma, adenocarcinoma, large-cell carcinoma and small-cell carcinoma. Because of the markedly different growth rates and response to certain treatments of small-cell carcinomas, there is a tendency for investigators to

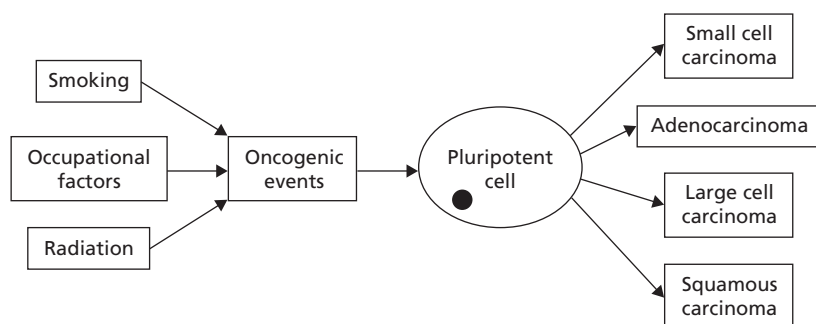
simplify even further and to apply their treatment protocols to small-cell carcinoma and non-small-cell carcinoma groups. Although this approach may be pragmatic, it has the obvious shortcomings inherent in assigning several different pathological entities to a convenient clinical category.

## Histological classification

The ideal classification of lung cancer should list histologically distinguishable groups of tumours according to clearly recognizable criteria so that different pathologists can reliably and independently arrive at the same diagnosis on the same piece of tissue. It should also be of value to physicians and surgeons who have to choose appropriate therapies and to investigators who seek to establish the value of different treatment regimens or the validity of possible aetiological links. The mere fact that several different classifications have been proposed is an indication that an ideal one has not yet been devised. The pathologist's difficulties are further increased by the now widespread submission of small quantities of biopsy material. Although the cellular characteristics of the same tumour may vary significantly in a standard section, these variations may not be detectable in a tiny fiberoptic bronchoscopy specimen or from a cytological preparation of a small number of malignant cells.

The 1981 World Health Organization (WHO) classification (Table 41.3) is still widely used [46]. Even at the time of its introduction it was criticized on the grounds that no account had been taken of differentiation and that some of the listed subtypes were of doubtful significance. It is also clear from immunoperoxidase and electron microscopic studies that lung cancers are heterogeneous in differentiation [47]. Well-differentiated squamous carcinoma may contain foci of adeno- or neuroendocrine differentiation, and tumours that are anaplastic on light microscopy may show glandular or squamous features at an ultrastructural level.

In an attempt to overcome these problems two new classifications of lung cancer have been suggested depending on the type of pathological specimen submitted. The first



**Fig. 41.2** Hypothesis for the development of different histological types of lung cancer from a single cell.

**Table 41.3** World Health Organization (1981) classification of lung tumours. Group C: malignant epithelial tumours.

1 Squamous cell carcinoma (epidermoid carcinoma) Variants: <i>spindle cell (squamous) carcinoma</i>
2 Small-cell carcinoma (a) <i>Oat cell carcinoma</i> (b) <i>Intermediate cell type</i> (c) <i>Combined oat cell carcinoma</i>
3 Adenocarcinoma (a) <i>Acinar adenocarcinoma</i> (b) <i>Papillary adenocarcinoma</i> (c) <i>Bronchioloalveolar carcinoma</i> (d) <i>Solid carcinoma with mucus formation</i>
4 Large-cell carcinoma Variants: (a) <i>Giant-cell carcinoma</i> (b) <i>Clear-cell carcinoma</i>
5 Adenosquamous carcinoma
6 Carcinoid tumour
7 Bronchial gland carcinoma (a) <i>Adenoid cystic carcinoma</i> (b) <i>Mucoepidermoid carcinoma</i> (c) <i>Others</i>
8 Others

(Table 41.4) is proposed for use with large specimens (resections or large open biopsies) [48] and is an adaptation of the pioneering work of Lamb [49]. It can be seen that the degree of differentiation is important in both squamous carcinomas and adenocarcinomas, and that tumours of neuroendocrine type are grouped together. This classification is clearly unsuitable for small biopsies. In 1993 the Lung Cancer Working Party of the UK Coordinating Committee for Cancer Research (CCCR) highlighted the problems with small specimens in a study comparing the diagnosis made on biopsy with that made on the resected specimen [50]. A diagnostic accuracy of 75% was achieved for squamous cell carcinoma, 66% for small-cell carcinoma but only 50% for adenocarcinoma. A new simplified classification (Table 41.5) was proposed that should improve the diagnostic accuracy of small biopsy specimens. The results of clinical evaluation of both these classifications are awaited.

For most pathologists, four major subgroups of lung cancer still predominate and account for about 95% of cases: squamous cell carcinoma (40–60%), small-cell carcinoma (7–25%), adenocarcinoma (10–25%) and large-cell carcinoma (5–15%) [49]. Carcinoid tumours, which account for up to 10% of cases, are discussed with other rarer tumours in Chapter 42.

### Squamous cell carcinoma

This is the most common type of lung cancer. It shows histological evidence of squamous differentiation, with

**Table 41.4** Classification of lung cancer proposed for use with large biopsy specimens. (From Edwards [48].)

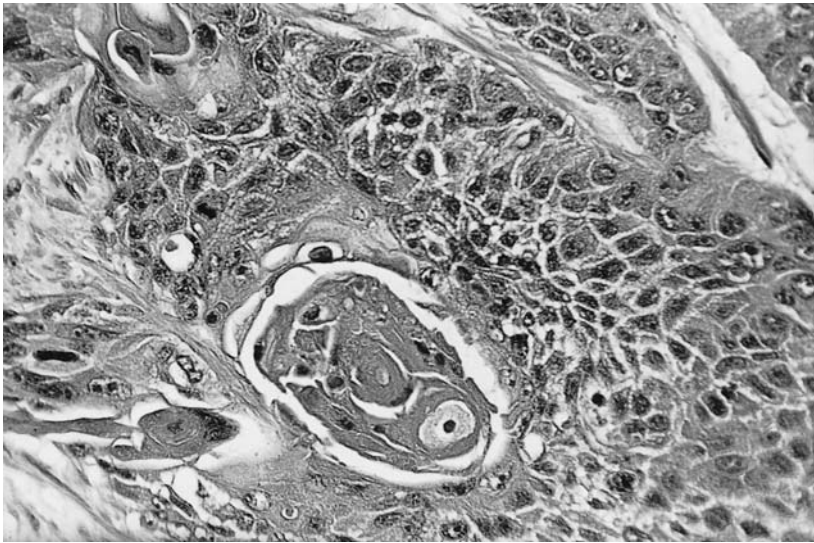
Type	Tumour
1/0	Squamous carcinoma 1/1 Well differentiated 1/2 Moderately differentiated 1/3 Poorly differentiated 1/4 Undifferentiated (squamoid)
2/0	Neuroendocrine carcinoma 2/1 Carcinoid tumour 2/2 Well-differentiated neuroendocrine carcinoma 2/3 Large-cell neuroendocrine carcinoma 2/4 Small-cell carcinoma
3/0	Adenocarcinoma 3/1 Well differentiated 3/2 Moderately differentiated 3/3 Poorly differentiated 3/4 Undifferentiated
4/0	Large-cell undifferentiated carcinoma
5/0	Miscellaneous carcinomas 5/1 Tumours of mixed differentiation (i.e. adenosquamous carcinoma) 5/2 Bronchial gland carcinomas 5/3 Bronchioloalveolar carcinoma 5/4 Giant-cell carcinoma 5/5 Clear-cell carcinoma 5/6 Carcinosarcoma 5/7 Spindle cell carcinoma
6/0	Malignant epithelial tumours of uncertain type

**Table 41.5** Classification proposed by the UK CCCR Lung Cancer Working Party for routine use in the diagnosis of small biopsy specimens. (From Thomas *et al.* [50].)

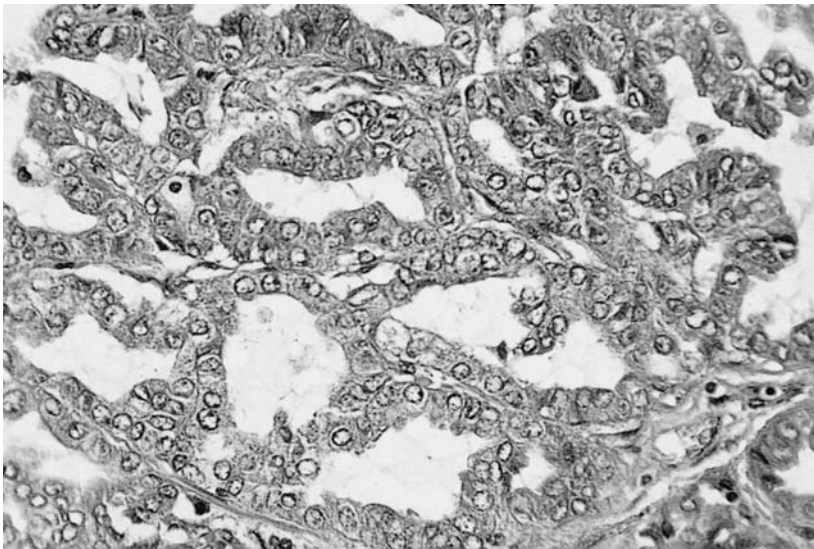
Category	Tumour
1	Squamous carcinoma
2	Small-cell carcinoma
3	Adenocarcinoma
4	Non-small-cell carcinoma of specified type
5	Non-small-cell carcinoma, not otherwise specified
6	Malignant tumour, not otherwise specified
7	Technical failure
8	Carcinoma, not otherwise specified

stratification, the formation of intercellular bridges and intracellular keratinization (Fig. 41.3). The majority of squamous cell carcinomas are centrally situated, and those that are more differentiated grow more slowly and are less likely to give rise to extrathoracic metastases. Those squamous cell carcinomas that are more poorly differentiated tend to behave aggressively, extrathoracic metastases being more frequent. However, the relation-





**Fig. 41.3** Well-differentiated squamous carcinoma showing keratin pearl formation and intracellular cytoplasmic bridges (haematoxylin & eosin  $\times 305$ ).



**Fig. 41.4** Moderately differentiated adenocarcinoma showing a well-marked acinar pattern (haematoxylin & eosin  $\times 305$ ).

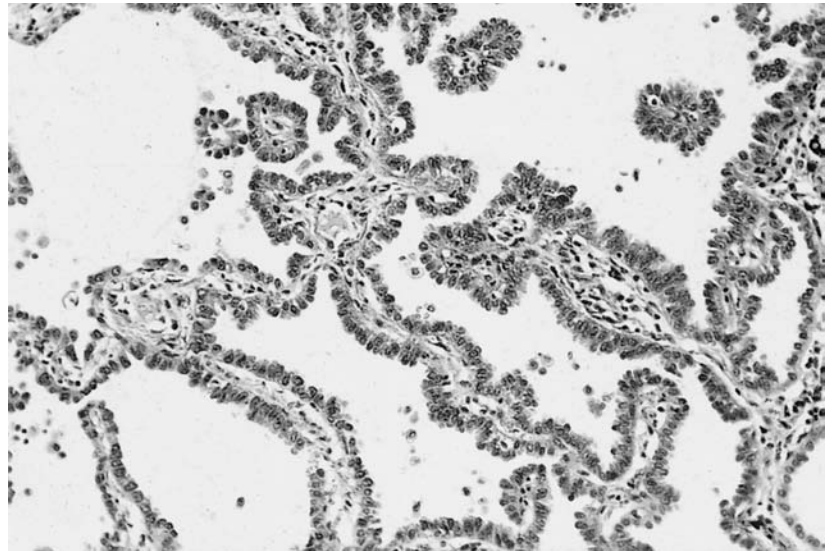
ship between differentiation and prognosis remains uncertain [51]. It is not uncommon for squamous cell carcinomas to cavitate.

### Adenocarcinoma

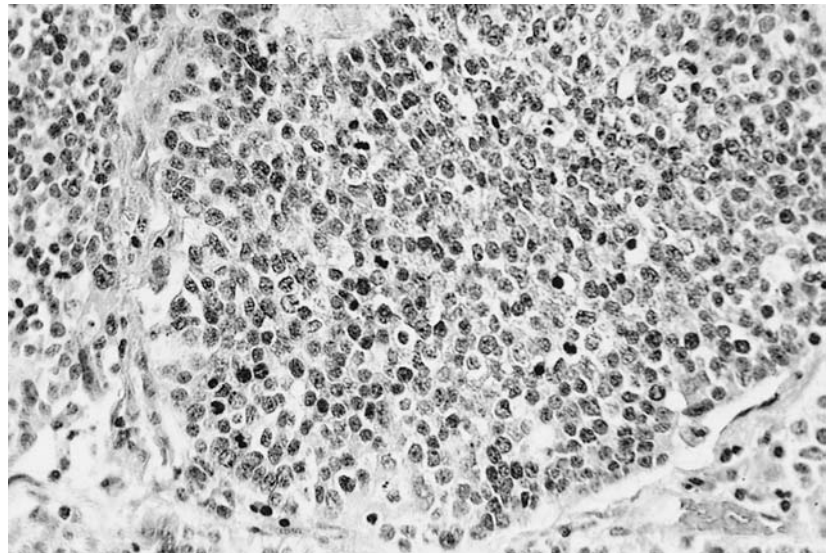
Adenocarcinomas of the lung often present a wide variety of patterns. The WHO classification, which splits tumours into acinar or papillary types, is confusing since in practice these patterns may coexist in the same tumour [52] (Fig. 41.4). Both types tend to produce mucin. There appears to be quite a wide geographical variation in the incidence of adenocarcinoma and some evidence that it is becoming more common. These tumours, unlike squamous cell varieties, are less related to cigarette smoking and are usually situated in the periphery of the lung. Often they are unrelated to bronchi other than by spread.

The WHO classification includes bronchioloalveolar carcinoma (also known as alveolar cell carcinoma) along with other adenocarcinomas. Electron microscopic studies imply that these tumours are a heterogeneous group of peripheral lung tumours that arise from any epithelial cell within or distal to the terminal bronchioles [52]. They account for about 5% of all lung cancers. Apart from their lepidic mode of spread, they behave in a similar fashion to other malignant lung tumours. On gross inspection their margins are less well defined than other members of this group, often appearing as multiple pulmonary nodules or an area of peripheral 'pneumonic consolidation'. It is common for tumour cells to exfoliate and be detected in sputum (Fig. 41.5). Regional and more distant metastases may occur less commonly than is the case with other lung tumours. At the light microscopic level these tumours as well as other adenocarcinomas may be indistinguishable

**Fig. 41.5** Bronchioloalveolar carcinoma showing tumour cells lining alveolar walls, forming papillary structures with shedding of clumps of malignant cells into alveolar spaces (haematoxylin & eosin  $\times 150$ ).



**Fig. 41.6** Undifferentiated small-cell carcinoma showing many mitoses (haematoxylin & eosin  $\times 305$ ).



from metastatic adenocarcinoma arising from an extrathoracic primary site, the most common of which are pancreas, colon, breast, stomach and kidney.

### Small-cell carcinoma

This group contains the most malignant tumours of the lung and accounts for 20–25% of cases. The WHO classification [46] divides small-cell carcinoma into three main types.

**1** Small or oat-cell carcinomas characterized by a proliferation of cells with round or oval nuclei and scanty cytoplasm (high nuclear/cytoplasmic ratio) (Fig. 41.6). These cells are about twice the size of lymphocytes, which they superficially resemble.

**2** The intermediate cell subtype, which contain cells less

regular in shape with more abundant cytoplasm. There is some evidence that this subtype containing some large cells is more resistant to chemotherapy.

**3** A combined subgroup, which includes rare examples of small-cell carcinoma containing areas of squamous carcinoma or adenocarcinoma. Probably only about 1% of tumours fall into this category [53]. It is accepted that they should be managed as small-cell carcinoma and carry the same prognosis.

Small-cell carcinomas usually arise in central bronchi. They are often grouped with carcinoid tumours as they probably originate from common neuroendocrine precursor cells. Small-cell carcinomas grow rapidly and metastasize early and widely, so that disease is rarely limited to the chest at necropsy. At presentation over two-thirds of patients have evidence of extensive disease, the most

important clinical sites of metastases being the liver, central nervous system (CNS) and bone. Other frequent sites include the abdominal lymph nodes, adrenals and other abdominal organs.

### Large-cell carcinoma

These tumours account for about 15% of lung cancers. The group is somewhat heterogeneous and many authorities now regard it as a diagnostic wastebasket [48]. The tumours tend to be anaplastic, light microscopy showing no features of maturation and the presence of large, less well-differentiated, polygonal, spindle-shaped or oval cells with abundant cytoplasm (Fig. 41.7). Electron microscopy may show features of squamous cells or adenocarcinoma. Many authors feel that they may be undifferentiated examples of squamous carcinoma or adenocarcinoma in which only anaplastic material has been sampled. It is obviously significant that the entity of large-cell carcinoma does not exist in the UK CCCR proposed classification for the pathology of small biopsy specimens [50]. The majority of large-cell carcinomas arise towards the lung periphery and are bulky. The two variant forms in the WHO classification are rare. Clear-cell carcinoma contains large rounded cells with clear cytoplasm and is commonly mistaken for metastatic renal cancer.

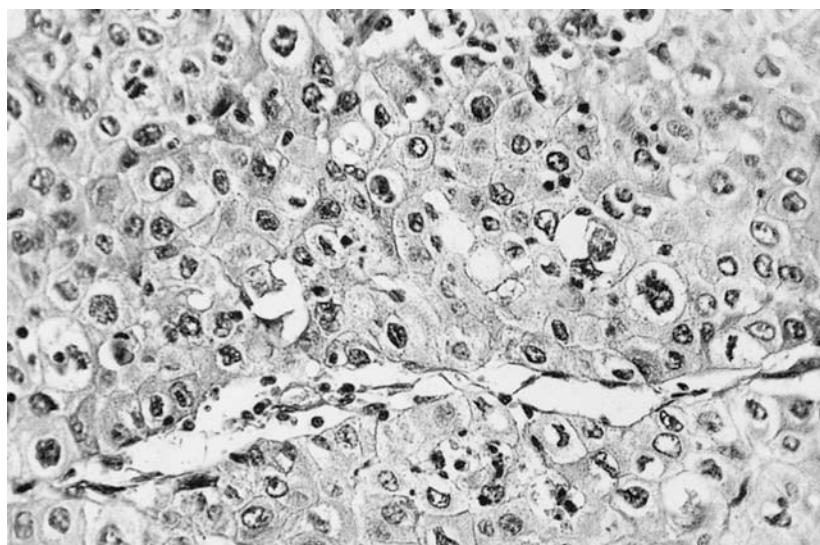
### Biology

The lack of progress in the treatment of lung cancer has led to a growth of interest in the biology of the disease, with the hope that an increase in knowledge could be translated into therapeutic advances. It is now possible to take tumour cells from a patient with lung cancer and grow them in the laboratory in the form of cell lines or as

xenografts in immunosuppressed animals [53,54]. These models of human lung cancer have facilitated the study of the biology of the disease. The tumours can be maintained indefinitely and remain cytologically identical to the original biopsy specimen. There are a number of areas where advances in our understanding of basic mechanisms at the cellular level may soon be translated into benefits for the patient with lung cancer.

### Growth factors

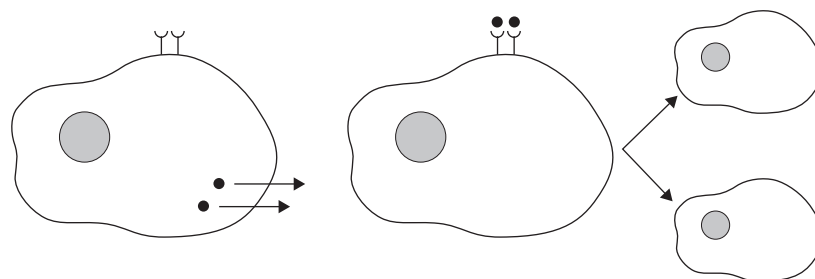
Growth factors are polypeptides that take part in the control of cell differentiation and proliferation. They act locally on tumour cells via growth factor receptors but may also be found in the circulation [55]. It has long been known that small-cell tumours are able to synthesize a wide range of peptides and hormones and that these substances can readily bind to cell receptors causing autocrine growth stimulation (Fig. 41.8). Bombesin/gastrin-releasing peptide has been shown to be an important growth factor both *in vitro* [56] and *in vivo* [57]. It has also been shown that the growth of small-cell lung cancer in the laboratory can be inhibited by a monoclonal antibody to bombesin [58]. Other important growth factors in small-cell lung cancer include vasopressin and bradykinin [59], opioids [60] and insulin-like growth factor 1. Numerous other substances have been shown to be secreted by small-cell lung cancer cells and have the potential to regulate their growth [55]. Non-small-cell lung cancer appears to have fewer recognized growth factors, although epidermal growth factor and transforming growth factor  $\alpha$  have been shown to bind to specific cell receptors and to stimulate growth [55,61]. The expression of growth factors and their receptors in some non-small-cell lung cancers appears to be related to aggressive clinical behaviour and the increased likelihood of a



**Fig. 41.7** Undifferentiated large-cell carcinoma showing large pleomorphic tumour cells (haematoxylin & eosin  $\times 305$ ).



**Fig. 41.8** Autocrine growth stimulation: a lung cancer cell produces a growth factor that binds to a receptor to stimulate proliferation.



response to chemotherapy. Results of clinical trials involving the manipulation of these autocrine growth factors are eagerly awaited.

### Genetic abnormalities

It is surprising that only 15% of male smokers contract lung cancer, given the close association between smoking and the disease. It seems likely that the remaining 85% have an inherited resistance to the disease and that the small number of non-smokers who develop lung cancer may be inherently susceptible [62]. This has led to much interest in genetic abnormalities in patients with lung cancer and in laboratory models of the disease [63]. A plethora of genetic abnormalities has been detected and this has created some confusion as to their significance in the genesis and progression of the disease. One of the earliest and most consistent chromosomal deletions seen is the loss of the short arm of chromosome 3 (p14–p23) in small-cell lung cancer [64,65]. This suggests that loss of specific gene function may be a critical step in the development of lung cancer. This model certainly seems to fit for the development of another, rarer tumour, retinoblastoma, where a specific tumour suppressor gene is also lost from chromosome 3, and indeed there is a close association between small-cell lung cancer and retinoblastoma [66]. Similar genetic abnormalities are seen in tumour cells from non-small-cell cancers [67,68], although the situation is less striking and inactivation of the *CDKN2* gene on chromosome 9 may be more important in this histological subtype [69].

### Oncogenes

Activation of small parts of the genetic code is seen in many cancers and the role of these oncogenes is unclear. Members of the *myc* gene family are often activated in lung tumours, particularly of small-cell type, and may be associated with increased aggressiveness of tumour growth [70]. The normal function of these genes has remained elusive and it is not clear how overexpression contributes to tumour growth. Activation of the *K-ras* oncogenes is usually detected in adenocarcinoma of the lung and patients carrying these mutations have been

shown to have a more aggressive clinical course [71]. It is to be hoped that a greater understanding of the importance of oncogenes will lead to innovative therapies for the patient [63,70,72].

### Tumour markers

Tumour markers are substances produced by tumour cells that are released into the bloodstream where they can be measured. They may be helpful in screening and in the early diagnosis of cancer, in an assessment of the extent of disease and in response to treatment. Many of these markers are produced by normal cells, for example neurone-specific enolase, creatine phosphokinase BB and carcinoembryonic antigen. A long list of tumour-associated antigens has also been discovered. However, despite the deliberations of large international workshops in this field [73], the large variations in sensitivity and specificity of all these compounds has made their precise clinical usefulness uncertain [74,75].

## Clinical features

### Common modes of presentation

Patients with lung cancer can present in many different ways. The majority of patients present as the result of the investigation of some new respiratory symptom or because their pre-existing respiratory state has worsened. A small percentage have no respiratory symptoms and the diagnosis is made by the chance finding of an opacity on a chest radiograph ordered for some other reason. A third group develop non-specific symptoms of malignancy, including malaise, anorexia and weight loss. A fourth group presents as a result of metastatic disease and usually have an extremely poor prognosis.

### Central tumours

Three-quarters of patients with lung cancer have their primary disease in the central airway. This is especially true of squamous and small-cell carcinomas. The commonest symptoms at presentation are cough, haemoptysis, dyspnoea and chest pain, either alone or in

combination. Cough is by far the most common symptom at presentation and any 'new' cough that persists longer than 2 weeks should be regarded with suspicion, especially in patients over the age of 40 years who are tobacco smokers. Unfortunately this group tend to have a chronic cough due to chronic bronchitis and this may often lead to some delay in diagnosis. Haemoptysis is usually an alarming symptom for the patient and one that should always be thoroughly investigated. It may amount to only minimal streaking of blood in mucoid sputum and the patient often presents in order to be reassured. Copious haemoptysis is uncommon. However, it should be recognized that most patients who have haemoptysis do not have lung cancer; nevertheless all patients with this symptom require investigation. Breathlessness may arise because of central airway narrowing or because of partial or complete collapse of a distal segment of lung. Poorly localized deep chest discomfort occurs in up to 60% of patients at diagnosis. The exact cause of this symptom in patients with centrally placed tumours is unclear but it may be due to involvement of peribronchial or perivascular nerves.

### Peripheral tumours

Peripheral neoplasms, commonly adenocarcinoma or large-cell types, often have a different mode of presentation. They may cause no respiratory symptoms at the time of diagnosis, which may follow a chest radiograph taken for some other reason or as part of the investigation of non-specific symptoms. Cough and haemoptysis are less common than in central lesions. Cough with large amounts of mucoid sputum (bronchorrhoea) is described in 10% of cases of bronchioloalveolar carcinoma, although this is an unusual symptom [76]. Dyspnoea is also less common and if present is likely to be due to either pleural involvement with tumour or blockage of lymphatics in lymphangitis carcinomatosa. Pleural effusion also causes breathlessness if it is large enough to compress the lung. Adenocarcinoma is particularly noted for seeding the pleura. Spread beyond the pleura into the chest wall produces dull, continuous pain that commonly interferes with sleep.

### Distant spread

Approximately one-third of patients with lung cancer present with symptoms due to metastatic spread outwith the thorax. Skeletal metastases, which are most commonly seen in small-cell and large-cell lesions, may present with bone pain and even pathological fractures. Cerebral metastases may present with progressive neurological symptoms and are common in patients with widespread disease. Cervical lymph gland and adrenal involvement are also common but do not usually produce symptoms.

Spread to the liver similarly rarely produces symptoms unless the metastases are large.

### Common clinical findings at presentation

Frequently, physical examination of the chest in a patient with lung cancer reveals no abnormal signs. However, physical signs may be elicited that are helpful for not only reaching a diagnosis but also making a preliminary assessment of the extent of disease and determining the most appropriate sequence of further investigation and perhaps treatment in an individual case. For instance, if the patient is obviously breathless while undressing this is usually an indication of coexisting chronic obstructive airways disease, which may preclude attempts at surgical treatment.

The hoarse voice of vocal cord paralysis is easily detectable and may be the only complaint of the patient. When asked to cough the patient often produces a relatively ineffectual expiratory noise, the so-called 'bovine cough'. This lacks the explosive quality of a normal cough produced by proper juxtaposition of two fully adducted cords. The left recurrent laryngeal nerve is most commonly involved as it loops round the aortic arch where it passes over the left main bronchus, a site that may be involved directly by tumour or by mediastinal lymph node metastases. Involvement of the right recurrent laryngeal nerve indicates a thoracic inlet tumour or invasion of the cervical nodes since the nerve loops around the right subclavian artery in the root of the neck. Vocal cord paralysis is therefore only seen in irresectable tumours because of mediastinal involvement.

Clubbing of the fingers and toes is commonly seen, although in one series was not present in patients with small-cell lesions [77]. The cause is unknown and may be associated with hypertrophic osteoarthropathy (discussed below).

Lymphatic spread is common and the scalene and supraclavicular lymph glands are usually the first to become enlarged. Axillary lymph glands are rarely involved and indicate invasion of the chest wall. The palpation of a lymph node provides ready access for histological sampling and positive histological confirmation indicates inoperability also.

Narrowing of the trachea or a lesion in either main bronchus at the level of the carina may cause stridor, an easily audible sound during inspiration. With more distally placed obstructing tumours this sound assumes the quality of a wheeze, which may be audible without a stethoscope. It may persist despite coughing, implying the presence of a fixed mechanical obstruction. A central obstructing lesion may cause a decrease in the intensity of breath sounds over a lobe or entire lung. Such patients are likely to develop atelectasis of the affected portion of lung if treatment is delayed.

The presence of a pleural effusion in a patient with lung cancer is more likely to be due to neoplastic pleural involvement than to be secondary to complicating infection or some other process. A pleural friction rub may be heard over an area of pleuritic pain.

About 5–10% of patients may present with symptoms due to obstruction of the superior vena cava (SVC). The patient notices swelling of the face and neck with tightness around the collar, which may progress to gross oedema. Occasionally the patient may be misdiagnosed as having an allergic reaction, especially if persistent flushing of the face is seen. The earliest and most common sign is bilateral jugular venous engorgement and superficial varicosities over the area drained by the SVC. Obstruction of the SVC is caused by either mediastinal lymph node metastases or direct venous compression of a tumour in the right upper lobe.

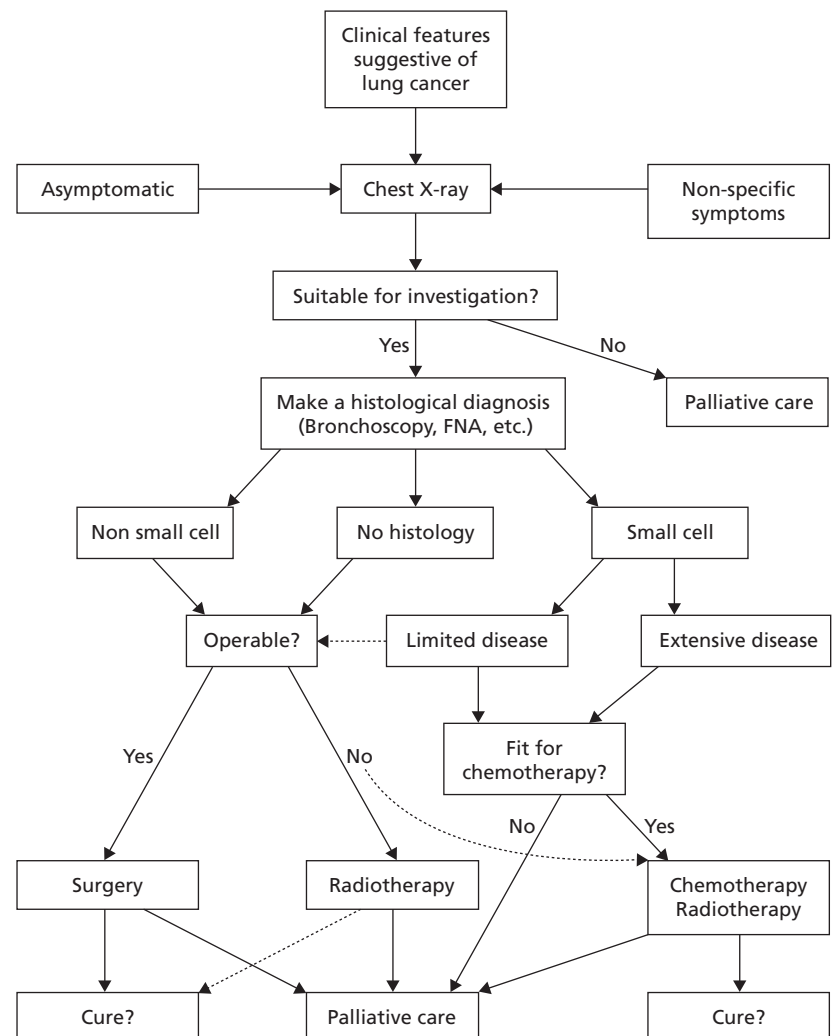
Dullness to percussion at a lung base may be due to not only perfusion or collapse but also to a raised and paralysed hemidiaphragm. This may be confirmed

radiologically or on ultrasound by the presence of paradoxical movement on sniffing and it may contribute significantly to dyspnoea. The majority of cases of phrenic nerve paralysis indicate widespread mediastinal involvement.

A palpably enlarged liver due to hepatic involvement is an unusual finding at presentation, as are the symptoms and signs of raised intracranial pressure resulting from cerebral spread. Dysphagia due to mediastinal node compression of the oesophagus is also a late symptom. The clinical features of superior sulcus (Pancoast) tumours and paraneoplastic syndromes are discussed below.

## Investigation

Clinicians faced with the management of a patient with a likely bronchial carcinoma need to instigate investigations in order to allow a rational management plan for that patient (Fig. 41.9). The purpose of any investigations performed are to confirm the clinical diagnosis, including if possible the histological type, and also to assess the extent



**Fig. 41.9** Outline of the investigation and management of patients with lung cancer. (FNA, fine-needle aspiration.)

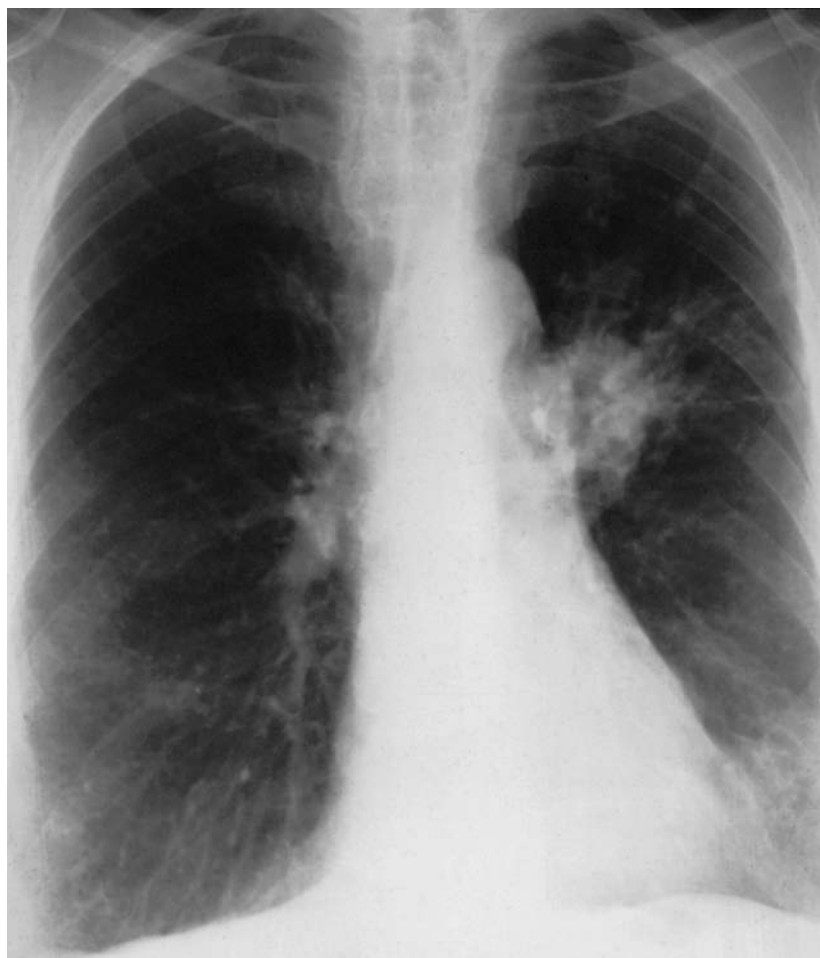
or stage of the disease in order to plan the most appropriate management. Clearly the complexity of investigations should correlate with the patient's suitability for active treatment. Lung cancer commonly presents at an advanced stage in predominantly older patients who often have other significant medical conditions related to cigarette smoking, and in the past there was a feeling that investigating these patients was not justified as effective treatment was not available. However it is now felt that obtaining a precise diagnosis helps patients come to terms with their disease and allows some indication concerning prognosis to be given to them and their families. In most countries the initial assessment of lung cancer patients is performed by respiratory physicians [78], and a case is now developing for recommending that all patients with the possible diagnosis should be assessed by a team involving respiratory physicians as well as clinicians who may be responsible for further treatment, such as cardiothoracic surgeons and oncologists.

### Chest radiography

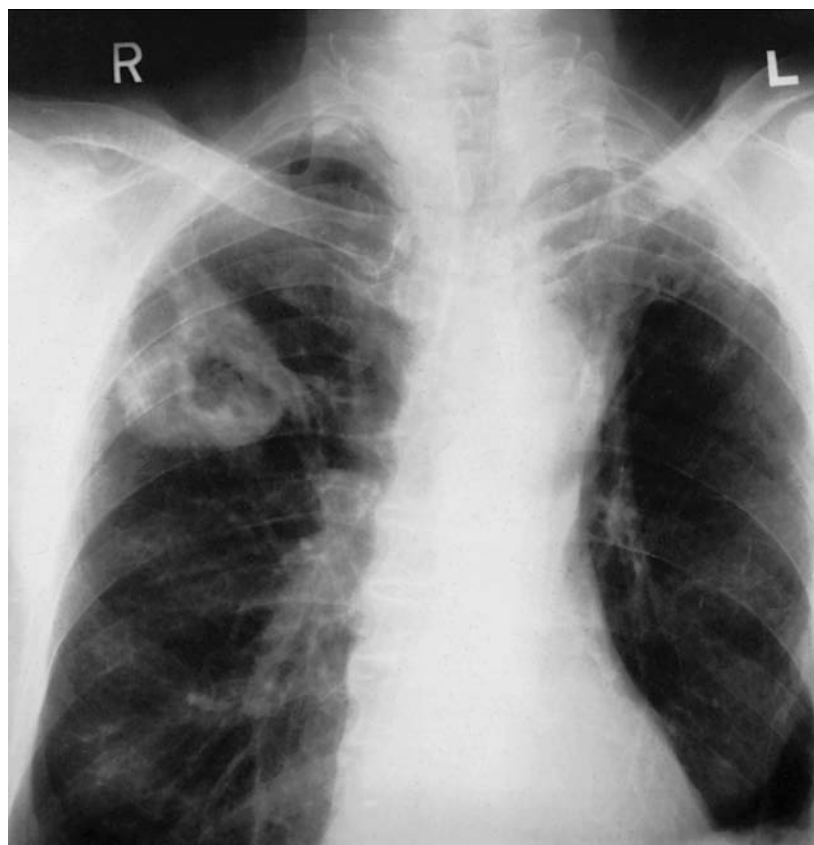
The chest radiograph is nearly always abnormal in

patients with lung cancer at presentation [78]. Common early findings include slight prominence of a hilar shadow in the case of a central tumour and a small pulmonary nodule in the case of a peripheral tumour [79]. By the time the patient presents with symptoms there is more commonly obvious unilateral hilar or perihilar enlargement that is highly suggestive of a primary carcinoma or hilar lymph node spread (Fig. 41.10). Often it may be difficult to distinguish between a prominent hilar shadow due to a normal but prominent pulmonary vessel and an early central tumour.

More peripherally situated lung cancer usually produces a homogeneous mass shadow. The margins are often poorly defined so that they may be mistaken for inflammatory disease. The average diameter of rounded lesions at presentation is 3–4 cm; lesions of less than 1 cm in diameter are likely to be missed [80]. When central necrosis in the tumour occurs, cavitation may be evident and this is most commonly seen in squamous carcinomas [81]. Cavitation is not a feature of small-cell carcinoma. The inner lining of the cavity is often irregular and the shadow may be indistinguishable from that produced by a lung abscess, particularly if a fluid level is present



**Fig. 41.10** Chest film of 60-year-old woman with left hilar squamous tumour arising at the origin of the upper lobe bronchus and causing some distal consolidation.



**Fig. 41.11** Irregularly cavitated carcinoma in right upper lobe. The fibrosed left upper lobe was due to the after-effects of tuberculosis.

(Fig. 41.11). Bronchial obstruction by tumour may produce a true lung abscess, although consolidation without cavitation is more common.

Frequently the most striking radiographic features in lung cancer are the result of the mechanical effects of the tumour which, by obstructing a bronchus, may cause total or partial collapse of a segment, lobe or lung (Fig. 41.12). An ipsilateral unaffected lobe tends to overinflate, becoming more lucent as it expands to fill the additional space provided by the area of collapse, and characteristic displacement of interlobar fissures may be seen. Extensive atelectasis or consolidation may conceal the central causative lung cancer, as may a large pleural effusion.

Elevation of one or other hemidiaphragm may indicate phrenic nerve paralysis. This may be confirmed by fluoroscopy or ultrasound when paradoxical movement of the paralysed leaflet is seen on sniffing. Mediastinal lymph node involvement is often not radiographically visible on plain films unless very advanced, in which case widening of the mediastinum may be seen. In a few cases, lymphatic spread may extend from mediastinal or hilar nodes to pulmonary lymphatics, producing fine, lace-like shadows that may involve the whole of both lung fields, a form of dissemination known as lymphangitis carcinomatosa [82] (Fig. 41.13).

The radiographic features of bronchioloalveolar carcinoma

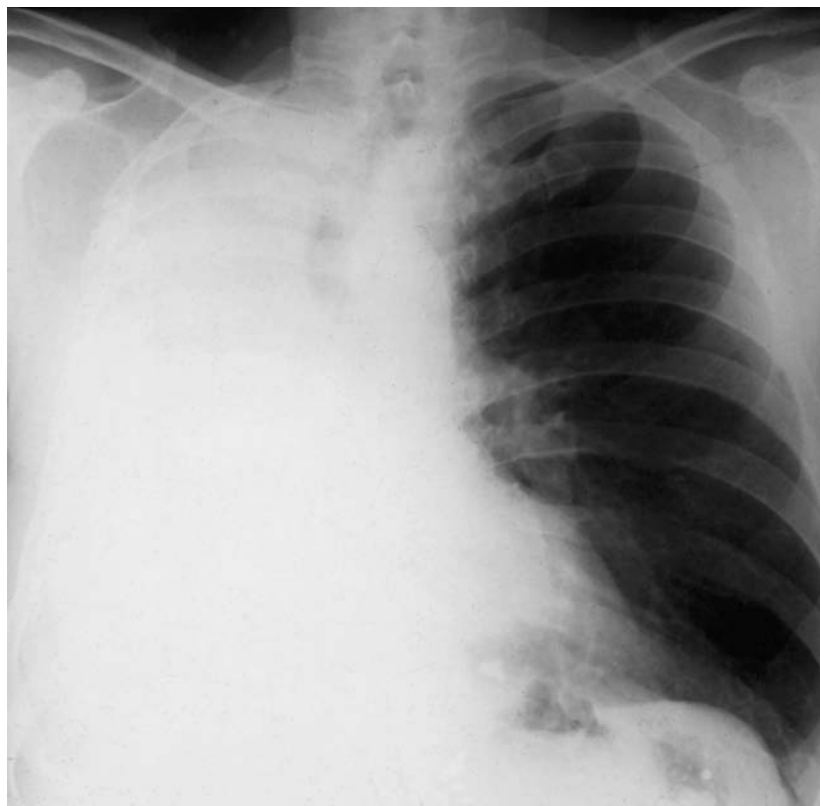
are frequently indistinguishable from those of other histological types. However, this tumour may sometimes produce diffuse ill-defined fluffy infiltrates resulting from its tendency to spread along the airways at bronchiolar level [83] (Fig. 41.14). Radiographically this may resemble pneumonic consolidation but it obviously does not respond to standard antibiotic therapy.

Carcinomas at the extreme apex of the lung are known as Pancoast, thoracic inlet or superior sulcus tumours. In their early stages they may produce only a thin rim of shadowing at the apex that is indistinguishable from pleural thickening due to other causes. As these tumours enlarge, they may also erode and destroy adjacent ribs and infiltrate nerves of the brachial plexus to produce the familiar clinical syndrome (Fig. 41.15).

It is possible, although unusual, for a patient with lung cancer to have a normal chest radiograph [78,84]. This usually occurs when a primary tumour is small and central. Such patients require further investigation, usually by bronchoscopy, if there are other clinical features suggesting bronchial carcinoma, such as haemoptysis.

### **Sputum cytology**

The examination of sputum expectorated by patients suspected of having lung cancer is a simple investigation to



**Fig. 41.12** Complete collapse of the right lung secondary to main bronchial tumour. Note tracheal deviation and absence of air bronchogram in right lung.

perform and often a valuable diagnostic aid. In experienced hands a definitive diagnosis of lung cancer may be made in 60–70% of all cases in whom the diagnosis is subsequently confirmed histologically [84]. The likelihood of this test being positive increases when the tumour is centrally placed, with increasing tumour size and when the lesion is situated in the lower lobe [85,86]. Not surprisingly, squamous and small-cell tumours, which are usually central, have a higher positive yield. Establishment of the correct histological group by sputum cytology has an accuracy of 50–80% depending on the degree of differentiation. Poorly differentiated tumours are more difficult to subtype [84].

The collection of adequate samples is extremely important. The first sputum in the morning or one produced after a bronchoscopy tends to produce a higher positive yield. The yield from a single sample in patients with lung cancer is approximately 40%, although this can be increased by repeated collections to in excess of 80% with four specimens [87]. In experienced hands, false-positive results do not usually exceed 1%.

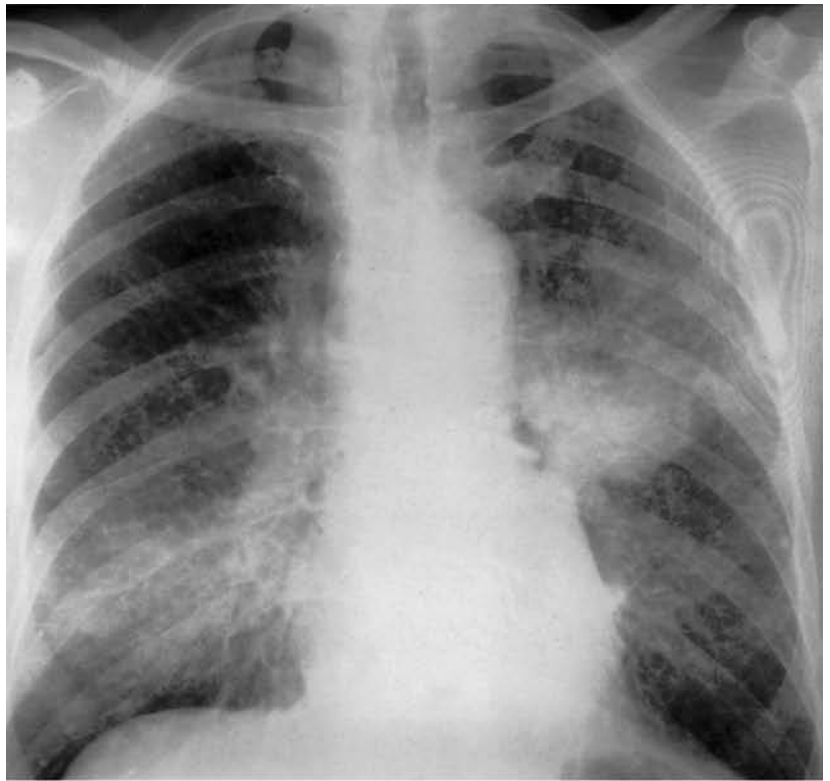
### Bronchoscopy

Bronchoscopy is the most useful investigation in the evaluation of a patient suspected of harbouring a lung cancer, as it can provide histological confirmation as well as information regarding the extent of the disease. The

procedure itself is discussed fully in Chapter 8. Tumours that are situated centrally on a radiograph may be visible bronchoscopically as a neoplastic mass within the lumen. Frequently the presence of a tumour is indicated by bronchial stenosis or external compression due to surrounding tumour tissue or lymph node metastases.

Tumours that are beyond bronchoscopic vision may be biopsied using the transbronchial technique or by blind brushings and washings. Positive diagnoses have been made in 60% of such lesions when they are greater than 2 cm in diameter [88]. Techniques have also been developed for transbronchial needle aspiration of mediastinal nodes [89].

Bronchoscopic evidence of inoperability is provided by the endobronchial site of the tumour and any evidence of mediastinal involvement. Tumours confined to a lobar bronchus may be removed by a lobectomy but those growing to within 1 cm of the carina require pneumonectomy. Mediastinal involvement is suggested by a paralysed vocal cord and by widening of the main carina due to subcarinal lymph node enlargement. External compression of the lateral wall of the lower trachea by enlarged paratracheal lymph nodes also suggests inoperability, assuming that the lymph nodes are involved with tumour. Previously it was common practice for thoracic surgeons to repeat a physician's bronchoscopy prior to surgery. Modern bronchoscopic techniques involving video imaging may allow the surgeon to view the bronchoscopic



(a)



(b)

**Fig. 41.13** (a) Bronchial carcinoma in left mid zone with lymphangitic spread. Note diffuse nodular change and Kerley's lines in lower zones. (b) Magnified view of right lower zone.





**Fig. 41.14** Diffuse confluent shadowing through left lung and nodular lesions in right lung due to bronchioloalveolar carcinoma.



**Fig. 41.15** Extensive pleural infiltration at right apex with destruction of first and second ribs together with the second transverse process: Pancoast tumour.

findings and perhaps save the patient from a repeat procedure.

### Other initial investigations

The vast majority of patients have blood tests as part of their initial assessment [78]. These provide no diagnostic information, although they may point to hepatic involvement or the presence of a paraneoplastic endocrine syndrome (see below). In patients with peripheral lesions a definitive histological diagnosis may only be obtained by percutaneous needle biopsy of the lung or pleura, by aspiration of subcutaneous swellings, lymph nodes or pleural fluid, or by aspiration or biopsy of distant metastases in bones, liver, adrenals, etc. Intrathoracic disease may be confirmed at thoracoscopic lung biopsy, mediastinoscopy or thoracotomy (see below).

### Determination of operability

Once a diagnosis has been made, the investigation of a patient with lung cancer is aimed at deciding the most appropriate therapy available for that individual. Surgical resection has the greatest impact on survival, although at the time of diagnosis the majority of patients are clearly inoperable. If the patient is a prospective surgical candidate, further evaluation has to be carried out in order to ensure that he or she is fit for an operation and that metastatic disease, which would render the patient incurable despite removal of the primary lesion, is excluded.

### Assessment of fitness for surgery

It is common for the lung function of patients with carcinoma of the bronchus to be impaired, as a result of total or partial occlusion of a large bronchus by a central lesion and because of coexisting chronic bronchitis and emphysema which, like lung cancer, are causally related to cigarette smoking. Careful consideration must be given to the effect of the removal of *functional* lung tissue in the tumour-bearing lung in order to prevent, at worst, postoperative respiratory failure and even death or, at best, extreme and persistent dyspnoea that would greatly impair the patient's level of physical activity and quality of life.

The forced expiratory volume in 1 s ( $FEV_1$ ) and forced vital capacity are simple to measure, reproducible and form the basis of the most reliable predictable measurement in the evaluation of suitability for lung resection. Studies have shown that the risk of postoperative chronic ventilatory insufficiency is high if the postoperative  $FEV_1$  is less than 1 L [90], although allowance for the height of the patient should be made in view of the increasing numbers of women presenting with lung cancer. Spirome-

try is reduced by approximately 10–15% of predicted values as a result of lobectomy and by 20–30% with pneumonectomy; in general, patients with a preoperative  $FEV_1$  exceeding 2 L tolerate surgery without severe postoperative breathlessness. Patients who are considered marginal for surgery require further investigation. A quantitative assessment of regional lung function may be useful in borderline patients. It may demonstrate that the patient has already undergone the physiological equivalent of a pneumonectomy or lobectomy by virtue of the tumour occluding a main or lobar bronchus. In such situations resection may do nothing to worsen lung function and may even produce physiological improvement by removing a major cause of ventilation-perfusion mismatch. There is no consensus about the best method of carrying out split lung function studies but most rely on radioisotopes [91,92].

Other useful tests that can be performed preoperatively include the measurement of diffusing capacity, since it is known that postoperative complications are more common if this is less than 40% of predicted before the operation [90]. Most clinicians place considerable reliance on the history of breathlessness and observation of the patient, for example, breathlessness while undressing is a good indication that the patient will be more breathless after surgery, unless of course the tumour has already caused a physiological pneumonectomy. The original lung function test prior to pneumonectomy, carried out by the pioneers of this operation, was to induce an artificial pneumothorax and observe the patient! Nowadays, a 6-min walking test gives a good indication of preoperative function, and difficulty completing this test at a reasonable pace should cause one to think twice before advising surgery.

Consideration also needs to be given to other medical conditions, such as ischaemic heart disease and peripheral vascular disease. Patients who have well-controlled angina usually need to undergo an exercise ECG test and any significant abnormality may need further evaluation with coronary angiography. Subjects whose exercise tolerance is limited by significant intermittent claudication are usually not deemed good surgical candidates.

### Assessment of local spread

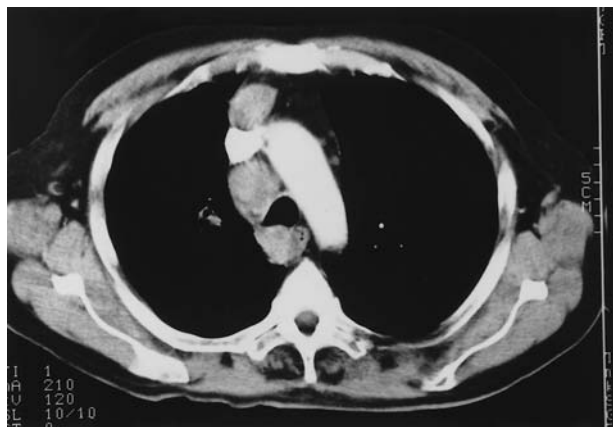
Evidence of spread of tumour into local structures and the mediastinum may be obvious from a history of dysphagia, hoarseness or obstruction of the SVC. A pleural effusion usually means that the subject is inoperable, although it should be further evaluated with pleural aspiration and biopsy. Some centres do not exclude patients if the effusion is small and does not contain malignant cells on repeated aspiration. However, results of surgery in these patients is poor.

The results of surgery correlate well with the extent of

mediastinal node involvement (see below) and assessment of the mediastinum is essential in all patients being considered for surgery. While the initial chest radiograph may show obvious mediastinal lymphadenopathy, a normal mediastinal appearance on a plain radiograph still requires the patient to undergo further mediastinal evaluation.

### *Computed tomography*

Computed tomography (CT) (Fig. 41.16) is now established as the best non-invasive method for assessing the mediastinum in patients with lung cancer being considered for resection [93]. Technological advances over the last two decades, with the introduction of much faster scanners, have enhanced the sensitivity of the investigation (see Chapter 7). The most important limitation of preoperative CT is the fact that although it is good at detecting enlarged lymph nodes, it cannot distinguish between neoplastic and reactive nodes, nor can it tell whether a normal-sized lymph node contains microscopic deposits of tumour. Studies that have measured the sensitivity and specificity of preoperative CT compared with mediastinal node sampling at either mediastinoscopy or thoracotomy show considerable variability in sensitivity and specificity [94–96]. Earlier studies were limited by the technical ability of the available scanners, although many studies using modern machines have given comparable results. A meta-analysis of over 40 studies published in 1990 showed a sensitivity of 79% and a specificity of 86% [97]. The authors used 1 cm as the cut-off value for normality, while most reports assume a 1.5-cm diameter as the upper limit of normal. There is a correlation between nodal size and the likelihood of malignancy, although the association is fairly weak. In one study [94] only 13% of 336 nodes less than 1 cm in diameter contained metastases, while 36% of 78 nodes greater than 1 cm were malignant.



**Fig. 41.16** Thoracic CT showing three enlarged lymph nodes at the level of the aortic arch.

Even in the group with very large nodes (>2 cm in diameter) only two-thirds were subsequently found to contain tumour. While a normal-sized node may well contain a small focus of tumour cells, the predictive value of a negative result on CT has been shown to be in the order of 90%. However, a recent study [98] has questioned this value, finding mediastinal lymph node metastases in 19 of 90 patients (21%) with non-small-cell lung cancer who underwent thoracotomy and who had normal-sized nodes (<1 cm) on CT.

A consensus view about the place of preoperative CT in non-small-cell lung cancer is now emerging. Patients with abnormal scans require mediastinal lymph node sampling to confirm malignant involvement. This allows a significant number of patients to undergo successful thoracotomy who might otherwise have been denied surgery by the presence of enlarged lymph nodes on their scan. Patients with a negative scan who are otherwise operable should proceed directly to thoracotomy, although mediastinal lymph nodes should be sampled at the time of operation. CT may also be useful for identifying tumour invasion of the mediastinum and pleura [99] but its main role would appear to be in detecting which patients should have mediastinoscopy prior to surgery.

Magnetic resonance imaging (MRI) may be useful in assessing Pancoast tumours and chest wall invasion but appear to have no specific advantage over CT in the routine evaluation of a patient. Likewise the place of positron emission tomography has not been established in lung cancer [100] and it is not widely available to most clinicians.

The use of radioactive isotopes taken up by tumour cells, such as gallium, has been evaluated but adds nothing to the sensitivity or specificity of CT. A major advance in this field would be the discovery of a technique by which malignant tissue could be discriminated from non-malignant tissue, therefore allowing accurate documentation of tumour spread.

### *Mediastinoscopy*

As stated above, patients who have abnormal mediastinal nodes on CT should have mediastinoscopy to confirm or refute the presence of metastatic spread. This allows for better selection of patients for surgery, since those with metastatic disease can be excluded and those with enlarged benign nodes can proceed to operation. Mediastinoscopy can thus improve the survival figures of surgical patients, although in the UK it is not universal practice among thoracic surgeons to sample the mediastinum preoperatively [78,101]. Mediastinoscopy cannot increase the number of patients cured by surgery but can prevent some futile operations being performed on some patients.

For anatomical reasons it is not possible for the surgeon to sample the whole of the mediastinum at medi-

astinoscopy and false-negative rates of around 10% are recorded [100]. Complications are not usually significant and mortality is rare. Some surgeons prefer to perform an anterior mediastinotomy if access is required to sample nodes draining into the left upper lobe or the anterior segment of the right upper lobe. It is also possible to sample periaortic and subaortic glands by this route.

### Assessment of distal spread

Spread of bronchial carcinoma to a site outside the thorax, such as the brain, liver or skeleton, clearly makes a patient inoperable. Patients who have abnormal biochemical tests or specific symptoms that may point to evidence of distant spread should have further evaluation.

### Liver metastases

The finding of an obviously enlarged, hard and irregular liver on physical examination is strong evidence of hepatic metastases. However, this is unusual at presentation, as is jaundice. Liver function tests should be requested routinely on all patients requiring staging of lung cancer. Although normal values do not exclude hepatic spread and elevated values may be due to non-metastatic liver disease, further investigations are required if the patient's management is likely to be affected as a result. Liver ultrasound and CT have a similar degree of accuracy in the detection of hepatic metastasis [102]. In the UK, it has become routine practice for radiologists to include the liver (and adrenal glands) when asked to perform CT of the thorax to assess operability. Occasionally, if there is doubt about the presence of hepatic involvement, histological clarification may be obtained by fine-needle aspiration or liver biopsy, either of which can be performed under ultrasound or CT guidance.

### Bone metastases

The skeleton is a common metastatic site for bronchial carcinoma. Usually these metastases are symptomatic, and pain suggestive of a bony metastasis should lead to radiographs of the affected area. Lytic lesions are usually seen on these films. Isotope bone scanning is much more sensitive than conventional radiography in the detection of bony metastasis, false-negative rates being less than 2% (Fig. 41.17). The main disadvantage of bone scanning is its lack of specificity. False-positive rates of 40–50% have been reported, the increased uptake presumably being due to benign metabolic bone disease [103,104]. It is known that patients who are asymptomatic and have no biochemical abnormalities have a truly negative bone scan in more than 95% of cases [105]. It seems clear therefore that there is no place for routine bone scanning in all patients pre-operatively and that this investigation should be reserved



**Fig. 41.17** Bone scan showing multiple spinal, shoulder girdle and rib metastatic deposits.

for those in whom there is clinical or biochemical evidence to suggest skeletal spread. As with liver metastases, occasionally it may be necessary to obtain further information with local biopsy.

Patients with small-cell carcinoma have a much higher incidence of bony metastases and in this situation scans may be useful to document both the extent of disease and its response to chemotherapy [106].

### Brain metastases

Intracranial spread may come to light as a result of headache, vomiting, personality change or fits, or because of the development of focal neurological deficit. Occasionally, intracranial metastases present at a stage when the lung primary is neither symptomatic nor even radiologically apparent, the diagnosis being made retrospectively after craniotomy. When cerebral metastases are suspected as a result of these clinical features, the investigation of choice is CT with contrast enhancement. Routine CT of the brain in asymptomatic patients gives a very low yield (approximately 2%) [107] and is not indicated as a screening procedure.

The likelihood of detectable intracranial metastases being present at the time of diagnosis varies according to cell type, being most common in patients with small-cell carcinoma. In one necropsy study, the frequency of cerebral metastases varied from 14% in squamous cell tumours to 31% in small-cell lesions [108]. The clinician therefore may have a much lower threshold for requesting this investigation in patients with small-cell lesions.

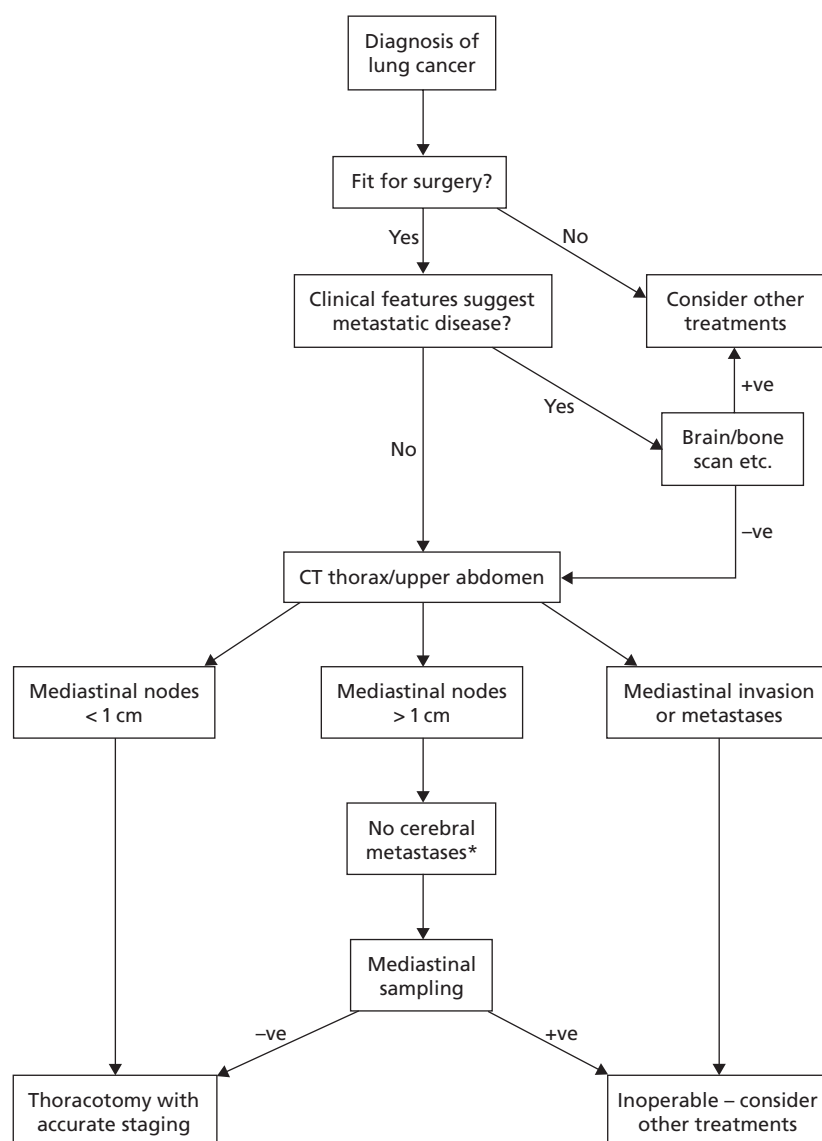
### A routine preoperative management plan

The assessment of suitability for resection is an important part of the management of lung cancer patients, as this form of treatment offers the best chance of significant prolongation of survival. The various steps in this management process are illustrated in Fig. 41.18. Patients should have a definite diagnosis, with histological subtype if possible, prior to evaluation. Those with small-cell lesions are usually more suitable for systemic treatment with chemotherapy (see below). The place of surgery in patients with small-cell lesions is controversial and clinicians considering this form of treatment in these patients should conduct a comprehensive search for metastatic disease.

Patients thought to be fit for surgery, with no symptoms or signs to suggest metastatic disease, should undergo CT

of their thorax and upper abdomen. Those patients without significant mediastinal node enlargement (<1 cm) should proceed directly to thoracotomy. Those with mediastinal invasion or metastases are inoperable and should be assessed for other forms of therapy. Patients with enlarged lymph nodes should have mediastinal sampling at mediastinoscopy. Positive nodes at this stage make the patient inoperable. Patients with a negative mediastinoscopy should proceed to thoracotomy.

A more vexed question is the role of CT of the brain and bone in otherwise operable patients. Hillers and colleagues [109] performed a meta-analysis in order to determine the proportion of patients with potentially operable non-small-cell lung cancer who could have been spared thoracotomy by these investigations. They concluded that fewer than 5% of patients thought operable on previous CT of the thorax had evidence of distant metastases on



**Fig. 41.18** Management of a potentially operable patient (see text on cerebral metastases).

scans. However, the likelihood of metastatic disease increases if the mediastinum has been found to be abnormal preoperatively. For instance in one study [107], 4% of patients with normal CT of the thorax had occult metastases compared with 32% who had an abnormal mediastinum on CT.

Muers, in his excellent reviews of the situation [110,111], concluded that patients with a normal mediastinum should not undergo routine brain and bone scanning as 95% of them are normal. Patients with enlarged mediastinal nodes should be investigated. They should have a bone scan if they have suggestive symptoms or biochemical abnormalities and he also recommends that they should have CT of the brain. Clearly the decision is between mediastinal sampling or scanning of distant organs. The latter is certainly cheaper and can be done on an outpatient basis. There is a clear need for large multi-centre trials to try to clarify this situation.

## Staging

The clinical staging of lung cancer is an attempt to define the anatomical extent of the tumour. Staging has been used primarily as a means of allowing management decisions to be based on published data relating to survival of clearly defined groups or 'stages'. Separate systems have evolved for non-small-cell and small-cell tumours.

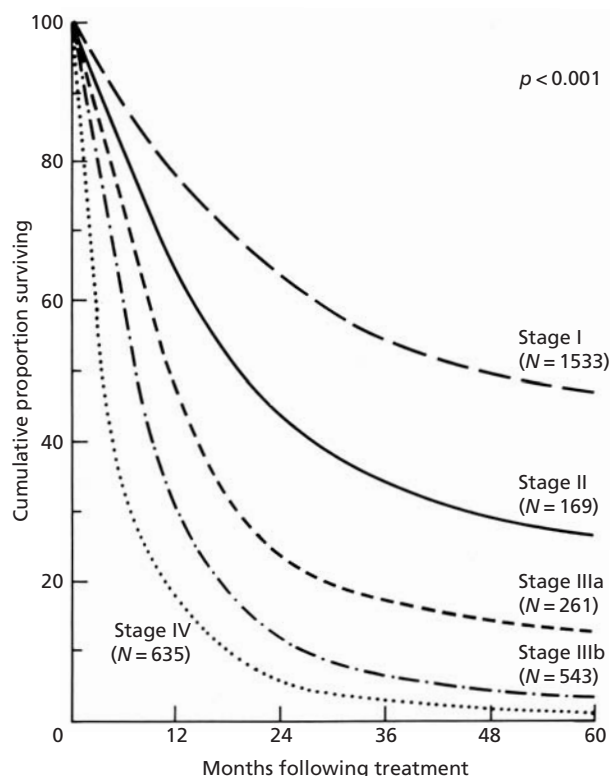
### Non-small-cell lung cancer

Patients with non-small-cell lung cancer are staged by the application of a process using 'T' for primary tumour, 'N' for regional lymph nodes and 'M' for distant metastases. Each letter is qualified by numerical suffixes that describe the size or local extent of the tumour, the extent of regional lymph node spread if present, and the presence or absence of distant extrathoracic metastases. The use of such a TNM system in non-small-cell lung cancer has shown that the stage of the tumour clearly influences prognosis [112]. The TNM staging classification currently in use was upgraded in 1997 and is presented in Table 41.6 [113]. The various TNM classifications have been divided into stages I–IV. Stage III is split into stage IIIA, which accommodates the potentially operable T3 and N2 patients, and stage IIIB, which contains inoperable patients whose disease may be controlled locally by thoracic radiotherapy. Stage I and II tumours are clearly operable, while patients in stage IV have distant metastases. It can be seen from Fig. 41.19 that this staging classification clearly separates the different prognostic groups and allows accurate prediction of survival at the time of diagnosis. The clinical methods used for establishing the stage of lung cancer have been described above. Providing that staging has been thorough, the number of patients found at thoracotomy to be

**Table 41.6** TNM definitions in the international staging system for lung cancer. (From Mountain [113].)

Extent of primary tumour (T)				
T0	No primary tumour detected.			
Tis	Carcinoma <i>in situ</i> .			
TX	Primary cannot be assessed / positive cytology only.			
T1	A tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, not in main bronchus.			
T2	A tumour more than 3 cm in size, or in main bronchus more than 2 cm from main carina, or invading visceral pleura, or associated with partial atelectasis (not entire lung).			
T3	Involves any of following: chest wall (including superior sulcus), diaphragm, parietal pericardium, mediastinal pleura. In main bronchus less than 2 cm from main carina (but not involving it), atelectasis of entire lung.			
T4	Invasion of mediastinum, heart / great vessels, trachea, carina, oesophagus, vertebral body. Separate nodules in same lobe as primary, malignant pleural or pericardial effusion.			
Condition of regional lymph nodes (N)				
NX	Regional lymph nodes cannot be assessed.			
N0	No regional lymph node metastases.			
N1	Ipsilateral peribronchial or hilar nodes involved.			
N2	Ipsilateral mediastinal or subcarinal nodes involved.			
N3	Contralateral hilar or mediastinal nodes involved, or any scalene / supraclavicular nodes involved.			
Presence or absence of distant metastases (M)				
MX	Distant metastases cannot be assessed.			
M0	No distant metastases.			
M1	Distant metastases, includes separate nodule in different lobe.			
Stage groupings (5-year survival rates in parentheses)				
Stage 0	Tis	N0	M0	(?)
Stage IA	T1	N0	M0	(60%)
Stage IB	T2	N0	M0	(38%)
Stage IIA	T1	N1	M0	(34%)
Stage IIIB	T2	N1	M0	(24%)
	T3	N0	M0	(22%)
Stage IIIA	T1	N2	M0	(13%)
	T2	N2	M0	(13%)
	T3	N1–2	M0	(9%)
Stage IIIB	T4	N0–2	M0	(7%)
	T1–4	N3	M0	(3%)
Stage IV	Any T	Any N	M1	(1%)

inoperable should not exceed 5%. A few are found to have N2 disease when macroscopically involved mediastinal nodes are beyond the reach of the mediastinoscope. Such patients may still undergo surgery but have a 5-year survival of around 10% [113]. Although it is not widespread practice, it is recommended that surgeons should methodically sample and separately submit lymph nodes from differently numbered mediastinal gland groups and



**Fig. 41.19** Cumulative proportions of patients with lung carcinoma surviving 5 years, by clinical stage of disease. (From Mountain [113] with permission.)

from the hilum in order to allow pathological staging following thoracotomy. In general, pathological staging (pTNM) tends to downgrade the preoperative stage by finding previously undetected disease, and it is not surprising therefore that the median survival of pTNM subsets is much better than that of equivalent TNM stages based on clinical investigations [113].

### Small-cell lung cancer

Small-cell lung cancers grow more aggressively and often metastasize earlier from a much smaller primary than other cell types; because of this, the TNM system of staging is irrelevant for small-cell tumours. Clinicians have adopted a simple staging system using the terms 'limited' and 'extensive' disease. Limited disease refers to a group of approximately 30% of patients who at presentation appear to have disease confined to the ipsilateral hemithorax (lung, pleura, and hilar, mediastinal and supraclavicular lymph nodes). Extensive disease refers to spread beyond these confines.

Since the majority of patients with small-cell tumours have inoperable disease at presentation, systemic therapy with drugs, to which the tumour is initially fairly sensitive, has become the mainstay of treatment. However,

there is a small subgroup of patients who do present with operable disease and they should be considered for operation in the standard way using routine staging procedures. It would seem reasonable to perform fairly intensive investigations for metastases in this group of patients, including CT of the thorax, upper abdomen and brain, as well as bilateral iliac crest marrow aspiration since bone marrow deposits are common in small-cell lung cancer. However, the natural history of small-cell lung cancer means that prolonged investigation delaying treatment may leave some patients unfit for active intervention.

In the same way as the TNM staging system gives a useful prognostic guide in non-small-cell lung cancer, disease extent (limited or extensive) is also a useful prognostic aid. Other factors influencing prognosis are a measure of the patient's ability to function (performance status) and a few simple biochemical investigations (serum sodium, and a measure of liver function such as lactate dehydrogenase or alkaline phosphatase). It can be seen therefore that in a patient with known small-cell lung cancer, taking a history, performing a clinical examination and arranging a simple blood test and chest radiograph are all that is required to give a fairly accurate guide to prognosis [114].

### Treatment

When discussing the current treatments available for patients with lung cancer it is relevant to divide the subject into the management of non-small-cell and small-cell types. As stated above, these two groups of patients have different prognoses and their tumours respond differently to the currently available therapies. The majority of patients have non-small-cell tumours and the treatment modality that gives the best result is still surgery. However, most patients are inoperable and palliation is the aim of any treatment offered. In this respect radiotherapy is very helpful; indeed, some patients who are not suitable for surgery may be treated with radical radiation therapy. The role of chemotherapy in non-small-cell lung cancer is controversial but is gaining acceptance, especially in North America.

Chemotherapy gives the best hope of prolonged survival and improved quality of life in patients with small-cell lesions. The tumour is radiosensitive, although the exact place of radiotherapy is not clear. There is a small subgroup of patients who are operable and their survival is as good as that seen with the best chemotherapy results. However, long-term survival in patients with this tumour is rare.

The place of different treatment modalities in the overall management of patients with lung cancer is outlined in Fig. 41.9. For the majority of patients, an attempt at curative therapy is not possible and efforts should be



directed towards palliation of the patient's symptoms. Quality of life is a term that is seen more commonly in studies of the treatment of lung cancer and is something that clinicians are now attempting to measure and to influence.

### **Non-small-cell lung cancer**

The prognosis for patients diagnosed with non-small-cell lung cancer is poor, most large series of unselected patients giving an overall 5-year survival of less than 10% irrespective of treatment [115]. This figure has not changed over the last 30 years [116] and the best results are in patients treated with surgery.

### **Surgery**

Although surgery is effective treatment for bronchial carcinoma, unfortunately the disease is only operable in a small minority of patients. Upwards of two-thirds of patients are inoperable at the time of presentation because of advanced age, poor respiratory function, other significant medical conditions or clinical evidence of tumour spread (see above). Of the remainder who are considered for surgery, 10–15% are rejected because of mediastinal involvement discovered at mediastinoscopy. Approximately 20–25% undergo surgery and up to 5% are found inoperable at thoracotomy. This means that only about 12–15% of all patients with non-small-cell tumours have a chance of receiving a potentially curable operation.

### **Types of operations**

Pneumonectomy involves ligation of the pulmonary veins, division of the pulmonary artery and suturing or stapling of the bronchial stump at the level of the carina. At lobectomy, corresponding vessels may be ligated at segmental level. Hilar and accessible mediastinal nodes should be removed at operation and labelled according to their site of origin in order to enable more accurate pathological staging. Serosanguineous fluid is allowed to accumulate in the empty haemothorax of patients undergoing pneumonectomy and this tends to stabilize the mediastinum. Following lobectomy, underwater seal drainage is mandatory to prevent the accumulation of fluid and to allow full expansion of the remaining lobe or lobes. As an alternative to pneumonectomy, a variety of bronchoplastic procedures have been devised to remove tumour and yet conserve part of the lung subtended by the involved bronchus. The most common of these procedures is 'sleeve resection' of a tumour, extending from the right upper lobe bronchus into the right main and intermediate bronchi. Anatomical considerations make such procedures less common on the left side. When sleeve resections are carried out, facilities for frozen section are required at

operation to ensure that both ends of the sleeve are clear of tumour.

When a peripheral pulmonary opacity is found at thoracotomy to be small and confined to a bronchopulmonary segment, the more limited procedure of segmental resection may be carried out, and it may be possible to perform this operation using a thoracoscope [117]. This procedure, which permits 'keyhole surgery' in the chest, allows much quicker rehabilitation postoperatively and a much shorter perioperative period in hospital. There is no large thoracotomy wound and postoperative pain is less of a problem. Some surgeons are concerned that thoracoscopic resections may be incomplete in malignant disease, although modern techniques have allowed for pneumonectomies to be carried out and it is possible to sample nodes in the mediastinum with this instrument [118]. The results of studies of long-term survival of larger series of patients operated on in this way are awaited with interest.

### **Complications**

Apart from the general complications that may beset any major surgical procedure, there are several problems peculiar to pulmonary resective surgery. Lower respiratory tract infection in residual lung tissue is common and requires treatment with appropriate antibiotics and physiotherapy. Postoperative infection of the resected space (empyema) can be a particularly difficult problem especially in an upper lobectomy. One or other of the phrenic nerves occasionally has to be sacrificed in a resection of a central tumour abutting the pericardium. The left recurrent laryngeal nerve may be similarly damaged during a left pneumonectomy.

Operative mortality has fallen over the years and is a reflection of better surgical techniques and the application of more stringent selection criteria. The intraoperative and 30-day postoperative mortality for over 2000 resections in 12 different North American centres carried out between 1979 and 1981 under the auspices of the Lung Cancer Study Group found the overall rate for pneumonectomy to be 6.2%, for lobectomy 2.9% and for segmental and wedge resections 1.4% [119]. Surgery in older patients used to be associated with a high mortality rate but published figures from the last decade have suggested an overall mortality of less than 6% [119,120]. The results of macroscopically complete resection in elderly patients justify active treatment, since the 5-year survival rate is about 35% [120]. It has become increasingly difficult to justify the decision that a patient is unsuitable for surgical resection on the grounds of age alone, provided the same careful staging procedures that are applied to younger patients are followed. It should also be remembered that the life expectancy in a developed country for a patient reaching the age of 70 is in excess of 10 years.

**Results**

Survival after resection for non-small-cell lung cancer is closely related to the stage and pathological type of disease. Stage I tumours (T1/T2N0M0) when treated surgically carry a 5-year survival rate of 40–60% [121,122]. In stage II tumours, the survival rate following operation falls to 20–50% depending on histology [122]. The survival of patients with stage IIIA disease is much poorer after surgery with between only 9 and 13% surviving for 5 years [123]. The overall 5-year survival figures for surgery for non-small-cell lung cancer is 35%. Patients with squamous cell tumours fare better than those with adenocarcinoma at all stages. Mountain [123] reported 4-year postoperative survival for stage IIB (T2N1) patients to be 53% for squamous carcinoma and 25% for adenocarcinoma, and for (T3N0) 37% and 21% respectively.

It is depressing that the vast majority of patients who die after resection do so from recurrent disease. The pattern of recurrence in surgically treated stage I and II disease was analysed by the Lung Cancer Study Group in a retrospective review of 771 patients [124]; 70% occurred initially outside the chest, presumably from occult distant metastases present at the time of surgical resection of the primary tumour.

**Radiotherapy**

Radiotherapy is most commonly used to achieve symptomatic relief when given in low palliative doses to patients who are clearly inoperable and have appropriate symptoms due to their disease. Radical radiotherapy may offer the chance of cure in a small proportion of patients with non-small-cell lung cancer who are considered unsuitable for surgery on medical grounds but otherwise have 'operable' disease. Treatments are usually administered by means of a megavoltage linear accelerator, with some centres still using a cobalt-60 source for palliative treatments. The collimated beams of ionizing radiation are positioned to produce a tumoricidal dose in an area where the beams cross, with as much sparing of normal tissue as possible. Tissue absorption of radiation is measured in grays (Gy), 1 Gy being equivalent to 1 J of energy absorbed per kilogram of tissue; the relationship between the SI unit (Gy) and the old unit (rad) is shown in Table 41.7. Radiotherapy is the most frequently employed treatment in

patients with non-small-cell carcinoma of the bronchus [78].

**Radical radiotherapy**

This term implies an intention on the part of the radiotherapist to employ a relatively large dose of treatment in order to increase the patient's survival time or even to achieve a cure. Patients with stage I and II non-small-cell lung cancer are best treated by surgical resection; however, if this form of treatment cannot be followed, either because an operation has been declined or because of some medical contraindication, then radiotherapy does offer a small chance of cure. It should be recommended provided that the patient's general condition is good and that he or she has sufficient ventilatory capacity to survive the loss of functioning lung tissue that results from radiation damage to normal lung. Trials comparing radical radiotherapy with surgery in otherwise operable patients were performed more than 30 years ago. Initial results suggested that radical radiotherapy was the more effective treatment [125], although subsequent studies have not supported this and the place of surgery in these treatments is well established [126]. Patients who have stage IIIB (inoperable) disease have a much poorer outlook but may benefit from radical radiotherapy provided that their disease is limited to one hemithorax and can thus be encompassed by the radiotherapy field. This type of treatment is prolonged and requires the patient's performance status to be good; it is these fitter patients who seem to benefit most from this form of treatment.

A variety of techniques are employed in the delivery of radical radiotherapy, making comparison between reported studies difficult. The identification of those areas to be treated is determined from conventional chest radiographs and bronchoscopic findings. CT of the chest gives a much more precise location of the tumour, especially in the anteroposterior plane where lateral films may be difficult to interpret [127]. It is routine practice for the treatment field to include the primary tumour mass, ipsilateral and contralateral hilar lymph nodes and the mediastinum. Ipsilateral supraclavicular nodes may also be included and this is always the case in upper lobe tumours [128]. A dose-metric compromise has to be reached between delivery of a tumoricidal dose to this large area and the avoidance of injury to normal tissues, including the spinal cord, larynx and oesophagus.

In addition to planning the treatment field, the further important variables that have to be determined are the total dose of radiation, the number of fractions in which it is given and the duration of the course. In general, doses of 50–60 Gy over a period of 4–6 weeks are used. Trials from various centres using different scheduling techniques have demonstrated that survival is related to the dose of

**Table 41.7** Units of absorbed radiation.

1 joule/kg	=	1 gray (Gy)
1 Gy	=	100 rad (old units)
1 cGy (centigray)	=	1 rad

radiotherapy given. It has also been shown that small numbers of large fractions are less effective in controlling local tumour in the chest than large numbers of small fractions, even though the total dose remains the same [128]. Some workers have preferred split-course therapy, in which the same total dose is given in two half-dose courses with a 'rest period' of about 4 weeks between them, and have claimed similar results to continuous treatment [129]. Split-course treatment carries the added advantages of initial palliation due to tumour shrinkage with mild side-effects and a chance for further assessment of extrathoracic spread before the second course of treatment. This may allow the avoidance of unnecessary radical irradiation in patients with rapidly progressive disease. The argument against this form of therapy is that the design of treatment does not allow for initial local control, which could therefore deny an otherwise curable patient long survival.

The survival results of radical radiotherapy in inoperable patients are generally disappointing. Many authors report good 1-year survival figures (30–60%) but 5-year survival rarely exceeds 20% [129–131]. The subset of patients with stage I disease have a better outcome, some authors reporting up to 40% survival at 5 years [132,133]. Several factors make the results of radical radiotherapy difficult to evaluate. Firstly, the populations studied are not homogeneous as different cell types are usually lumped together as non-small-cell tumours. Also staging procedures differ within studies and by definition only inoperable patients are included. Patient survival time often reflects the spread of tumour beyond the radiotherapy field prior to treatment and need not indicate the success or failure of the local treatment. Lastly, radiotherapy itself may cause radiographic changes in normal lung that make the detection of local recurrence difficult to monitor. Despite this, the similarity of survival figures reported from various studies is striking and perhaps the most useful benchmark in a form of treatment where prolonged survival is the aim.

An interesting recent development in the scheduling of radical radiotherapy has taken into account evidence from cell kinetic studies that tumours may repopulate in the standard intervals between treatments. A regimen of continuous hyperfractionated accelerated radiotherapy (CHART) has been developed where treatment is given three times daily at intervals of 6 h for 12 consecutive days, including the weekend [134]. Although initial reports suggest that this may be a toxic regimen [135], the schedule has been modified and initial survival and local control results have been impressive [136]. CHART treatment was compared with conventional radical radiotherapy (60 Gy in 30 fractions over 6 weeks) in a randomized trial in patients with locally advanced non-small-cell lung cancer [137]. In the CHART group, there was a significant

improvement in survival at 2 years (29% vs. 20%), especially in patients with squamous histology (33% vs. 19%). However more severe dysphagia (19% vs. 3%) was seen in the first 3 months with this treatment.

*Palliative treatment*

The majority of patients with non-small-cell lung cancer who have extrathoracic metastases die within 6 months of diagnosis, and when radiotherapy is used in these patients its only aim is to relieve distressing symptoms (Table 41.8). Since this may be achieved by restraining tumour growth rather than by attempting to eradicate it totally, lower doses of radiation are generally used. Many fractionation schemes are practised throughout the UK [138], usually with a total dose of 20–30 Gy given in up to 10 fractions. Randomized controlled trials carried out by the Medical Research Council (MRC) have shown that, for fit patients, two treatments of 8.5 Gy 7 days apart are of equal efficacy to 10 daily treatments of 3 Gy [139]. In patients with poor performance status, a similar study showed that one treatment of 10 Gy is as effective as two treatments of 8.5 Gy in palliating symptoms [140].

Treatable symptoms due to intrathoracic disease, including haemoptysis, may be relieved in over 80% of cases [139], distressing cough in about 60% [139,141] and breathlessness due to bronchial obstruction in 60% [139]. However, areas of atelectasis are not re-expanded in more than one-quarter of patients [128], and dyspnoea due to lymphangitis carcinomatosa is also unrelieved. Well-localized pain due to chest wall or rib involvement responds in over 70% of patients [139,141], although more diffuse chest discomfort is often not responsive. Obstruction of the SVC is reported to be relieved in 60–86% of cases [142] and dysphagia due to oesophageal compression by nodes responds in a similar proportion of patients.

Brain metastases are nearly always multiple, and symptomatic relief may be achieved in a significant group of patients by total brain irradiation using a 30-Gy dose given as 10 fractions over 2 weeks [143]. However, improvements may be small and dense neurological deficit rarely responds. The median survival time for untreated patients with cerebral metastases is about 3 months and therefore the fractionation scheme should be

**Table 41.8** Palliative radiotherapy for distressing symptoms.

Haemoptysis
Pain: bony, chest wall, nerve root
Cough
Dyspnoea due to large bronchus obstruction
Mediastinal compression: obstruction of superior vena cava
Symptoms due to intracranial metastases
Symptoms due to spinal cord compression

as short as possible. The Royal College of Radiologists in a randomized controlled trial of patients with cerebral metastases due to various primaries showed that 12Gy in two fractions was as useful as 30Gy in 10 fractions. Median survival was 7 days longer in the second group (84 vs. 77 days), who required 8 days more treatment [144]. Dexamethasone, given initially in a dose of 16mg daily, may also produce temporary relief by reducing intracranial pressure. Spinal cord compression due to tumour is a particularly distressing complication. Prompt treatment is required to prevent permanent neurological damage, which at worst may result in paraplegia with a sensory deficit and loss of sphincter control. In this emergency situation corticosteroids should be given and, if neurosurgery is not advised, urgent palliative radiotherapy is indicated. There is still debate about the optimal treatment schedule [145]. The spinal level involved may be indicated by clinical features and confirmed more precisely by plain radiography, CT and MRI.

Other extrathoracic metastatic disease that responds to palliative radiotherapy includes bony deposits, in which pain may be relieved in the vast majority of cases, and cervical lymph node enlargement. Radiotherapy is of no value in relieving systemic symptoms, such as malaise, anorexia or weight loss, nor can it reverse a recurrent laryngeal or other frank nerve palsy. The response of the paraneoplastic syndromes (see below) to radiotherapy is variable and unpredictable.

### *Side-effects*

Side-effects tend to be dose-related and are therefore much more common in patients undergoing radical treatment. Since the aim of palliative radiotherapy is to relieve the patient's symptoms, any side-effects should be kept to a minimum. Cutaneous erythema is seen with large doses of radiotherapy but is not a serious problem. There may also be a general feeling of weakness and malaise. The patient should be warned to expect dysphagia, which is due to oesophagitis. This occurs after about 2 weeks of treatment and usually subsides spontaneously or with local anaesthetic preparations.

Radiation pneumonitis may occur following radical radiotherapy, the radiographic changes becoming evident 2–6 months after the completion of treatment. The changes are seen as a non-specific hazy infiltrate initially caused by inflammation but later as a result of fibrosis. The margin of the radiographic abnormality may be characteristically straight, matching the shielding around the radiotherapy portal. In the majority these changes are unaccompanied by symptoms, although 5–15% of patients may notice the insidious onset of breathlessness and a dry cough. The symptoms may respond to steroids but may be long-standing where progression to fibrosis occurs [146]. Radiation myelitis, potentially a most serious side-effect, may be

transient and self-limiting, in which case pain and paraesthesia occur about 3 months after radiotherapy only to disappear gradually over the space of a few weeks or months. These symptoms result from spinal cord vascular damage and demyelination. Fortunately, progression to complete paraplegia with loss of sphincter control is extremely unusual. It is estimated to occur in 1–5% of patients after a spinal cord dose of 50Gy in 25 fractions over 5 weeks [147]. The risk is increased in shorter courses with higher dose fractions. Clearly it is important to exclude cord compression from recurrent tumour before making this diagnosis. Radiation pericarditis may occur 3–6 months after radiotherapy in about 4% of patients and is associated with sternal discomfort, breathlessness and ECG changes [148]. The condition is self-limiting and treatment is symptomatic.

### *Endobronchial treatments*

Endobronchial techniques have evolved in the last two decades to help palliate symptoms such as haemoptysis and critical obstructions of main airways [149]. Most experience has been gained with laser therapy. A laser is an electrical device for producing an extremely powerful and narrow beam of light. Various types of laser are available and that most widely used in respiratory work is the Nd-Yag laser. The beam is transmitted endoscopically using fibreoptic techniques. The fibre can be passed down the suction channel of the fibreoptic bronchoscope and the beam is directed against tissue. Its energy evaporates moisture and coagulates blood in vessels to a depth of about 5mm. At present laser therapy remains a palliative treatment, as most tumour is beyond bronchoscopic view and therefore beyond the reach of the laser. Its use is confined to symptomatic relief by debulking proximal endobronchial or tracheal tumour in the treatment of dyspnoea and the coagulation of vessels in order to relieve haemoptysis. However, results from laser therapy do not add much to standard palliative radiotherapy.

Modern endobronchial radiotherapy techniques deliver high-dose irradiation to the tumour via a catheter positioned next to the tumour at bronchoscopy. Treatment takes about 10–15min and can relieve the symptoms of bronchial obstruction caused by tumour or of extraluminal pressure caused by nodes. Unfortunately, secondary haemorrhage appears to be an important complication of the procedure and studies comparing endobronchial radiotherapy with standard techniques have not yet been published.

Photodynamic therapy involves the intravenous administration of a light-sensitive drug (a haematoporphyrin derivative) that has an affinity for malignant tissue and is activated by laser light delivered at bronchoscopy. This produces necrosis of tumours in animals but its use in patients is not yet established. Another problem with

these new techniques is that they are only available in a few centres in most countries.

### Chemotherapy

The main limitation to the effectiveness of surgery and radiotherapy in patients with non-small-cell lung cancer is that evidence of metastatic spread at presentation may prevent treatment or that treatment may fail because of recurrent disease commonly occurring at distant sites. There is a clear need for 'systemic' treatment for the vast majority of patients and this has inevitably led to trials of cytotoxic drugs. Unfortunately, while chemotherapy is the mainstay of treatment of small-cell carcinoma of the lung, non-small-cell tumours are relatively resistant to the drugs currently available. Single-agent drugs have modest activity in terms of objective response rates (Table 41.9). Some authors have claimed prolonged survival for patients who respond compared with 'non-responders'. However, for such an approach to be valid, both groups must have the same prognosis with no treatment and this often cannot be assumed. Moreover, these drugs, either singly or in combination, are capable of considerable toxicity and the price paid in terms of quality of life for modest survival benefit has rarely been measured. Trials comparing chemotherapy with a control group of best supportive care have only recently appeared. Most have shown a modest survival advantage to chemotherapy treatment, although no study has accurately measured quality of life and therefore the effect of treatment on palliation of symptoms is not yet available. In a major meta-analysis published in 1995 [150], the Non-Small Cell Lung Cancer Collaborative Group analysed data published from 11 trials involving 1190 patients. Despite considerable statistical heterogeneity, the results suggested that the use of alkylating agents was detrimental to survival compared with best supportive care but that cisplatin-based regimens conferred benefits. A reduction in the risk of death of 27% was seen, equivalent to an absolute improvement in survival of 10% at 1 year. Although this may sound impressive, the overall increase in median survival was only 6 weeks. No measurements of the toxicity of the treat-

ment were performed. Many enthusiasts are keen to extrapolate these findings to the millions of people worldwide who have this disease [151] while others, worried about toxicity with such little benefit, sound a note of caution [152]. Well-designed clinical studies examining the place of chemotherapy in the management of non-small-cell lung cancer are required. It may well be that chemotherapy has a place in a multimodality approach to the disease and future studies should consider this role for chemotherapy.

### Combined modality treatment

#### *Surgery and radiotherapy*

The combination of radiotherapy and surgery was first reported in the early 1950s for tumours that were originally believed to be inoperable but which were subsequently resected after initial radiotherapy and tumour shrinkage [153]. However, no clear survival advantage has ever been shown for this scheduling of radiotherapy and surgery [154], and the concept of preoperative radiotherapy has largely been abandoned. The exception to this is with superior sulcus tumours (see below).

Compared with surgery alone, the use of *postoperative* radiotherapy for patients with N1 and N2 disease has been demonstrated to improve local control within the chest [155], and one study [156] has also shown a statistically significant survival benefit. However the exact effect of postoperative radiotherapy on survival has been questioned by a meta-analysis of nine trials showing worse survival in irradiated patients in the first 3 months [157]. This difference may be related to radiotherapy techniques (cobalt source vs. linear accelerator). It is common practice for thoracic surgeons to refer patients for postoperative radiotherapy when they know they have left disease in the chest postoperatively. These patients do particularly badly, and radiotherapy does not improve their survival.

#### *Surgery and chemotherapy*

A retrospective review performed by the Lung Cancer Study Group of the pattern of recurrences in 771 patients undergoing surgery showed that 70% initially recurred outside the chest, presumably from occult distant metastases present at the time of surgical resection of the primary tumour [124]. This has led to interest in combining good local control (surgical resection) with systemic treatment (chemotherapy) [158]. In the past chemotherapy was given postoperatively (adjuvant therapy). More recently, encouraging results have been obtained from the use of chemotherapy given before the operation (neoadjuvant) [159].

The meta-analysis conducted by the Non-Small Cell

**Table 41.9** Activity of single-agent drugs in non-small-cell lung cancer.

Drug	Response rate (%)
Ifosfamide	26
Cisplatin	21
Mitomycin	20
Vindesine	18
Doxorubicin	13
Carboplatin	11
Etoposide	9

Lung Cancer Collaborative Group [150] examined 14 trials involving a total of 4357 patients that compared surgery alone with surgery plus postoperative chemotherapy. The results are very similar to those quoted above for surgery and radiotherapy. The earlier trials that used alkylating agents showed better survival in the patients treated with surgery alone, i.e. the use of this kind of postoperative chemotherapy was actually hazardous to the patient. However, for regimens containing cisplatin there was a survival advantage for postoperative treatment. This amounted to a 13% reduction in the risk of death, with an absolute benefit from chemotherapy of 3% at 2 years and 5% at 5 years. These results are encouraging, although postoperative chemotherapy is not routine practice at present and further good clinical trials are required to confirm the suggestion of any such benefit.

The results of surgical treatment on stage IIIA patients are disappointing, with 5-year survival usually less than 30%. A number of reports have described the use of chemotherapy given prior to surgery [160,161]. Most have shown a good response to therapy and some increased resectability. In 1994 the first two randomized studies comparing neoadjuvant chemotherapy plus surgery with surgery alone appeared [162,163]. Both were small studies but appeared to show a significant benefit for neoadjuvant treatment. Roth and colleagues [162] entered 60 patients thought to have resectable stage IIIA disease; 28 patients were randomized to receive preoperative chemotherapy with cyclophosphamide, etoposide and cisplatin every 4 weeks for a total of three cycles. Patients who responded to chemotherapy were given three cycles after surgery. The objective response rate to chemotherapy was 35% including one complete response. Only 15% progressed while receiving chemotherapy. The resectability rate did not differ significantly between the two groups. Only 39% of patients in the chemotherapy group and 31% in the surgery alone group achieved complete resection. The estimated median survival in the chemotherapy group was 64 months compared with 11 months for surgery alone. In a similar study from Spain [163], 30 patients at a similar stage received mitomycin, ifosfamide and cisplatin prior to surgery. An identical number had an operation alone. Both groups received mediastinal radiotherapy following surgery. A higher proportion of patients had a complete resection compared with the first study. Median overall survival in patients receiving surgery and radiotherapy alone was 8 months compared with 26 months for the group receiving chemotherapy in addition. This trial has provoked a lot of comment. Patients in the control group did very poorly, none of the 30 patients surviving more than 20 months. The trials are small and larger studies are required to see whether this is an appropriate use of chemotherapy in this disease. Two interesting points arise: firstly, patients did not become inoperable while receiving chemotherapy for a number of weeks

prior to surgery and, secondly, the Spanish group identified the *K-ras* oncogene as a significant prognostic indicator in resected specimens. It is possible that in the future the use of this marker may be helpful in identifying which patients require adjuvant therapy [164].

### *Radiotherapy and chemotherapy*

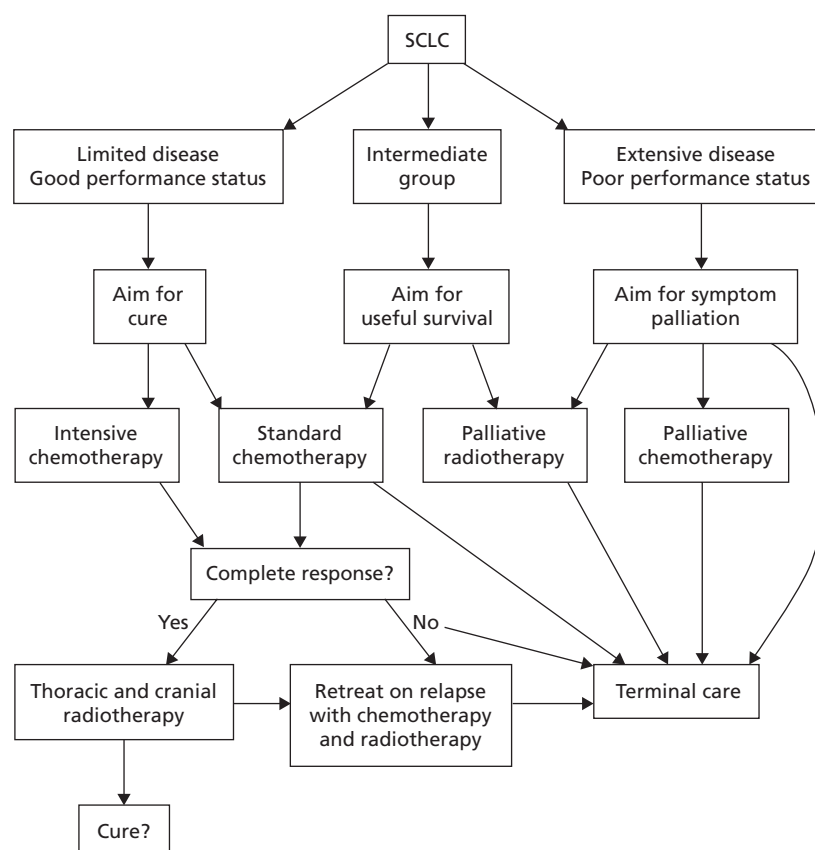
The aim of combined chemotherapy and radiotherapy is to optimize local control and to control distant metastases. In general, studies comparing radical radiotherapy alone with radiotherapy and chemotherapy have been performed in inoperable patients who have a poor prognosis. In the 1995 meta-analysis of chemotherapy [150], 22 trials involving 3033 patients were assessed. There was a definite benefit for combined therapy compared with radiation therapy alone. Cisplatin-containing regimens gave an absolute benefit of 4% at 2 years and 2% at 5 years. The optimal sequence of chemotherapy before or during radiotherapy is not known. There is evidence that platinum-based chemotherapy before radiotherapy gives a modest survival advantage, possibly in its role in controlling micrometastases, and that concurrent treatment can improve local control [165]. As with most combinations involving chemotherapy, there would appear to be more unanswered questions than answers and further randomized clinical trials are required [166].

### **Small-cell lung cancer**

Of all patients with bronchial carcinoma, 25% have small-cell tumours. These lesions grow more aggressively and patients usually present with a short history and evidence of metastases. As explained above, the disease is usually staged in terms of limited and extensive groups. Without treatment the median survival for patients with limited disease is 6–8 weeks and patients with extensive disease fare even worse [167]. At presentation more than 70% of patients have extensive disease. An outline for the management of patients with small-cell tumours is illustrated in Fig. 41.20.

### **Chemotherapy**

Unlike non-small-cell lung cancer, small-cell tumours have been found to be more sensitive to chemotherapy and this is now the accepted modality of treatment for most patients with the disease [167,168]. Many drugs have been found to have activity against this tumour, although if used singly their duration of action is brief with minimal impact on long-term survival. Responses in the range of 15–40% are seen with drugs such as cyclophosphamide, doxorubicin, vincristine, cisplatin, ifosfamide and etoposide when given alone, but fewer than 5% of patients gain a complete response [168]. Not surprisingly, when agents



**Fig. 41.20** Management of patients with small-cell carcinoma (SCLC, small-cell lung cancer).

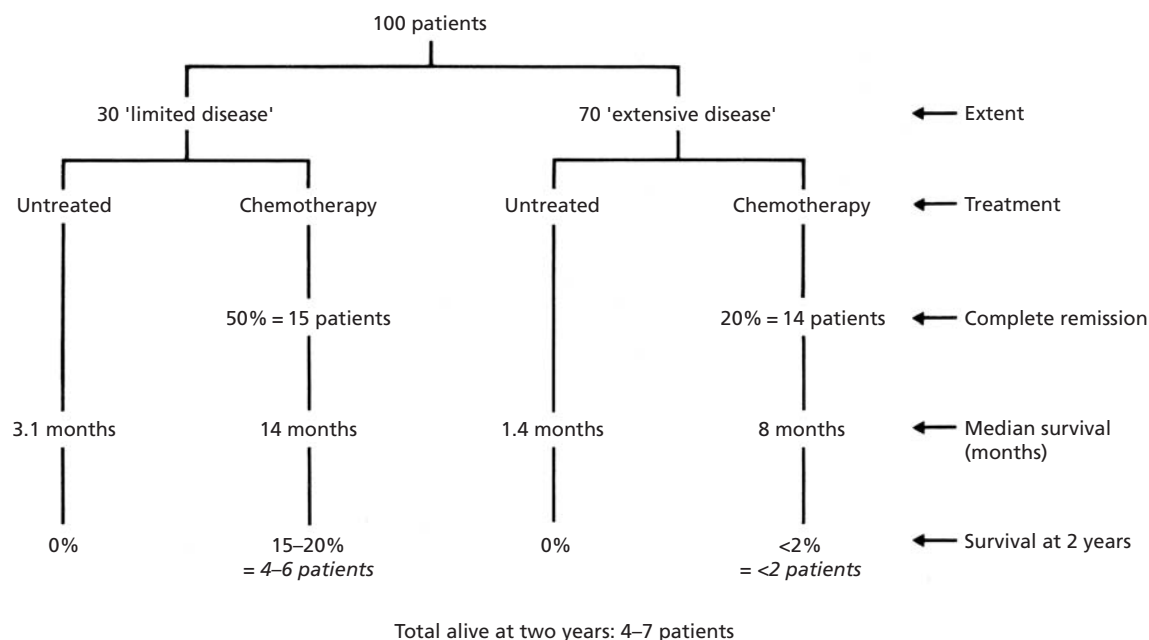
are added together and given as combination treatments the results are more encouraging. In the last two decades combination chemotherapy has improved the prognosis significantly. The median survival time in patients with limited disease is now 14–16 months and in those with extensive disease 8–10 months. The disease may show an objective response (partial and complete) to therapy in up to 90% of patients treated, and those who do respond live longer than those who do not. Drug regimens that have been well used and which have predictable results include cyclophosphamide/doxorubicin/vincristine, doxorubicin/cyclophosphamide/etoposide and cisplatin/etoposide. However, Fig. 41.21 shows the poor survival even in patients who have an apparent complete response to chemotherapy. Of 100 patients with small-cell lung cancer treated with combination chemotherapy, perhaps half a dozen survive for over 2 years, this number representing 15–20% of those with limited disease and less than 2% of those with extensive disease [169].

It is conventional to administer these combination drug regimens to the patient every 3–4 weeks. This can largely be done on an outpatient basis. Treatment with platinum requires careful hydration and antiemetic therapy and should only be given in specialized units. Patients should be assessed for response to treatment after a minimum of two or three cycles unless the disease is obviously

progressive or the patient cannot tolerate the treatment. Oncologists often measure activity of treatment in terms of response rates. An objective response to therapy may be either partial or complete. In a partial response, shrinkage of the tumour by at least 50% in a measurable diameter must have occurred. A partial response is not recorded if tumour at another site is progressing. It is clear that there must be inaccuracies in this form of assessment. Measuring a shadow on a chest film gives definitive data but it is often not known whether the radiographic opacity is due to tumour or perhaps to atelectasis or consolidation behind the tumour. Clearly, opening up a small endobronchial lesion may cause dramatic 'improvement' on a chest film when in fact the response of the tumour may be minimal. Complete responses, seen in approximately half the patients with limited disease and one-quarter of the patients with extensive disease [168], are defined as the total removal of all tumour as evaluated by physical examination, radiography, scanning or bronchoscopy.

Although the early results of drug treatment in small-cell carcinoma were very promising, the survival of patients with 'conventional' treatment has reached a plateau with little change over the last decade [170]. A variety of different therapeutic manoeuvres have been tried in order to improve this situation.





**Fig. 41.21** Probable results in 100 patients with small-cell lung cancer.

### High-dose chemotherapy

It is known that combinations of two and three drugs have much more activity than single-drug therapy in gaining a remission and it is likely therefore that a definite dose–response relationship exists in the treatment of this disease. Several strategies have been tried to increase the initial dose of induction chemotherapy in order to try to prevent later relapses. The main problem with increasing the intensity of drug treatment is that the toxicity experienced by the patient is also increased. In a typical early study of high-dose chemotherapy, fit patients with limited disease were prospectively randomized to either a double dose ( $1.5\text{g}/\text{m}^2$ ) or a standard dose ( $0.75\text{g}/\text{m}^2$ ) of cyclophosphamide in a regimen also containing methotrexate and lomustine at conventional doses. The high-dose group had a significantly increased median survival rate of 56 weeks compared with 42 weeks for standard therapy. This was at the expense of 'a life-threatening complication' rate of 53% compared with 7% and a drug-related death rate of 4% vs. 1% [171]. The toxicity of this treatment is clearly unacceptable for the small benefit in survival.

The principal drug-related toxicity that threatens life is myelosuppression. Two strategies have been developed to try to overcome this problem. Autologous bone marrow transplantation [172] involves taking marrow from a patient prior to chemotherapy, giving high doses of chemotherapy that would normally cause complete marrow failure, and managing this by replacement with

the patient's own harvested bone marrow. High doses of chemotherapy can be given with this technique, although complete eradication of the disease rarely occurs. One potential problem with this method is that malignant cells may be harvested as well as normal marrow cells; thus when marrow cells are reinjected after chemotherapy, the patient also receives untreated cancer cells. Attempts have been made to overcome this by 'cleansing' the bone marrow after harvesting. The other strategy involves the use of haematopoietic growth factors that can stimulate normal haematopoiesis [173]. Granulocyte colony-stimulating factor can be produced by recombinant DNA techniques and allows clinicians to increase the production of bone marrow cells by patients after myelotoxic chemotherapy. The results of randomized studies using this technique to allow higher doses of chemotherapy are awaited.

In intensive regimens it is important to be aware that there may well be a selection bias, with patients whose general condition is poor being excluded as they would be unable to tolerate the rigours of high-dose chemotherapy. Valid comparisons can only be drawn if the performance status, the extent and size of the tumour, and the age of the patient are known.

### Scheduling

Several randomized trials have attempted to determine the minimum number of courses of chemotherapy that can be given without compromising survival, aiming to minimize toxicity and improve the quality of life of the patient. The MRC reported a trial in 265 patients who had responded to induction chemotherapy (six courses of

etoposide, cyclophosphamide, methotrexate and vincristine). Patients were then randomized to receive a further six courses of the same chemotherapy (maintenance chemotherapy) or no further treatment until relapse. No overall survival advantage was seen for maintenance chemotherapy [174]. The same researchers have compared six courses of the same treatment to three courses in a randomized study of 458 patients [175]. There appeared to be a marginal survival advantage for the six-course regimen.

In an interesting study reported by the London Lung Cancer Group [176], 616 patients were randomized to receive either four or eight courses of chemotherapy (etoposide, cyclophosphamide and vincristine) and at relapse to receive either symptomatic treatment or further chemotherapy with new agents (methotrexate and doxorubicin). The results showed that patients receiving only four courses of chemotherapy and then symptomatic treatment at relapse had a much poorer median survival compared with the other three treatment groups (30 weeks vs. 39–42 weeks). There was no advantage to relapse chemotherapy in the group given eight courses initially.

The concept of introducing at relapse further combinations of new drugs to which the residual tumour cells would not be resistant has been tried before. Many studies have compared alternating (crossover) regimens but consistent benefit in terms of increased median survival has not been shown. As with high-dose induction chemotherapy, this strategy has largely been abandoned. In summary therefore it seems that patients given chemotherapy for small-cell lung cancer should receive, if possible, no less than four but no more than six courses of induction therapy. Maintenance chemotherapy is of no value but retreatment on relapse is worth while.

### Complications

The main agents currently used in combination chemotherapy for small-cell lung cancer may produce significant toxicity. Myelosuppression may lead to bleeding problems and infections. Febrile episodes in neutropenic patients are associated with infection in about 60% of cases [177,178] and require immediate broad-spectrum antibiotic treatment. Likely pathogens include *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. Although treatment may be modified in the light of subsequent microbiological culture, it is inadvisable to withhold antibiotics pending these results [179]. Nausea and vomiting commonly accompany treatment with cytotoxic drugs, especially platinum compounds. Pharmacological techniques have been developed to counteract this, with the use of intravenous antiemetics such as metoclopramide and ondansetron. Patients often express fears of alopecia. However this is transient and is best managed by early counselling and an appropriate wig.

In general it is clear that chemotherapy is best given by experts. Oncology units are obviously well geared to support patients both physically and psychologically through chemotherapy, and most of the clinical trials of treatment in this condition are conducted by oncologists rather than respiratory physicians. However, patients with lung cancer are almost always referred to respiratory physicians who are keen to give chemotherapy themselves. Once again, a team approach involving interested clinicians would appear to be in the patient's best interests.

### Palliative effects

Patients with small-cell lung cancer have a dreadful prognosis if untreated and in general the results of chemotherapy in terms of long-term prolongation of survival are poor. Some clinicians take the view that the use of chemotherapy is not always justified because of toxicity and the adverse effects of treatment. For many years there was a feeling that it was cruel to inflict treatment on old and ill patients and that any prolongation in life would be of poor quality. Is this protective attitude by clinicians reasonable or does active treatment have any palliative benefit? In the MRC trial comparing three and six courses of chemotherapy [175], effects of the treatment on the patient's symptoms were recorded. Good relief of local symptoms was seen, the vast majority of patients reporting palliation and, in many, disappearance of symptoms. Also, systemic problems such as anorexia were greatly improved, a feature not seen with local treatment such as radiotherapy.

Some clinicians believe that patients who are well at diagnosis should be left until they develop symptoms, which should then be palliated. This approach was compared with standard immediate treatment in an MRC trial [180]. Patients given immediate treatment had much better survival and, although adverse effects of treatment were more common in this group, other aspects of quality of life as recorded by clinicians were better. Other authors have also shown that patients who respond to chemotherapy have improvement in symptoms and quality of life [176], and it can be concluded that if patients are fit to have chemotherapy it should not be withheld since good control of disease and good palliation go together.

A more difficult decision can be whether to treat patients who have extensive disease and poor performance status. Obviously it is important that chemotherapy is not given to a patient for whom there is no realistic prospect of useful palliation or improvement in the quality of life. Recently, many groups have been investigating the use of simple more 'gentle' chemotherapy regimens that have minor side-effects but adequate anti-tumour activity. This would allow outpatient treatment, with modest improvement in survival and good palliation

of symptoms without the cost, toxicity and need for in-patient care of more intensive regimens. Oral treatment with etoposide often forms the basis of these regimens [181]. Pharmacokinetic studies with this drug have shown that it is much more active when given in a chronic schedule, which makes its oral administration more attractive than intravenous use. Its safety and efficacy have been demonstrated in a large phase II trial in elderly patients [182]. Etoposide capsules were administered for 5 days to a total dose of 800 mg/m<sup>2</sup>. A response rate in excess of 70% and a median survival of 9.5 months was seen, results comparable with the efficacy of more toxic and complicated combination chemotherapy regimens. Haematological and gastrointestinal toxicities were minimal and admissions to hospital for treatment related to toxicity were seldom necessary. However when oral etoposide was compared to 'standard' combination intravenous chemotherapy in a randomized trial it was found to be less effective in terms of survival [183]. Its place in the management of this disease is thus uncertain as it appears to be reasonably tolerated but relatively 'weak' therapy.

### Radiotherapy

As with chemotherapy, small-cell tumours are in general more radiosensitive than non-small-cell varieties. However, the precise role for radiotherapy in small-cell tumours remains undefined. It may fulfil a useful palliative role in the treatment of distressing symptoms such as haemoptysis, localized pain and intractable cough, as well as those symptoms arising from CNS metastases, bone secondaries and obstruction of the SVC. What is the place of radiotherapy in patients with small-cell carcinoma in whom the ultimate yet remote objective is to cure or at least further prolong survival significantly?

### Primary tumour control

It is clearly evident that radiotherapy, like surgery, is a local treatment and is therefore unlikely to be successful in disease that disseminates widely at an early stage. Since chemotherapy has the theoretical potential to treat disseminated disease and radiotherapy that of augmenting any effect the drug treatment has on more bulky localized intrathoracic disease, many centres have investigated the place of thoracic radiotherapy as an adjunct to chemotherapy. The primary site is by far the most common location for disease to relapse after failure of chemotherapy and therefore it is to be expected that combining radiotherapy with chemotherapy might improve survival. Almost all studies comparing chemotherapy and thoracic radiotherapy with chemotherapy alone have shown a reduction in local recurrence rate, from an average of 80% to about 30%, although few have shown much impact on survival [184–187]. It has taken two large meta-analyses [188,189]

involving more than 2000 patients in more than a dozen randomized trials to show any impact on survival for the addition of radiotherapy to combination chemotherapy in patients with limited small-cell lung cancer. More modern chemotherapeutic regimens using platinum drugs have not been reported or included in these meta-analyses [190] nor has the optimal dose and scheduling of radiotherapy been established. Reports from a French study [137,191], where dose escalation was performed, have shown that at least 40 Gy are required for a clinical response but that toxicity with this kind of treatment is common. The scheduling effect is also important since it is known that the therapeutic ratio of radiotherapy improves with division of the total dose into fractions (see above). A larger-than-standard fraction dose (>2 Gy) produces a larger kill of tumour cells but causes an increased risk of late effects to normal tissues. Dividing the total daily dose into smaller doses (hyperfractionation) improves this therapeutic index. Accelerated fractionation allows for frequent treatments in a shorter time span. The interval between treatments allows some repair of the damage to both cancer and normal tissues. The theory behind hyperfractionation and accelerated schedules is to optimize the effects of radiotherapy on tumour cells while allowing normal cells to recover. The precise sequencing of radiotherapy with chemotherapy is important, although an optimal schedule could not be discerned from the recent meta-analyses [188,189]. Two studies looking at early radiotherapy or late treatment, i.e. at the end of chemotherapy, have shown conflicting results [192,193].

It is generally accepted that if patients are to be submitted to thoracic radiotherapy as an adjunct to chemotherapy they should have limited disease at presentation, show a complete regression with chemotherapy or have local symptoms attributable to the disease. The optimal dose, fractionation and timing in relation to chemotherapy are undetermined and combined modality treatment may produce substantial toxicity [194].

### Prophylactic cranial irradiation

The use of prophylactic cranial irradiation (PCI) in order to prevent the emergence of intracranial metastases is controversial. The reasons for its use are (i) the brain is a common site for spread of small-cell carcinoma, (ii) cytotoxic drugs in general do not cross the blood–brain barrier and (iii) the incidence of brain metastases increases as survival is prolonged by chemotherapy. In a meta-analysis of 11 studies, Pedersen [195] calculated that about 10% had CNS metastases at diagnosis of small-cell lung cancer, while a further 20% developed these during therapy. At autopsy the frequency was found to be approximately 50%. The small group of patients surviving for more than 2 years after diagnosis has been shown to have a probability of developing brain metastases of 50–80% [195,196]. Brain

metastases are associated with considerable morbidity for the patient and distress for the relatives. Patients are often hospitalized [197] and their survival is short. Irradiation of the brain does not of course prevent new metastases in a relapsed patient and therefore strictly speaking the term 'prophylactic' is inappropriate.

By 1995, 11 trials that randomized patients into groups receiving and not receiving PCI had been published [198]. All showed a significant reduction in the CNS relapse rate, from approximately 25% to 5%, but none showed a significant survival advantage favouring PCI. In the largest recorded study [199], in which 219 patients with limited disease were randomized to either PCI with 30Gy over 10 fractions ( $n=107$ ) or no brain therapy ( $n=112$ ), the CNS relapse rate was reduced from 20% to 5% by PCI but there was no impact on survival.

The adverse effects of PCI may also be significant. An acute organic syndrome, with memory loss, confusion and additional neurological deficits, can be seen 6–8 weeks after treatment in a small proportion of patients [200]. Late neurological toxicity has been reported in retrospective series of long-term survivors who have received PCI [201]. There appears to be a link between these effects and the timing and dose of radiotherapy. In summary therefore PCI is not advised as routine treatment and should only be given to patients with limited stage disease who are in complete remission following chemotherapy [202].

However, palliative cranial irradiation is often helpful in relieving distressing symptoms due to cerebral metastases. Dexamethasone is also useful in these patients and their response to this treatment is often taken as a guide to whether cranial irradiation should be attempted. The results from patients who have been treated show an intracranial response rate of approximately 70%, with 40% having a clinically complete remission [198]. Patients presenting with intracranial metastases from small-cell lung cancer have been shown to respond to systemic chemotherapy and this should still be part of the primary treatment [203].

## Surgery

The early MRC studies on the treatment of small-cell carcinoma compared surgery unfavourably with radiotherapy and found no long-term survivors after operative treatment [204]. This led to a widespread belief that small-cell lung cancer was a 'systemic' disease regardless of clinical stage at presentation and that surgery was contraindicated in all patients. The early promise of chemotherapy in the 1970s led to its emergence as the standard form of treatment and physicians largely forsook surgery as a treatment option. However, this was not true of those many thoracic surgeons who had seen cures following operation. In the last decade chemotherapy results have

reached a plateau (see above) and manipulations of combination chemotherapy and radiotherapy seem to have had little or no further impact on survival. These observations, coupled with reports of occasional long-term survival following surgical treatment, has led to questioning of the dogma that small-cell carcinomas are inoperable. The Veterans Administration Surgical Oncology Group entered over 2000 patients into a study to evaluate the role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer [205]. It was found that 148 patients with early-stage small-cell lung cancer were inadvertently included. Review of these patients showed remarkable 5-year survival rates: patients with T1N0 tumours had 60% survival, those with T2N0 27.9% and those with T1N1 31.3%. The overall 5-year survival rate, which included patients with T3 and N2 disease, was 23%.

Other workers have shown that when solitary pulmonary nodules removed from asymptomatic patients were subsequently found to be small-cell carcinomas, and when no obvious lymph node metastases were present, the 5-year survival rate was about 36% [206]. Although fewer than 5% of patients with small-cell carcinoma are found to have stage I disease after extensive staging, those that do so comprise a small subgroup that may benefit from surgical resection.

Patients with limited small-cell lung cancer treated with chemotherapy and thoracic radiotherapy have a high incidence of local recurrence, and this has led a number of investigators to re-explore the role of surgery in combination with other treatment in limited small-cell lung cancer [207,208]. Three uncontrolled studies in small groups of patients with limited small-cell lung cancer treated with preoperative chemotherapy followed by attempted surgical resection have shown that combined modality therapy is possible. All studies showed a high local control rate and, perhaps more interestingly, a high incidence of mixed histology or a conversion to non-small-cell histology following chemotherapy [208–210]. This presumably reflects the emergence of a chemoresistant clone of cells in mixed tumours and explains the poor eventual results of chemotherapy.

The largest study that has evaluated the role of surgery in small-cell lung cancer was by a group from Toronto [211]; 119 patients with limited disease were treated with combined modality therapy including surgical resection. The projected 5-year survival in stage I patients was 51%, stage II 28%, stage III 19% and the overall survival was 39%. The pattern of recurrence showed good local control, with local recurrence only in 8.3%. The Lung Cancer Study Group has performed the only prospective randomized trial evaluating the role of surgery in patients with limited small-cell lung cancer [212]; patients with stage I disease were excluded. All patients were treated with standard chemotherapy and were then randomized to receive radiotherapy (thoracic and PCI) with or without

thoracotomy. The resectability rate was 83%, 19% had a complete pathological response and 9% of patients had no residual small-cell lung cancer but only non-small-cell lesions. The 2-year survival was 20% irrespective of whether an operation was performed.

It is appropriate in the present stage of knowledge for limited small-cell lung cancer to be further classified using the TNM system and for peripheral lesions to be assessed for surgery. Mediastinoscopy should be performed even when CT is normal and the patient should probably undergo bone and brain scanning. The question of whether postoperative adjuvant chemotherapy is beneficial is at present unanswered but the reports so far show no favourable impact on survival. However, results of surgical treatment in this very select group of patients with small-cell lung cancer is certainly as good as chemotherapy alone.

**Paraneoplastic syndromes**

The term ‘paraneoplastic syndrome’ encompasses a variety of non-metastatic metabolic or neuromuscular manifestations of lung cancer [213,214]. Although such syndromes may occur with all major types of lung cancer, they are most frequently associated with small-cell carcinoma, which commonly elaborates ectopic hormones from neurosecretory granules within its cells. In healthy subjects, these peptide hormones (Table 41.10) are produced not only in neural tissue, including the hypothala-

**Table 41.10** Peptide hormones detected in small-cell lung cancer. (After Maurer [213].)

Hormone	Normal site of production
Thyrotropin releasing hormone Somatostatin	Hypothalamus
Thyrotropin Growth hormone β-Melanocyte stimulating hormone Adrenocorticotropin β-Endorphin β-Lipotropin Pro-opiomelanocortin	Anterior pituitary
Vasopressin Oxytocin VP-HNP OT-HNP	Posterior pituitary
Bombesin Neurotensin Glucagon	Gut-brain
Calcitonin	C-cells (thyroid)

mus and pituitary, but also in gut-derived tissues and are therefore sometimes referred to as gut-brain peptides. Although increasing numbers of these peptides are being detected by sensitive radioimmunoassay techniques, most of them are unassociated with gross clinical disturbances. However, a number of metabolic paraneoplastic syndromes are well recognized clinically. The mechanisms by which the paraneoplastic neuromuscular syndromes arise remain for the most part obscure. These syndromes may antedate discovery of a tumour by months or even years [215].

**Hypercalcaemia**

Malignant neoplastic disease is the most common cause of hypercalcaemia in the hospital population, accounting for about 60% of cases. Approximately 8% of patients with lung cancer are found to have hypercalcaemia and the majority of these have squamous cell carcinoma [216]. The most common cause of malignant hypercalcaemia is destruction of bone by osteolytic metastatic disease, but it may also result from the production of abnormal circulating factors by the tumour. True ectopic parathyroid hormone production is extremely rare [217], although lung cancers, especially squamous carcinoma, can produce parathyroid-like hormones that cause hypercalcaemia via increased mobilization of calcium from bones and by increased renal tubular absorption [218]. Hypercalcaemia produces polyuria, nocturia and thirst that if persistent result in dehydration, hypovolaemia and ultimately renal failure. The patient may experience malaise, weakness, anorexia, nausea, vomiting and constipation. Mental slowing, confusion, drowsiness and ultimately coma may mislead the physician into supposing that intracranial metastases are present. The symptoms may develop insidiously or so rapidly that the patient presents as a medical emergency.

In advanced or terminal malignancy, a decision not to treat hypercalcaemia may be taken with justification. However, if it is felt that the patient’s quality of life would benefit from lowering the serum calcium, then treatment should be vigorous. If there are no obvious bony metastases it can be assumed that the tumour is producing parathyroid hormone-like substance. Treatment of the primary should therefore result in biochemical improvement, and resection or radiotherapy should be planned in the usual way, first correcting the biochemical disturbance by medical means.

The mainstay of medical treatment is correction of associated dehydration with intravenous saline. Renal function should be closely monitored and adequate potassium supplementation given. Mild hypercalcaemia (<3 mmol/L) may respond to this alone but when hypercalcaemia is more severe, or does not respond to simple rehydration, a loop diuretic such as furosemide (frusemide) should be

given in addition to intravenous fluids. If hypercalcaemia persists despite these measures, agents can be used that inhibit calcium resorption from bones. Intravenous and oral bisphosphonates have an important role to play in the management of malignancy-associated hypercalcaemia and may cause fairly dramatic falls in serum calcium [219]. The cytotoxic antibiotic mithramycin is no more effective and is rarely used due to toxic effects. Oral steroids have an unreliable calcium-lowering activity in hypercalcaemia associated with bronchial carcinoma, but are often used nevertheless.

### **Syndrome of inappropriate antidiuretic hormone secretion**

When significant hyponatraemia (plasma sodium  $<120$  mmol/L) occurs in association with lung cancer, it is usually part of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This nearly always occurs in small-cell carcinoma, and SIADH is the most frequently encountered paraneoplastic syndrome associated with this cell type, being reported in 5–22% of patients [213]. SIADH is characterized by dilutional hyponatraemia, so that plasma sodium is low in the presence of abnormal water retention, resulting in low plasma osmolality (usually  $<260$  mosmol/kg of water). There is continued urinary loss of sodium at a level inappropriate for the plasma sodium concentration so that urine osmolality is disproportionately high, being at least twice that of plasma. The syndrome is due to uncontrolled secretion of ADH by the tumour, and the diagnosis is made by measurement of urine and plasma osmolality.

The patient may be asymptomatic or may complain of anorexia, weakness, nausea, vomiting and headache. As hyponatraemia worsens, impaired concentration with forgetfulness and confusion may develop. With a plasma sodium concentration of less than 115 mmol/L, seizures and coma may occur.

The cornerstone of treatment of SIADH is water deprivation [220], 500–750 mL of fluid being given daily in addition to the losses in the previous 24 h. This water deprivation may be unpleasant for the patient, and where compliance is difficult, or where treatment has proved unsuccessful, the antibiotic demeclocycline may be given orally [221,222]. This drug competes for ADH binding sites in the renal tubule and is given in a maintenance dose of 600–900 mg daily. It undergoes hepatic metabolism and is best avoided in patients with renal insufficiency or liver disease, otherwise nephrotoxicity may result. It may also cause a photosensitivity reaction.

As with other ectopic hormone production, treatment of the primary tumour (usually with chemotherapy) may produce a prompt response [223]. However, many chemotherapeutic agents used in the management of small-cell lung cancer, such as cyclophosphamide, vin-

cristine and cisplatin, can produce SIADH themselves [224].

### **Ectopic adrenocorticotrophin secretion**

Abnormalities of cortisol metabolism may be found in almost 50% of patients with small-cell carcinoma. Raised concentrations of immunoreactive adrenocorticotrophin (ACTH) can be detected and there is a loss of diurnal variation or failure of cortisol to suppress following dexamethasone [225,226]. Despite this, the clinical syndrome of ectopic ACTH secretion has been found to be present in only 5% of patients with small-cell carcinoma and is even less common in other cell types [213,225]. Patients do not usually develop the signs associated with Cushing's syndrome such as moon face, central obesity and cutaneous striae, presumably because the relatively short natural history of the small-cell carcinoma does not allow the development of these abnormalities. Indeed it has been shown that ectopic ACTH secretion seems to carry a poor prognosis [225].

The diagnosis is usually made when symptoms such as anorexia, mental slowing and muscle weakness, which may be profound, are associated with a hypokalaemic metabolic alkalosis due to urinary loss of potassium. The most common physical findings are oedema (83%) and proximal myopathy (61%) [227]. Progressive cutaneous pigmentation is sometimes a feature of the syndrome and results from associated  $\beta$ -melanocyte stimulating hormone production. Confirmation of the diagnosis is made by finding an elevated cortisol level that fails to fall following dexamethasone administration. Plasma ACTH assay also shows elevated levels.

The most effective treatment of this syndrome is treatment of the tumour itself. This usually takes the form of chemotherapy of small-cell carcinoma, although successful resolution has occasionally resulted from resection [228]. Inhibition of adrenal steroid synthesis with the anti-fungal agent ketoconazole has been shown to be beneficial [229], and this drug should be administered to patients with the syndrome while a response to chemotherapy is awaited.

### **Hypertrophic pulmonary osteoarthropathy**

Hypertrophic pulmonary osteoarthropathy (HPOA) is a syndrome characterized by periostitis of long bones, most commonly affecting the tibia, fibula, radius and ulna at their distal ends. The patient complains of bony pain in these involved areas, which are often hot and tender to touch, and there may be associated pain and swelling of the wrists, ankles and knee joints [230]. Clubbing of the digits is found in over 90% of cases, and is often gross [231].

The pathogenesis of the condition remains obscure but

lung cancer is by far the most common cause. Although some authors believe that HPOA is usually associated with adenocarcinoma [232], other workers have shown an equal distribution between major cell types with the exception of small-cell carcinoma [233]. HPOA is closely associated with finger clubbing and has been recorded in a variety of other malignant and non-malignant conditions associated with clubbing. It has been shown that blood flow to the calf and forearm is increased in HPOA and that this hyperaemia is directed particularly towards connective tissue and bone. The increased vascularity of subcutaneous tissues and periosteum leads to periostitis, resulting in loosely packed new bone being laid down outside the original cortex [234] and this produces the characteristic bony radiographic changes.

The mechanism by which lung cancer produces HPOA remains obscure. There is some evidence to support a role for vagally mediated afferent neural output from the tumour-bearing lung, as it was noted in the 1950s that division of the vagal branches around the hilum during unsuccessful attempts to resect lung cancer resulted in symptomatic relief, whereas 'open and shut' thoracotomy without nerve section produced no relief [235]. A number of possible pathogenic mechanisms have been put forward but none are universally accepted. When the diagnosis is suspected, radiographs of the lower ends of the radius, ulna, tibia and fibula, and of the hands are indicated. If the knees are painful, radiography of the proximal tibia and fibula and distal femoral shaft should be performed. The characteristic radiographic finding is a 1–2 mm line shadow running parallel to the cortex starting a few centimetres beyond the wrist or ankle joint and running for a variable distance along the shaft of the bone (Fig. 41.22). The active deposition of new bone along the inner aspect of the periosteum can be demonstrated on bone scans by the avid uptake of technetium in affected areas, although this investigation is seldom necessary in clinical practice.

Despite the reported success of vagotomy [235], this invasive procedure is unjustified unless thoracotomy is undertaken for an attempt to cure. In cases where successful resection of tumour is achieved, HPOA responds dramatically. Most other cases respond gratifyingly to treatment with a non-steroidal anti-inflammatory drug and corticosteroids may produce similar relief.

### Other endocrine and metabolic complications

#### Gynaecomastia

This may occasionally occur in association with lung cancer, most frequently with large-cell and adenocarcinoma types. The mechanism is thought to involve the production of human chorionic gonadotrophin by tumour cells, this substance resulting in overproduction of testicu-



**Fig. 41.22** Hand of patient with hypertrophic pulmonary osteoarthropathy showing subperiosteal new bone formation on metacarpals and phalanges.

lar oestrogen [236]. Drug-induced gynaecomastia (e.g. with spironolactone, cimetidine, digoxin) should be excluded before this physical sign is attributed to a tumour; however, when lung cancer is the cause, successful surgical resection also deals with the complication. If resection is not possible, then an antioestrogen such as tamoxifen may be effective in relieving symptoms.

#### Eosinophilia

As association between bronchial carcinoma and blood eosinophilia has been described [237]. This phenomenon, which may result from increased marrow production, prolonged eosinophil survival time or the production of an eosinophil chemotactic factor, is characterized by a high total white cell count and neutrophilia as well as eosinophilia [238]. It tends to be associated with advanced and rapidly progressive disease.

#### Non-metastatic neuromuscular syndromes

Paraneoplastic neurological syndromes have long been



recognized in lung cancer and these disorders are now thought to result partly from the cross-reaction of anti-tumour antibodies with antigens also present in neural tissue [239]. A variety of neuromuscular syndromes are recognized.

**1** A peripheral neuropathy, which may be motor, sensory or mixed, accompanied by muscle weakness and wasting with loss of tendon reflex and stocking and glove hypoaesthesia. An autonomic neuropathy has also been described that may result in postural hypotension or disturbances of gastrointestinal motility, including intestinal pseudo-obstruction (Ogilvie's syndrome) [240]. Patients with sensory neuropathy usually have small-cell lung cancer and often have high titres of antibody to the nuclear-associated HuD protein [241]. However, the pathogenesis of neural injury is uncertain [227].

**2** Neuromuscular junction and muscle syndromes include polymyositis/dermatomyositis, typified by proximal muscle weakness, pain and tenderness with a variety of systemic symptoms and a characteristic facial heliotrope rash. The myasthenic (Eaton-Lambert) syndrome is reported to occur in up to 6% of patients with small-cell lung cancer. In contrast to myasthenia gravis, the patient's muscle weakness improves with repeated efforts. The syndrome is thought to result from autoantibody-mediated functional blockade of the voltage-gated calcium channels involved in the release of acetylcholine at nerve terminals [227].

**3** Cerebellar ataxia, with nystagmus, impaired coordination and dysarthria, has been described in a small group of patients with small-cell lesions [242].

Paraneoplastic neurological syndromes associated with small-cell lung cancer often precede discovery of the underlying tumour. Apart from patients with Eaton-Lambert myasthenic syndrome, immunosuppression including plasmapheresis has not been shown to be particularly beneficial, even in patients with detectable antineural antibodies. Similarly, the neurological syndromes generally do not respond to cytotoxic chemotherapy, even when there is a gratifying antitumour effect [227].

## Special problems

### Obstruction of the SVC

Over 85% of all cases of obstruction of the SVC are caused by malignant disease. Bronchial carcinoma is responsible for over 60% of cases, about 20% being accounted for by other tumours such as lymphoma, mesothelioma and metastatic mediastinal lymphadenopathy. The few remaining cases are caused by rare benign conditions, including granulomatous disease, cryptogenic mediastinal fibrosis, intrathoracic goitre or aneurysm, or as a complication of central venous catheterization [243]. Small-cell

carcinoma is the commonest histological type of lung cancer involved and up to 10% of small-cell lesions present in this way [244]. The tumour usually compresses the vessel from without but occasionally invades its wall. Intraluminal thrombosis sometimes occurs and may be responsible for failure of treatment.

### Diagnosis

The diagnosis is usually obvious from the symptoms and signs, with swelling of the face and upper torso and distension of veins and venules across the chest, upper arms and neck. The next step is to obtain histological confirmation. Some hold the view that it is more important to initiate immediate treatment with radiotherapy before obtaining histology, but this approach has several pitfalls. Firstly, radiotherapy may be administered to a patient with a benign condition, thus subjecting the individual to the potential toxicity of treatment without any chance of benefit. Secondly, if radiotherapy is administered first it may make a subsequent histological diagnosis difficult or impossible, and in those patients whose survival is prolonged the subsequent management becomes increasingly problematical. Thirdly, if the tumour responsible is small-cell carcinoma, this responds well to chemotherapy and radiotherapy may not be required at all [244]. Obstruction of the SVC, although unpleasant, is unlikely to result in mortality but the underlying cause is and it is therefore important to determine this cause as accurately as possible. Histological diagnosis is usually obtained by bronchoscopy where a central pulmonary tumour is evident or by exploration of the mediastinum via mediastinoscopy or mediastinotomy. The risks of uncontrollable bleeding as a result of raised venous pressure proximal to the obstruction have probably been overstated and in practice routine biopsies should be performed [245]. In patients without an endobronchial lesion at bronchoscopy, mediastinotomy is almost always diagnostic and carries the potential advantage of providing larger tissue samples, which may be important in lymphoma and in more unusual causes.

CT with contrast venography may be helpful in determining the extent of the disease although usually adds little to clinical examination and chest radiography. Some radiotherapists claim to have found venography helpful in determining how far to extend the treatment field and this procedure is also required if stenting of the SVC is contemplated [246].

### Treatment

Treatment in cases due to cancer of the lung depends on whether histology is consistent with small-cell carcinoma or not. In a patient with small-cell carcinoma in whom a decision to use chemotherapy as primary treatment has

been taken, the additional use of radiotherapy appears to confer no extra benefit [244,247]. In non-small-cell carcinoma, chemotherapy has not been shown to produce any relief over and above that resulting from treatment with radiotherapy [248]. Studies with more modern drugs (e.g. cisplatin) in patients with obstruction of the SVC due to non-small-cell carcinoma have not been performed. Corticosteroids are frequently used but have not been convincingly shown to be of benefit.

Radiotherapy is the mainstay of treatment in cases due to non-small-cell lung cancer. The high initial dose of radiotherapy followed by a lower daily dose to a total of approximately 20Gy spread over 1–2 weeks is claimed to be more effective than initial low-dose treatment increased by gradual increments [248]. Symptoms usually begin to improve rapidly with signs diminishing more gradually, so that 90% of patients are free from oedema by 3 weeks. Radiotherapy in the treatment of obstruction of the SVC due to lung cancer is a palliative procedure and the ultimate prognosis depends on the cell type, the extent of the disease and the performance status. It has been reported that those who do not show a rapid response to radiotherapy die sooner than those who do, approximately 25% of patients overall surviving for 1 year [244,249]. In small-cell lung cancer, obstruction of the SVC is not in itself a poor prognostic indicator [244], and patients who relapse with obstruction of the SVC following initial chemotherapy should be treated with radiotherapy as there is a good chance of at least a partial response to both symptoms and signs.

Endovascular treatment of obstruction of the SVC has also been tried. Initial attempts using simple balloon angioplasty was occasionally successful in benign disease but recurrence rates in malignant disease are very high due to inability of the central veins to resist external compression. Since the first report of the successful placement of an intravascular stent in 1986 [250], there have been several reported series documenting the value of this technique [246,251,252]. So far its use appears to be confined to patients with malignant obstruction of the SVC who have failed to respond to conventional treatment or who require urgent relief of symptoms. Results of this form of treatment are impressive, with a primary clinical success rate in the region of 90% of patients [252]. There is no clear consensus on the need for thrombolysis or anticoagulation following stent insertion. There is no evidence that anticoagulation is required in patients in whom there is a good blood flow through the stent at the end of the procedure [246]. Thrombosis in the SVC is not a contraindication to stenting as this can be dealt with by local thrombolysis or dispersed with a mechanical device [253]. Few complications have been reported following stent insertion. Migration of stent into the right ventricle from the SVC has not been reported. The argument against stenting is its cost (approximately £1000 in 1998).

## Superior sulcus tumours

Pancoast [254] used the term 'superior pulmonary sulcus tumour' to describe a carcinoma situated at the extreme apex of the lung. The Pancoast syndrome comprises pain in the lower part of the shoulder and inner aspect of the arm (C8, T1 and T2 distribution) that may be severe and unremitting. It may be accompanied by sensory loss in the same distribution and wasting and weakness of the small muscles of the hand and of the medial forearm, wrist and finger flexors. It is caused by involvement of the lower part of the brachial plexus by tumour. A further neurological component is involvement of the sympathetic chain at or above the T1 (stellate ganglion) level to produce Horner's syndrome (ipsilateral partial ptosis, the appearance of enophthalmos, a small pupil and hypohidrosis of the face). The two radiological components of the syndrome are the presence of an apical mass shadow on the chest radiograph and local evidence of bone destruction, usually of the first and second ribs and/or a vertebral body or transverse process (see Fig. 41.15). Any histological type of lung cancer can occur in this situation and clearly incomplete forms of this syndrome are found.

## Management

The diagnosis is obvious where all components of the syndrome are present, although other diseases such as tuberculosis may occasionally produce confluent apical shadowing that is difficult to distinguish from tumour. In this situation bronchoscopy should be carried out, with the submission of washings for cytology and mycobacterial staining and culture, although the immediate results are often inconclusive. If this is the case and the lesion is thought to be an inoperable tumour, as most are by virtue of neurological or vertebral involvement, then percutaneous needle biopsy may provide histological confirmation of the diagnosis.

The best form of treatment for superior sulcus tumours remains the subject of controversy. These lesions were originally regarded as uniformly inoperable. In 1961 encouraging results were reported for radiotherapy followed by surgical removal of the tumour, usually by lobectomy [255]. This approach, with the addition of refinements such as completion of radiotherapy after surgical healing or placement of radioactive implants if the tumour is found to be unresectable at thoracotomy, continues to find favour in some places [256]. However, the evidence that preoperative radiotherapy improves either resectability or 5-year survival rate is weak [257] and requires confirmation with randomized prospective studies. Some take the view that if the lesion appears resectable after staging, surgery should proceed directly; if the tumour is deemed unresectable, radiotherapy should

be given as a single course. A good result is achieved in over 70% of cases when radiotherapy is given palliatively for pain relief [258]. Patients treated with radiotherapy alone or combined with surgery have a reported 5-year survival rate of 20–30% [257,258].

### **Malignant pleural effusion**

The presence of a malignant pleural effusion, whose origin has been determined by either pleural fluid cytology or pleural biopsy [259], indicates both incurability and a short life expectancy, survival rarely extending beyond 1 year with a median survival of approximately 6 months [260]. Once the diagnosis is certain, aspiration is necessary only if the pleural fluid is of sufficient volume to cause breathlessness. If reaccumulation is rapid or if repeated aspiration is required, then a chemical pleurodesis can be performed using one of a variety of available agents (see Chapter 43). When tetracycline is used for this purpose it may be mixed with local anaesthetic in order to reduce the pleural pain associated with the procedure [261].

### **Intracranial metastases**

The diagnosis of intracranial metastases and the frequency with which they occur have been discussed previously. It is notable that in non-small-cell carcinoma, intracranial metastases are found more commonly with adenocarcinomas and large-cell carcinomas than with squamous cell lesions [262].

Cerebral metastases may present with symptoms of raised intracranial pressure such as headache and vomiting. A personality change or impaired intellectual function is an unusual presentation. Focal or generalized seizures may occur. A motor or sensory deficit or impairment of coordination may become manifest.

### **Management**

If intracranial metastases become clinically evident in a patient who is clearly dying of advanced metastatic bronchial carcinoma, adequate narcotic analgesia may be the most appropriate treatment. Sometimes the general condition of the patient requires more active supportive treatment, even though the prognosis may only be a few months. Improvement is often obtained with oral corticosteroids given in a high initial dose, such as dexamethasone 16 mg daily, thereafter gradually reducing according to response. The results of treatment with cranial irradiation are discussed above, symptomatic relief being seen in up to 80% of patients.

Surgical treatment has a small role in the management of intracranial or brain metastases [263] when the disease can be shown to take the form of a solitary deposit that has arisen following an otherwise successful surgical resection

for primary lung cancer of non-small-cell origin. Before such neurosurgery is undertaken, evidence of other metastatic disease should be excluded by a careful search. This approach is justified since intracranial metastatic disease may be the only extrathoracic site of spread in a few patients [264]. Indeed sometimes the neurosurgery is performed as the primary treatment when the primary bronchial carcinoma remains occult within the chest. Prolonged survival has been seen in a group of patients who subsequently proceeded to thoracotomy [264].

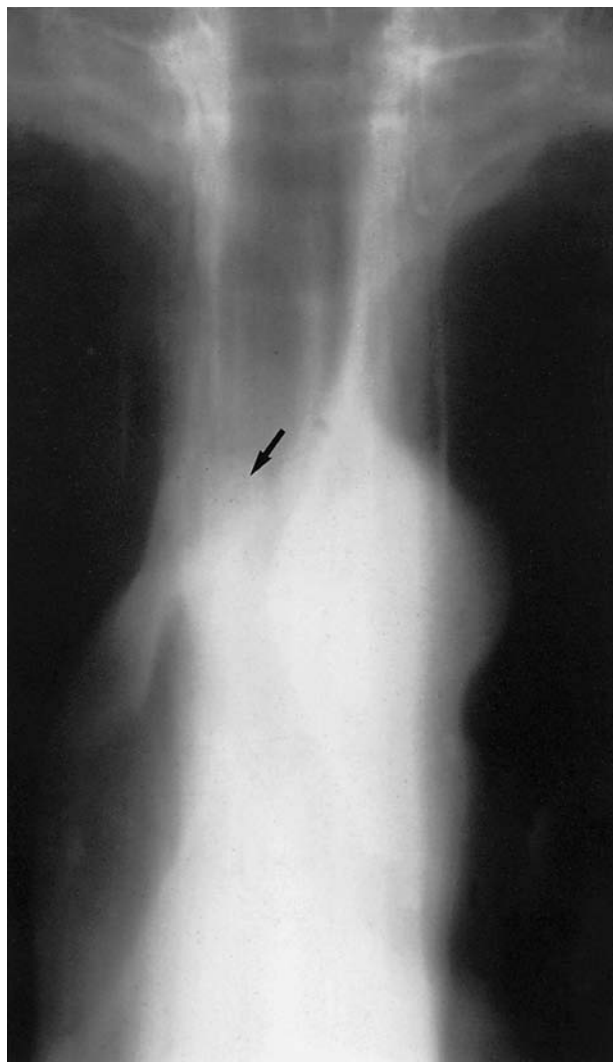
However, the prognosis for the great majority of patients with intracranial metastatic lung cancer is very poor, the overall median survival being variously reported as between 3 and 5 months [143,144]. Those whose symptoms respond to radiotherapy survive twice as long as those who do not [265], but only 14% of all patients are alive at 1 year [266].

### **Tracheal tumours**

The trachea may be involved by direct extension of adjacent tumour or, rarely, may be the site of primary malignancy [267], of which the slow growing and locally invasive adenoid cystic carcinoma is probably the most common type [268]. Tracheal malignancy may occur at any age and may be mistaken for other common disorders such as asthma, the increasing stridor of a few weeks' duration in a young or middle-aged adult being misinterpreted as wheeze. Haemoptysis may also occur.

The chest film is frequently normal but clinical suspicion may be heightened by the characteristic appearance of the flow–volume loop (see Chapter 2). The tumour may be demonstrated by conventional or computed tomography of the trachea (Fig. 41.23). Confirmation is by bronchoscopy, although caution should be exercised in the choice of instrument since the fibroptic bronchoscope may occlude an already narrowed opening. Where the stenosis is critical, biopsy using either instrument may result in complete occlusion of a small orifice.

Ideally, treatment of tracheal tumours is by complete surgical excision. This may not be possible because of the involvement of surrounding mediastinal structures. However, if the disease is apparently confined to the trachea, complete excision has been achieved in some centres using tracheobronchoplastic procedures [269]. Other methods of treatment frequently have to be employed, including radiotherapy, which may be administered externally or endotracheally [270], and laser devices [271]. One series described the use of an Nd–Yag laser in 21 patients with tracheal tumours, of which almost half were primary [272]. The majority were treated as emergencies for impending asphyxia and showed symptomatic benefit, allowing time to be gained for fuller diagnostic evaluation and treatment planning, including the use of further laser treatment, surgery or radiotherapy.



**Fig. 41.23** Tracheal tomogram showing carcinoma (arrowed) arising from right lateral wall above bifurcation.

Sometimes patients with tracheobronchial obstruction not amenable to curative surgery and not helped by radiotherapy may benefit from the insertion of a prosthetic stent [273].

### Quality of life

Traditionally, the outcome of treatment for patients with lung cancer has been measured in terms of the extent and duration of tumour response and patient survival, although differences between treatments as measured by these indices have been small. Since the vast majority of patients with lung cancer are treated with palliative intent, it has become increasingly more relevant to individual patient care and to policy-making to compare the cost, in both human and economic terms, of any gain achieved. Clinicians have therefore turned their attention to trying

to measure not only the length of their patient's survival but also the quality of any such extension of life. This aspect of lung cancer management has recently been comprehensively reviewed [274–276]. The concept of quality of life is largely subjective, varying from individual to individual, and many clinicians regard it as a 'soft science' that is impossible to define or measure scientifically. It is generally agreed that quality of life is multidimensional and involves a number of components, including the impact of disease symptoms, the side-effects of treatment, the ability of the patient to function and their psychosocial well-being. Attempts to measure quality of life should therefore reflect all these domains if possible and emphasis should be placed on the subjective experience of the patient whose quality of life is in question. Recently, attention has focused particularly on the development of questionnaires completed by patients themselves.

### Methods for measuring quality of life

Measurements of a patient's level of physical ability (performance status) and the response to treatment and its toxic effects are generally assessed by physicians. The Karnofsky Performance Index [277] has been in use for many years and is still widely favoured as a prognostic indicator. The WHO [278] and Eastern Cooperative Oncology Group [279] scales share many of the same limitations, scoring being influenced by whether the evaluation is performed at home or in hospital, with poor interindividual reliability. These instruments all neglect psychosocial variables and to this extent remain unsatisfactory as measures of quality of life (Table 41.11).

A bewildering array of questionnaires that attempt to measure different aspects of the patient's experience of quality of life [275] has been developed specifically for patients with cancer. These involve visual analogue self-assessment scales, diary cards [180] and, more recently, a modular approach where questions covering general cancer-related features are combined with those specific to lung cancer. The European Organization for Research on the Treatment of Cancer has developed such an instrument over several years [280]. This has a 30-item self-reporting questionnaire for use in cancer clinical trials, with a 13-item module specifically relevant to patients with lung cancer, for example covering cough, dyspnoea, pain and treatment-related side-effects [281]. The instrument is responsive to clinical change and has proved acceptable to patients. Other quality-of-life instruments that have proved popular and valid in the management of patients with lung cancer include the Rotterdam Symptom Checklist [282] and the Hospital Anxiety and Depression Scale [283].

There are surprisingly few reports of quality-of-life measurements in patients undergoing treatment for lung cancer, although things are improving [275]. As most

**Table 41.11** Comparison of Karnofsky [277], European Cooperative Oncology Group (ECOG) [279] and World Health Organization (WHO) [278] scales used to measure performance status.

Karnofsky scale		ECOG/WHO scale	
Status	Score	Score	Status
Normal; no complaints or evidence of disease	100	0	Able to carry out normal activity
Able to carry on normal activity; minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and capable of light work
Normal activity with effort; some signs or symptoms of disease	80		
Cares for self; unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all self-care. Unable to work. Up and about >50% of waking hours
Requires occasional assistance but is able to care for most personal needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair >50% of waking hours
Disabled; requires special care and assistance	40		
Severely disabled; hospitalization is indicated, although death not imminent	30	4	Completely disabled. Cannot carry out self-care. Confined to bed or chair
Very sick; hospitalization and active supportive treatment necessary	20		
Moribund; fatal processes progressing rapidly	10		

patients can only expect some palliation rather than significant prolongation of survival, there would appear to be a strong case for including measurements of quality of life in any future study. Indeed, there is an argument that measurement of quality of life should be part of the routine assessment of patients undergoing any form of intervention and that quality of life should be used to evaluate treatment outcomes in clinical trials. The data obtained could provide an objective basis for informed decision-making for individual patients and for making the case for allocation of appropriate resources to medical and supportive services [284,285].

## Prognosis

It is evident that lung cancer is not a single disease and any discussion of prognosis therefore requires qualification. However, if all types of lung cancer are considered together, the overall survival 5 years after diagnosis is 5–15% [122,286]. More meaningful results include details such as tumour histology, surgical stage, the type of treatment used, the performance status of the patient and the length of follow-up.

Some authors take the view that the growth of micro-

scopic lung cancer is approximately exponential, duration of survival being a function both of the size of the tumour at diagnosis and its doubling time [287,288]. Doubling time can be crudely calculated using a mathematical equation [289]: for small-cell carcinoma it is approximately 50 days, for squamous and large-cell carcinoma approximately 100 days and for adenocarcinoma about 180 days [290,291]. The shorter doubling time for small-cell carcinoma is in keeping with its poor overall prognosis, although the longer doubling time of adenocarcinoma appears to give it no prognostic advantage over squamous and large-cell carcinoma. A tumour cell with a diameter of 10  $\mu\text{m}$  produces a 1-cm diameter nodule weighing approximately 1 g after 30 doublings. It is therefore clear that in the lifespan of a tumour the majority of doublings must take place before the tumour is either clinically or radiographically detectable [292]. If exponential growth rates are assumed and if the tumour has arisen from a single cell, it is possible to extrapolate backwards to show that slow-growing tumours such as adenocarcinoma and squamous carcinoma may have been present for about 8–15 years prior to diagnosis and small-cell lesions for up to 3 years [288]. The natural history of lung cancer therefore is one of years of unrecognized growth from a single

cell, with the tumour becoming clinically apparent just prior to death. The clinician thus has very little chance of having any impact on what is the end stage of a condition. It is extremely disappointing that methods are not available to detect the disease in the preclinical state and large screening studies that have attempted to do this have had no impact on survival [293–296].

### Non-small-cell carcinoma

The overall prognosis for patients presenting with non-small-cell lung cancer is poor and survival rates have not changed over the last several decades. In large series of unselected patients, 5-year survival rates for this group of patients lie between 4 and 7%, irrespective of whether the patient received surgery, radiotherapy or chemotherapy [115,297].

The results of treatment in non-small-cell lung cancer have been well documented. Stage I tumours (T1/T2N0M0) when treated surgically carry a 5-year survival rate of 30–60% [122,298]. Unfortunately only about 20% of lung cancers are found to be stage I and the prognosis worsens as the stage advances. Thus for stage II tumours treated surgically, the survival rate falls to 20–40% at 5 years [122]. Studies that have examined radiotherapy as an alternative treatment to surgery in stage I and stage II non-small-cell lung cancer suffer from the disadvantage of lacking accurate pathological typing and staging, which is more easily achieved in surgically treated patients. Results reported show survival rates ranging from 6% at 4 years [126] to 40% at 5 years [146].

More extensive disease, where surgery is more difficult, carries an exceptionally poor overall outlook irrespective of treatment. Survival at 12, 24 and 60 months for stage IIIA disease is 37.7%, 12.7% and 6.1%, respectively, whereas for stage IIIB it is only 31.8%, 10.8% and 3.9% [299]. Patients with the least dismal outlook in this group are those with good pretreatment performance status and those with squamous histology. In the presence of distant metastases (stage IV disease), 1-year and 2-year survival is 19.8% and 5.4% respectively.

### Other prognostic factors

An analysis of prognostic factors in lung cancer found that for some surgically inoperable non-small-cell tumours the dominant factors were initial performance status and extent of the disease as determined by staging [300]. Other factors, such as anorexia, significant weight loss (>10% of body weight) and breathlessness, were relevant to a lesser degree. For operable non-small-cell lung cancer the most important prognostic factors were the stage of disease and, to a much lesser degree, the histological type and degree of differentiation [301]. The prognosis in so-called scar carcinomas is dependent upon the stage and histological type of the tumour, the associated scar being of aetiological rather than prognostic significance [44].

### Small-cell carcinoma

Untreated patients with small-cell lung cancer have a median survival of 2.8 months [302,303]. Those who have limited disease (i.e. confined to one hemithorax including ipsilateral supraclavicular nodes) have a median survival of 3.1 months compared with 1.4 months for the remaining majority (70%) who have more extensive disease. Aggressive chemotherapy extends the median survival for limited and extensive disease to about 14 and 8 months respectively; 15–20% of those with limited disease treated in this fashion survive for more than 2 years compared with less than 2% for those with extensive disease [167–169]. A very small proportion (<5%) may have stage I disease and 5-year survival rates of around 30% have been reported for these patients when treated surgically [205].

It is disappointing that there has been little change in the prognosis of all patients with lung cancer over the last three decades. This is almost certainly due to the fact that most patients present with advanced disease and effective systemic therapy is not available. While effective anti-smoking campaigns would have a profound effect on the incidence of the condition in the long term, what is urgently required is newer agents with activity in patients with established metastatic disease.

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# OTHER PULMONARY NEOPLASMS AND RELATED CONDITIONS

ANTHONY SEATON

The previous chapter describes the various types of bronchial and alveolar cell carcinomas. Apart from metastases, all other lung tumours are relatively rare, in one series from the Mayo Clinic comprising less than 1% of all primary lung tumours [1]. In that series, the most common were non-Hodgkin's lymphoma, carcinosarcoma and mucoepidermoid carcinoma, representing 41, 20 and 15%, respectively. This chapter deals with these other primary lung tumours, both benign and malignant, and also gives a brief account of the different patterns of lung metastases from tumours of other organs. It includes a description of some diseases that, though not strictly neoplastic, are related to the tumours described. An attempt is made to classify the primary tumours according to the tissue from which their cell type originates, although in a number of cases this is uncertain. The classification adopted is given in Table 42.1. For further pathological information on the many different types of lung tumour, the reader is referred to the bibliography of Whimster [2].

## Tumours of the blood and reticuloendothelial system

### Hodgkin's lymphoma

The clinical syndrome described by Thomas Hodgkin in 1832 is now taken to be confined to a particular histological type of lymphoma characterized by destruction of lymph node architecture, proliferation of large abnormal cells derived from monocytes and, usually, Reed-Sternberg cells (Fig. 42.1). It may be subclassified into four histological types: nodular sclerosing, lymphocyte-predominant, mixed cellular and lymphocyte-depleted. Nodular sclerosing Hodgkin's lymphoma tends to be the most benign variant, the other types often progressing from lymphocyte-predominant through mixed to lymphocyte-depleted. It is usual to classify Hodgkin's disease according to its extent, the tissues involved and the presence of systemic symptoms [3], this classification

being used in prognosis and in the planning of treatment (Table 42.2).

### Clinical features

Hodgkin's disease primarily affects adults, with an annual incidence of 2–3 per 100 000, and peaks at the ages of 25 and 60–70. It is more common in men. Only occasionally does it present as a primary intrathoracic lesion, when it is usually found as a result of investigation of enlarged hilar nodes. They are usually asymmetrically enlarged, in contrast to those of sarcoidosis, and the disease commonly extends into the mediastinal and paratracheal nodes (Fig. 42.2). More frequently, these features are part of a more generalized lymphadenopathy. The patient may be free of symptoms or may have evidence of systemic disease, with fever, loss of weight or night sweats. Symptoms referable to intrathoracic disease may include pleuritic pain, cough due to bronchial or tracheal compression, stridor, hoarseness due to recurrent laryngeal involvement, facial swelling due to vena caval obstruction, or breathlessness due to pulmonary infiltration [4]. Very rarely, the first presentation of the disease may be a diffuse intrapulmonary infiltrate without node enlargement [5,6]. Again, it is more usual for pulmonary infiltration to be found as part of a generalized disease, and usually associated with involvement of the hilar and mediastinal lymph nodes. In one review of 284 patients with Hodgkin's disease, 52% were found to have intrathoracic involvement; in 43% this was in the lung, in 34% hilar nodes, in 23% mediastinal nodes and in 11% pleura [7]. Thus node involvement is not essential for the diagnosis of pulmonary Hodgkin's, the disease manifesting itself wherever there is lymphatic tissue in the lung [8].

Apart from mediastinal and hilar node involvement, the radiological features of intrathoracic Hodgkin's disease most frequently show peribronchial infiltration. Direct extension from involved nodes is the next most frequent appearance, while patchy infiltrates, diffuse pneumonic consolidation and nodular lesions occur rather less often

**Table 42.1** Classification of lung tumours and related conditions.

<i>Blood and reticuloendothelial system</i>
Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Leukaemias
Plasmacytoma
Histiocytic conditions
Lymphoproliferative conditions
<i>Vascular tissue</i>
Haemangiopericytoma
Intravascular bronchioloalveolar tumour
Angiosarcoma
Lymphangioleiomyoma
Tuberous sclerosis
Arteriovenous malformations
Lymphangiectasis
<i>Neural tissue</i>
Neurofibroma
Neurilemmoma
Neurosarcoma
Chemodectoma
<i>Epithelium</i>
Carcinoid
Cylindroma
Mucoepidermoid tumour
Melanoma
Papilloma
Clear-cell tumour
Adenoma
Sclerosing pneumocytoma
<i>Muscle and connective tissue</i>
Leiomyoma (sarcoma)
Rhabdomyosarcoma
Fibroma (sarcoma)
Lipoma (sarcoma)
Chondroma (sarcoma)
Myxoma
<i>Mixed-cell origin</i>
Teratoma
Hamartoma
Carcinosarcoma
Blastoma

[7] (Fig. 42.3). Pleural effusion and direct spread into ribs may occur. All histological types of Hodgkin's disease may involve the lung, although the lymphocyte-predominant type does so less frequently than do the others. Involvement of the lung, as opposed to intrathoracic nodes, tends to be a later feature of Hodgkin's disease, though it is found at presentation in about one-third of patients [7]. It generally appears between 1 and 4 years after presentation, albeit the early use of chemotherapy may well prevent its development in many cases.

The diagnosis of intrathoracic Hodgkin's disease is made by biopsy of appropriate tissue. The main differen-

**Table 42.2** Staging of lymphoma.

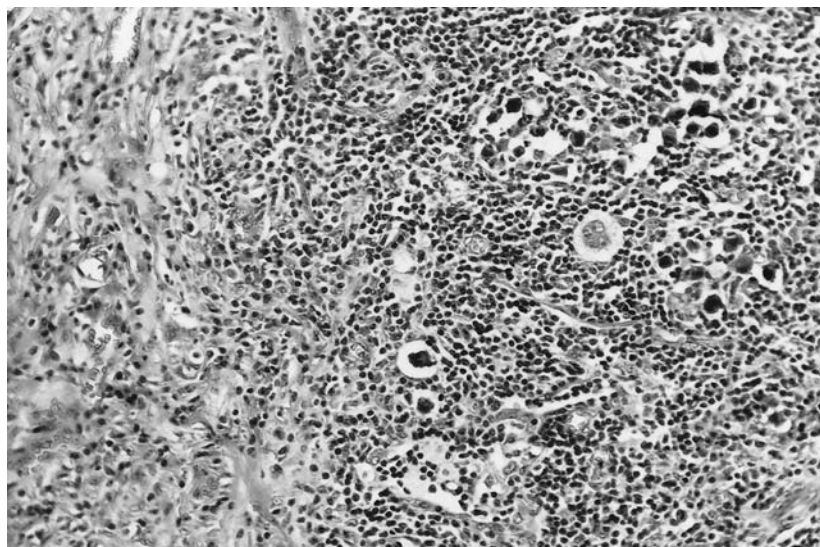
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I <sub>E</sub> )
Stage II	Involvement of two or more lymph node regions on same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II <sub>E</sub> )
Stage III	Involvement of nodes on both sides of the diaphragm (III). There may also be splenic involvement (III <sub>S</sub> ), localized involvement of extralymphatic organ or site (III <sub>E</sub> ) or both (III <sub>ES</sub> )
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement
Each stage is divided into A, those with no systemic symptoms, and B, patients with night sweats, loss of more than 10% of body weight in 6 months or unexplained fever above 38°C	

tial diagnosis is sarcoidosis (see Chapter 39), which also commonly presents with hilar, mediastinal and other node enlargement but less frequently causes systemic symptoms, fever and weight loss. At first presentation, it is usual to be able to obtain a node from a more accessible part of the body; however, if the disease is confined to the thorax, mediastinoscopy, mediastinotomy or thoracotomy is necessary, since needle biopsies are insufficient for proper histological assessment. Assuming the diagnosis can be made from an involved node, it may not be necessary to biopsy lung as well. However, if thoracotomy is performed, it is sensible to take a lung biopsy as well as a node. If the disease presents as a primary intrapulmonary lesion, biopsy is necessary, as it is if the lung shadowing occurs after the start of treatment. In this case, differentiation has to be made from other causes of lung infiltration that may affect people immunosuppressed by drugs, radiotherapy or the primary disease, including infections by *Pneumocystis carinii*, fungi and mycobacteria. Trans-bronchial biopsy with brushing and lavage have proved to be the investigations of choice in this situation. Other rare pulmonary complications of Hodgkin's disease include Langerhans' cell histiocytosis (histiocytosis X) and veno-occlusive disease [9,10].

### Treatment and prognosis

Treatment is planned on the basis of a staging procedure that usually includes CT, unless the disease is clearly stage IIIB or IV. Laparotomy and splenectomy were widely used in the past but probably confer no survival advantages and carry definite risks, so are rarely used nowadays.





**Fig. 42.1** Histological appearances of pulmonary deposit of nodular sclerosing Hodgkin's disease showing fibrosis to the left and a nodular tumour deposit to the right. This contains a background of small cells/lymphocytes, eosinophils and plasma cells mixed with large pleomorphic cells. One Reed-Sternberg cell is present in the centre of the nodule (haematoxylin & eosin  $\times 150$ ).



**Fig. 42.2** Enlarged right hilar and paratracheal nodes in 18-year-old girl that proved to be due to nodular sclerosing Hodgkin's disease.

Intrathoracic disease is rarely stage I. Stage IA and IIA disease are usually managed by megavoltage radiotherapy, although clear-cut symptoms of B disease lead to treatment with chemotherapy. Stages III and IV are treated with chemotherapy, usually without radiotherapy. Treatment differs in different centres, although chemotherapy is normally started with a combination of nitrogen mustard, vincristine or vinblastine, procarbazine and prednisolone, given for at least six courses. The different regimens and their immediate and long-term side-effects are best managed by a specialist oncologist [11]. Patients receiving both radiotherapy and chemotherapy are

known to have a much increased risk of developing other neoplasms [12]. In a recent series from The Netherlands, a second tumour occurred in 146 of 1939 patients over a mean follow-up of 9 years, over three times the expected rate [13]. The tumours with highest relative risks were leukaemia, non-Hodgkin's lymphoma, sarcoma and melanoma.

The prognosis in treated intrathoracic Hodgkin's disease is no worse than when any other part of the body is involved; at 10 years, some 75% of patients with stage II disease, 58% with stage III and 40% with stage IV may expect to be alive, most without relapse.





**Fig. 42.3** Posteroanterior (a) and left lateral (b) chest films of 20-year-old girl with anterior mediastinal Hodgkin's disease. There was spread of lymphoma into the lingula anterior to the left hilum.

### **Non-Hodgkin's lymphoma**

The term 'non-Hodgkin's lymphoma' includes several other malignant lymphoproliferative conditions that do not show the pathological features of Hodgkin's disease,

including those previously known as lymphosarcoma and reticulum cell sarcoma. Their classification (there are several in use) is confusing to the non-specialist but one, the Kiel classification [14], is given in Table 42.3. This is based on cell-marker and cytological studies and has some

**Table 42.3** Simplified classification of non-Hodgkin's lymphomas.

<i>Low-grade B cell</i>
Lymphocytic (including chronic lymphatic leukaemia)
Lymphoplasmacytoid (immunocytoma)
Plasmacytic
Follicle cell, centrocytic
Centroblastic/centrocytic (follicular or diffuse)
Centrocytic
<i>High-grade B cell</i>
Centroblastic
Lymphoblastic
Immunoblastic
Large cell anaplastic
Burkitt's lymphoma
<i>Low-grade T cell</i>
Lymphocytic (including chronic lymphocytic leukaemia)
Small cerebriform cell
Lymphoepithelioid
Angioimmunoblastic
Pleomorphic, small cell
<i>High-grade T cell</i>
Pleomorphic, medium and large cell
Immunoblastic
Large cell anaplastic
Lymphoblastic
<i>Unclassified rare types</i>

value prognostically, in that the high-grade tumours are the more malignant.

**Clinical features**

Non-Hodgkin's lymphoma is characteristically a disease of older people, with a peak incidence in those aged 60–80. Little is known of its pathogenesis, though it may affect people who have immune disturbances as a result of either disease, such as Sjögren's syndrome and coeliac disease, or immunosuppressive drugs. Epstein–Barr virus may be responsible in some cases, probably acting with another factor such as persistent stimulation of the immune system by another infection. In other cases infection with human T-cell leukaemia virus (HTLV)-1 may be responsible. Thoracic involvement most commonly takes the form of enlarged hilar and mediastinal nodes, although intrapulmonary involvement may occur, appearing as diffuse consolidation, peribronchial infiltration or single or multiple nodular lesions [15]. Pleural effusion is not infrequent. Altogether, intrathoracic involvement occurs in 20–25% of cases [16,17], with node enlargement and pleural effusion in about 20% and lung involvement in about 25%. Enlarged nodes may occur in any of the pathological types; however, lung infiltration is most frequent with the low-grade lymphocytic type

whereas nodular lesions occur, probably as blood-borne metastases, in the high-grade lymphoblastic types [17].

Primary lung involvement by non-Hodgkin's lymphoma is very rare. It presents with non-specific symptoms, including cough, breathlessness, chest pain and loss of weight [18,19]; finger clubbing and hypertrophic osteoarthropathy have been described [20]. Occasionally a lesion is found on routine radiography of a fit patient. The chest film usually shows a single area of diffuse infiltration, which may be nodular or involve as much as a whole lung [18]. Pathologically these are often low-grade lymphoplasmacytoid lesions (immunocytomas) [21].

The diagnosis of non-Hodgkin's lymphoma is made in the same way as that of Hodgkin's disease, i.e. an adequate piece of tissue is required for proper assessment. If the lung is involved at first presentation together with other organs, no further pulmonary investigation may be necessary, at least until there has been no response to antibiotics (in case of a pneumonic complication) and chemotherapy. However, sputum cytology is a useful non-invasive investigation [22]. If the only manifestation of disease is an intrathoracic lesion, mediastinoscopy and thoracotomy may well be necessary. Indeed, long-term remission has followed surgical removal of lymphocytic lymphoma confined to the lung [23].

In the case of lung infiltration occurring after diagnosis and initiation of treatment, other diagnostic measures are necessary, as the lesion may be due to opportunist infection. Transbronchial biopsy, together with brushing and local lavage, are the best techniques short of the more invasive procedures of thoracotomy or video-controlled thoracoscopy [24].

**Treatment and prognosis**

This is a matter for the specialist oncologist. In general, non-Hodgkin's lymphomas have a poorer outlook than the Hodgkin's type, and patients with the less-differentiated high-grade tumours, especially when they present with systemic symptoms, tend not to survive more than 2 years. However, in the few such patients who do respond to treatment, cure is possible; paradoxically at present, it is probable that low-grade tumours almost never respond completely to treatment [25]. The aim of management should therefore be to treat low-grade tumours with the minimum therapy necessary to relieve symptoms and ensure a good quality of life, whereas high-grade tumours should be treated with combination chemotherapy. Stage I disease and low-grade tumours, including chronic lymphatic leukaemia, have a much better prognosis, with 70% survival at 3 years [26]. Pulmonary infiltration occurring after the start of chemotherapy not surprisingly carries a worse prognosis than if it is found to be present *ab initio*. Treatment of stage I disease is usually with local radiotherapy. Low-grade lymphomas

are often treated with cyclophosphamide or chlorambucil alone, and some are not treated at all; the age of the patient, the course and cell type of the disease and the potential toxicity of the drugs are all factors that should be taken into account when planning treatment. Pulmonary involvement almost always requires treatment and this is usually radiotherapy combined with chemotherapy. The higher-grade lymphomas would normally be treated with combinations such as cyclophosphamide, vincristine and prednisolone, with or without doxorubicin and bleomycin. It should be remembered that these drugs themselves can be the cause of diffuse pulmonary infiltrates (see Chapter 55).

### Leukaemias

Chronic lymphatic leukaemia is now regarded generally as a variant of low-grade lymphocytic lymphoma in which the abnormal cells are found in the bloodstream. Involvement of intrathoracic nodes and of lung may occur, as discussed above [17]. Hilar adenopathy may occur in acute leukaemias as part of a generalized lymphadenopathy. Acute and chronic myeloid leukaemia may involve the lung secondarily, but usually only with microscopic

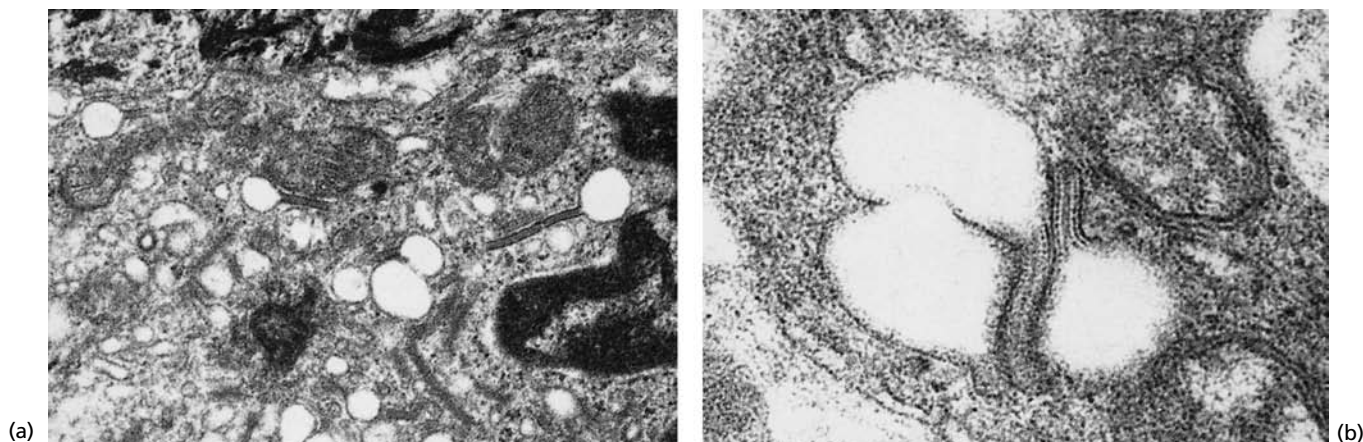
infiltration [27,28]. Thus the finding of pulmonary infiltrates in a patient with leukaemia should arouse the suspicion of either opportunist infection or lung haemorrhage. In acute leukaemias there is a strong case for instituting empirical treatment without further investigation, since such patients with pulmonary infiltrates usually die very rapidly (discussed further in Chapter 52). Briefly, treatment entails the administration of platelets if the platelet count is low and broad-spectrum antibiotics, including high-dose co-trimoxazole and amphotericin. If investigation is to be carried out, bronchoalveolar lavage or transtracheal aspiration is probably the safest and least traumatic [29,30].

### Plasmacytoma

The respiratory system is rarely involved in multiple myeloma, although deposits may occasionally be found presenting as tumours of trachea or bronchi [31,32]. Even less frequently, a solitary lung plasmacytoma may be the only manifestation of the disease [33]. A more usual presentation to the chest physician is an osteolytic lesion of rib or sternum associated with an intrathoracic extension of tumour (Fig. 42.4).



**Fig. 42.4** Expansion and irregular destruction of sternum due to myeloma.



**Fig. 42.5** (a) Electron micrograph of Langerhans' cell from patient with Langerhans' cell histiocytosis showing multiple characteristic tennis racquet or Birbeck bodies (uranyl acetate and lead citrate  $\times 33\,700$ ). (b) High-power view of three Birbeck bodies showing their tubular structure and terminal dilatation ( $\times 63\,500$ ).

The finding of a monoclonal band of immunoglobulin on electrophoresis of serum proteins is characteristic of myeloma, and such a band would be expected with solitary plasmacytoma of lung. However, it should be remembered that monoclonal gammopathies may be associated with other lesions, especially lymphoma, and may occur without obvious cause in association with a range of pulmonary diseases [34].

A solitary plasmacytoma is likely to be diagnosed at bronchial biopsy. The treatment of choice is probably excision, which has been associated with prolonged remission. Disseminated disease may occur subsequently but is not inevitable. Treatment of generalized myeloma with lung involvement would probably include local radiotherapy and chemotherapy with melphalan and prednisone. Multiple-drug therapy is not yet established as having substantial advantages, although in some patients with aggressive disease vincristine, doxorubicin and dexamethasone or similar combinations have been used to produce a remission.

### Histiocytoses

A number of conditions are characterized by abnormal proliferation of histiocytes; although not all are neoplastic, they are considered together here. All are extremely uncommon. Their classification has been changed frequently and at present they are differentiated into Langerhans' cell histiocytosis, histiocytoses of non-Langerhans' phagocytic cells, malignant histiocytoses, and a mixed bag of other histiocytoses. Langerhans' cell histiocytosis is the agreed name for the syndrome previously known by several names: histiocytosis X, eosinophilic granuloma, Hand-Schüller-Christian syndrome and Letterer-Siwe

disease [35]. Lung involvement is not uncommon and is described below. Malignant histiocytosis as described in the literature, a disease predominantly of young people and which may arise in the gastrointestinal tract of patients with coeliac disease, would probably now be regarded as histiocytic lymphoma. Lung involvement with diffuse acinar infiltrates is not uncommon at some stage in the course of the disease and occasionally pulmonary symptoms may be the presenting feature [36–38]. Lung disease is not a feature of the other histiocytoses.

### Langerhans' cell histiocytosis

Langerhans' cell histiocytosis was originally thought to be a lipid storage disease but is now classified as a condition of histiocytic proliferation [39]. Langerhans' cells are derived from the bone marrow and normally found in the skin. They secrete interleukin (IL)-1 and prostaglandin E and promote secretion of IL-2 and interferon  $\gamma$  by T lymphocytes. Pathologically, the disease is characterized by proliferation of histiocytes with vesicular and lobulated nuclei, basophilic nucleoli and eosinophilic cytoplasm. Tissue necrosis and infiltration with lymphocytes, plasma cells and eosinophils are also seen. The histiocytes may be seen on electron microscopy to contain characteristic Birbeck or tennis racquet bodies [40,41] (Fig. 42.5). Deposits of lipid material may be seen in the cytoplasm of the histiocytes. A spectrum of appearances may be present in lesions, from histiocytic infiltrates through granulomas and lipid-containing lesions to fibrosis.

Clinically, the disease affects infants and children primarily but may present as late as the fifth decade [42]. Its peak incidence is in the first few years of childhood and becomes progressively less frequent thereafter. The three original names reflect three characteristic clinical groups: group 1, in which there is primarily bone involvement (eosinophilic granuloma); group 2, in which bone and other organs such as lung, lymph nodes and liver are involved (Hand-Schüller-Christian disease); and group 3, in which skin, viscera and bone are involved (Letterer-Siwe

Siwe disease). However, there is considerable overlap between the three. In general group 1 lesions have the best prognosis and group 3 the worst. Age is also an important prognostic factor, very young children having a bad prognosis [43]. The condition is uncommon, having been estimated to occur in 1 per 350 000 annually in the UK [44].

The symptoms vary depending on the site of disease. Skin lesions present as papular and vesicular eruptions. Bone lesions often involve the skull, ribs and femur and may be palpable as subcutaneous lumps. Radiology shows punched-out lytic areas (Fig. 42.6). Granulomatous polyps may present in the external auditory meatus or in the orbit causing exophthalmos. Diabetes insipidus is a rare feature due to infiltration of the hypothalamus. When the lung is involved in the generalized disease, the prognosis has usually been thought to be bad [43]; however, a more recent study in which special efforts were made to detect subtle evidence of lung involvement suggests that this is not necessarily the case [45]. Involvement of the lung alone, primary pulmonary Langerhans' cell histiocytosis, may occur at any age but is seen most commonly in young male adults and seems to be associated with smoking [46]. All forms of the disease have a natural tendency to burn out, leaving fibrosis in the case of lung involvement, and the primary lung form is not necessarily associated with a fatal prognosis [47]. The onset is insidious, with cough, shortness of breath and loss of weight. Pneumothorax may be a presenting feature and is a frequent complication of all stages of the disease [48], often occurring repeatedly.

The radiographic appearances are of a diffuse pul-

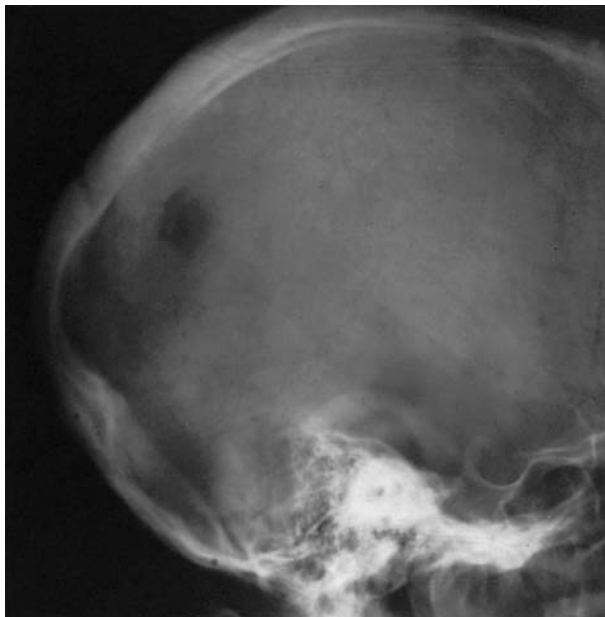


Fig. 42.6 Skull radiograph of patient with Langerhans' cell histiocytosis showing punched-out lesion in occiput.

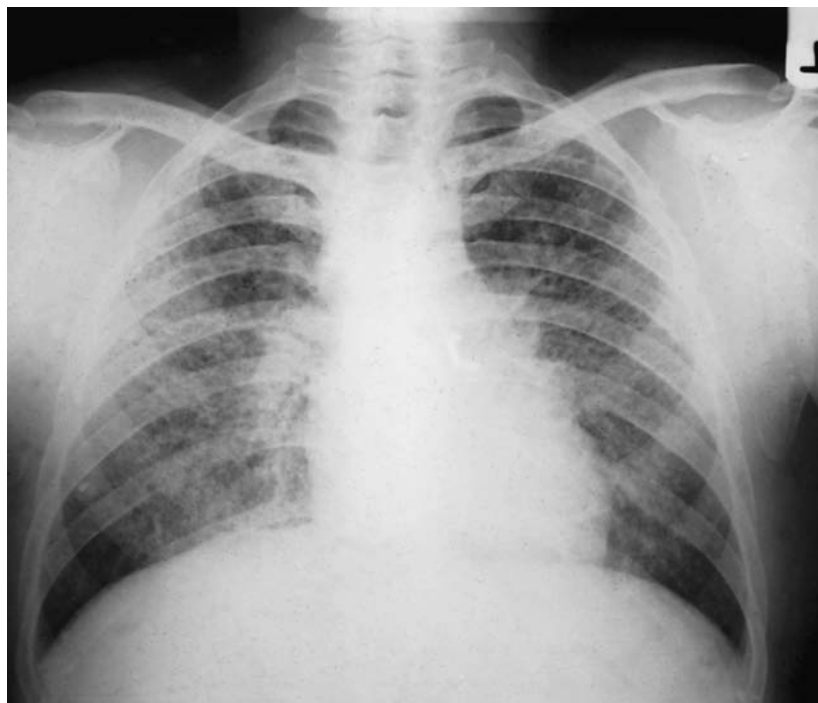
monary infiltration with a mixture of small nodular and irregular reticular shadows [49] (Fig. 42.7). There is no characteristic distribution, except that several zones of both lungs are involved and the costophrenic angles are often spared. Cyst formation is common and becomes a more marked feature as the disease progresses; some patients develop diffuse emphysematous changes. There is a tendency for nodular opacities to progress to cysts, reflecting histological changes from granuloma to fibrosis. High-resolution CT may show a characteristic combination of nodules and cystic change in keeping with these pathological features (see Fig. 7.49) [46]. Pleural effusion and mediastinal node involvement are rare [50,51].

The diagnosis is usually made by lung biopsy, although electron microscopy of lavaged bronchoalveolar cells may show the characteristic X bodies [41] (see Fig. 42.5). Monoclonal antibodies have been shown to be of value in the histological diagnosis [52–54]. Clinically, the diagnosis is suspected in a young male with diffuse reticulonodular radiographic change, especially if associated with pneumothorax; sarcoidosis is the disease most likely to cause confusion. Pulmonary function tests usually show reduced diffusing capacity but normal or increased lung volumes [40].

There is no consensus on treatment of Langerhans' cell histiocytosis. Spontaneous remissions may occur or the disease may pursue a rapidly downhill course over 2 years. The primary pulmonary type, as opposed to pulmonary involvement in the generalized disease, may often appear to arrest or, more usually, to progress rather slowly to diffuse honeycombing or emphysema and pulmonary hypertension. Survivals up to 20 years from diagnosis have been reported. In the present state of knowledge, it is probably wise to review the patient several times over a few months, with careful radiographic and functional assessment of any progression, before starting treatment [55]. The first line should probably be a course of high-dose prednisolone [56]. If this is ineffective over 3–4 months, consideration should be given to chemotherapy with chlorambucil, methotrexate, vincristine or, possibly, interferon  $\alpha$  [44,57]. If the disease has already reached the fibrotic stage, treatment is unlikely to be of value; in suitable patients transplantation may be considered, though recurrence after this procedure has been reported [58,59]. Pneumothoraces are often recurrent and pleurodesis may be necessary.

### Histiocytoma

Although the nomenclature of histiocytomas is confusing, there is a very rare benign tumour, which may be a neoplasm or possibly a granulomatous reaction, composed predominantly of histiocytes that occurs in the lung or bronchus [60,61]. The lesion may contain mast cells and spindle cells, and has also been called xanthoma or mast



**Fig. 42.7** Diffuse fine nodular and irregular infiltrates in a patient with Langerhans' cell histiocytosis.

cell granuloma. In addition, a fibrous histiocytoma has been described that usually presents as a small round lung lesion and which may occasionally metastasize [62,63]. It also is very rare and is probably analogous to the more common fibrous histiocytoma of the skin. One study of the pathology of these pulmonary tumours has distinguished benign, borderline and unequivocally malignant fibrohistiocytomas [64], and has reviewed the clinical correlates. Recurrence occurred occasionally after resection in the benign and intermediate groups as well as in the malignant. Pathological features of the malignant tumour linked to a poor prognosis included necrosis, bizarre giant cells, frequent mitoses and high cellularity. Those subjects with malignant tumours had a significant mortality. The niceties of diagnosis of these lesions and their cell of origin, if they are all indeed neoplastic, depend on electron microscopy and special histochemical techniques.

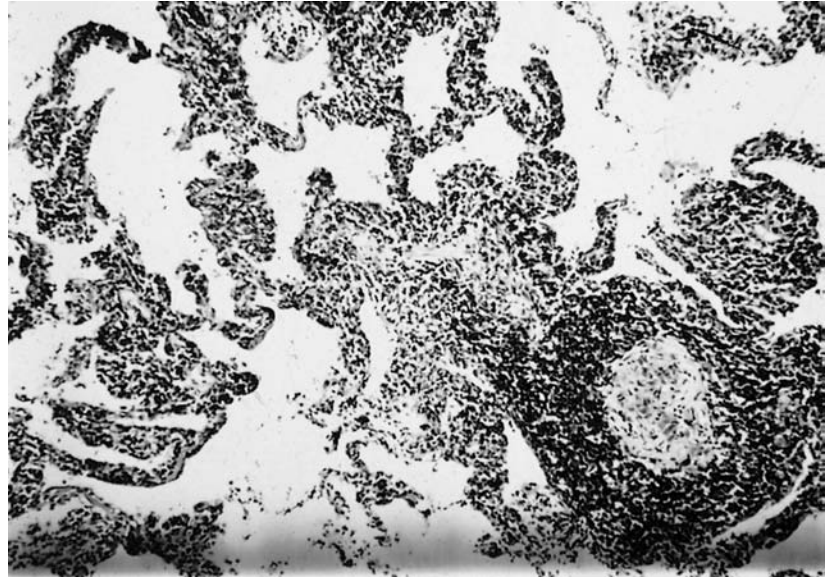
### **Lymphoproliferative conditions**

Several conditions characterized by proliferation of lymphocytes within the lung have been described. These include lymphoid interstitial pneumonia and pseudolymphoma, lymphomatoid granulomatosis (see Chapter 40) and plasma cell granuloma. The first two appear to be monoclonal proliferations of B lymphocytes and are therefore properly classified as low-grade lymphomas [65,66]. They may be associated with paraproteinaemia [67]. Evolution to clinically progressive lymphoma occurs but usually over a long time-scale, such that malignant change

often does not become apparent in the adult. The conditions are recognized complications of Sjögren's syndrome [68], human immunodeficiency virus (HIV) infection [69,70], bone marrow transplantation [71], primary biliary cirrhosis [72] and agammaglobulinaemia [73], and occasionally occur in families [74].

### **Lymphoid interstitial pneumonia**

This condition may cause no symptoms or may present with cough and shortness of breath. Chest films show a diffuse interstitial infiltrate, often bilateral but occasionally localized to a lobe or segment, when it may be mistaken for an infective pneumonia. The patient is often found to have paraproteinaemia. It may be associated with enlargement of the liver and peripheral lymph nodes. Histologically, the lung shows a diffuse infiltration of alveolar walls with mature lymphocytes and some plasma cells and histiocytes [75] (Fig. 42.8). The condition rarely if ever progresses to diffuse fibrosis, though evolution to malignant lymphoma [67] and lymphomatoid granulomatosis [76] has been described. It may respond to treatment with high-dose corticosteroids; if these are not successful, cyclophosphamide, chlorambucil or azathioprine may be effective [23,75]. Occasionally, as in one patient with acquired immune deficiency [69], spontaneous remission may occur; if the patient is symptom-free and without serious pulmonary impairment, a case may be made for withholding treatment and observing progress, as with other low-grade B-cell lymphomas.



**Fig. 42.8** Lung biopsy of patient with lymphoid interstitial pneumonia showing accumulation of lymphocytes in alveolar walls with follicle formation (haematoxylin & eosin  $\times 45$ ).

### **Pseudolymphoma**

These tumours are probably best regarded as the early stage of lymphocytic interstitial pneumonitis, where the disease process is still confined to the bronchial mucosal lymphoid tissue. They are thus sometimes referred to as MALT or BALT tumours. They are differentiated from malignant lymphoma by the presence of infiltration of lung by mature lymphocytes, true germinal centres and the absence of local node involvement [23,77]. They may present, usually in the middle-aged, with fever, breathlessness and general malaise [78], although they may be an incidental finding on a chest radiograph as a solitary lesion, a pneumonic infiltrate or as several discrete lesions. While they appear generally benign, change to (or subsequent development of) malignant lymphoma has been described [79,80]. Surgical removal has been followed by relief of symptoms [23] and this is the most likely method of management since most are removed under suspicion of being carcinomas. Otherwise they should be managed conservatively as other B-cell lymphomas.

### **Plasma cell granuloma**

This lesion, not to be confused with the rare primary plasmacytoma or with metastatic myelomatous deposits, is probably not a true neoplasm. It usually presents as a symptomless coin lesion on chest radiography but may cause bronchial obstruction and distal collapse or even diffuse lobar infiltration. It occurs predominantly in children and young adults and usually arises from a bronchus. Histologically it is composed of plasma cells, lymphocytes and histiocytes in a fibrous stroma [23,81]. Variations in this pattern may cause it to be confused with

other conditions, such as plasmacytoma or histiocytoma; however, plasma cell granuloma is always benign.

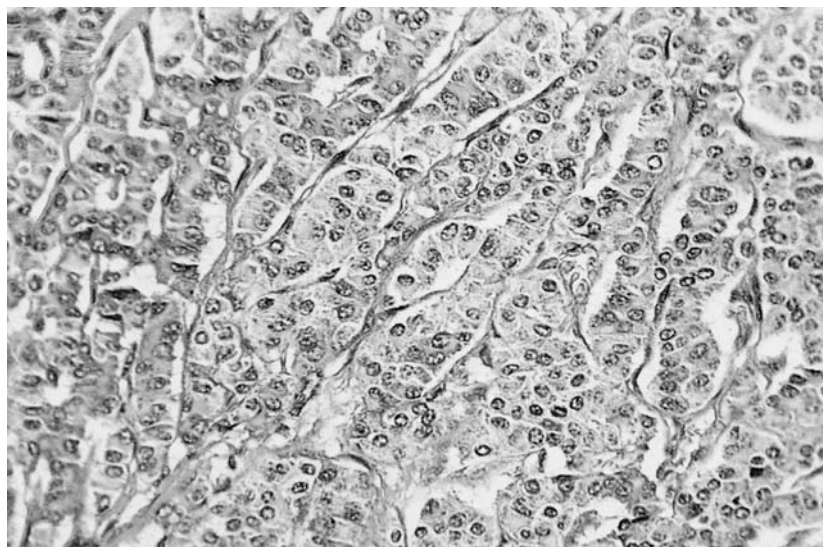
### **Tumours of epithelium**

These tumours, sometimes in the past loosely and misleadingly termed pulmonary adenoma, comprise 1–2% of pulmonary neoplasms. The most common is carcinoid tumour, followed by cylindroma. The others are very uncommon indeed.

#### **Carcinoid tumour**

This is not only the most common of the tumours originally grouped as bronchial adenoma but also the least rare of the primary lung tumours presenting in childhood [82–85]. It arises usually from a main or segmental bronchus and can often be seen bronchoscopically as an intraluminal tumour, generally covered with intact epithelium. This may be associated with spread into adjacent lung, so that the tumour may be larger than at first appears. Occasionally the tumour arises in peripheral lung. It is a neoplasm of the bronchial endocrine or APUD cell (see Chapter 1) derived from the primitive gut and therefore has the potential, rarely realized in bronchial carcinoid, to secrete substances responsible for various paraneoplastic syndromes. Histologically, it is composed of sheets or aggregates of small cells with dark central nuclei and pale cytoplasm in a vascular stroma. Often a pseudoglandular pattern is seen [86] (Fig. 42.9). So-called atypical carcinoid tumours show increased mitotic activity, irregular nuclei and prominent nucleoli, and areas of tissue necrosis [87]. These may have a greater potential to metastasize and are more difficult to distinguish from oat-cell





**Fig. 42.9** Histology of pulmonary carcinoid tumour showing regular polygonal cells with small round nuclei, forming regular trabeculae (haematoxylin & eosin  $\times 300$ ).

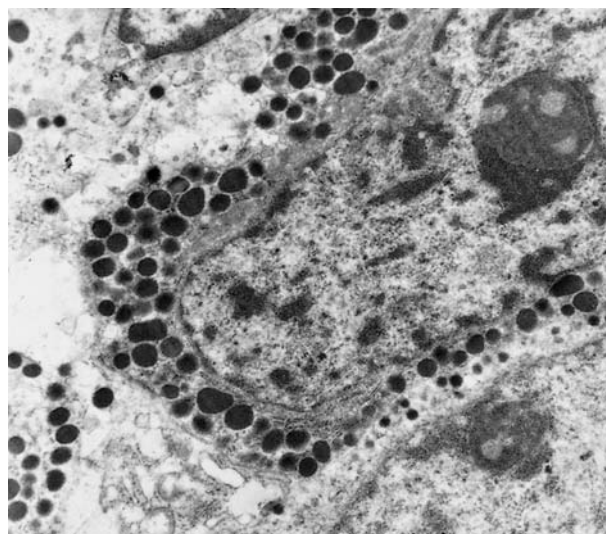
carcinoma. Occasionally, amyloid material [88] or bone [82] may be laid down in the stroma of carcinoid tumours. When histological diagnosis is difficult, special stains may demonstrate the various neuropeptides [85] and electron microscopy may be helpful, showing the neurosecretory material as dense rounded granules (Fig. 42.10).

### Clinical features

Carcinoid tumours, being predominantly slow-growing intrabronchial lesions, usually present with haemoptysis or symptoms due to bronchial obstruction [89,90]. They occur equally in either sex, usually at a younger age than bronchogenic carcinoma; the median age is between 40 and 50. About half of patients present with episodes of recurrent infection in the same lobe, one-third with haemoptysis, and small proportions with chest pain, cough, wheeze or shortness of breath [82]. The tumour may also be found on routine chest radiography in a symptom-free individual, especially if it is a peripheral one.

Important clinical features may be recurrent pneumonia, sometimes over several years [91], unilateral monophonic wheeze and signs of obstructive emphysema (see Chapter 6) [92]. These signs, which may be as subtle as slight reduction in movements and breath sounds over the affected lobe associated with a normal percussion note, are particularly important for detecting central tumours where the radiograph may not show an obvious abnormality.

Most patients have an abnormal radiograph at presentation [82], usually showing segmental or lobar collapse or consolidation. Discrete tumour may be seen in about one-quarter of cases and, especially in patients presenting with wheeze, the only abnormality may occasionally be lobar hyperinflation related to obstructive emphysema [92]; if



**Fig. 42.10** Electron micrograph of carcinoid cell showing dense rounded granules of neurosecretory material (lead citrate and uranyl acetate  $\times 4860$ ).

this is suspected, it may be confirmed by taking a film on expiration. All three features may be mimicked by bronchial carcinoma or other endobronchial lesions and inhaled foreign bodies, so diagnosis requires biopsy. This would normally be carried out at fiberoptic bronchoscopy, although caution should be used in interpretation of any such biopsies as there is much scope for confusion with oat-cell carcinoma when only small pieces of tissue are available to the pathologist. If the suspicion of carcinoid is raised, it is probably wise to obtain a larger biopsy via the rigid bronchoscope, since surgical treatment may well differ depending on which of these two neoplasms is present.

Very rarely, carcinoid may present with diffuse multi-

centric endobronchial lesions [88] or as multiple peripheral tumours [93], often associated with bronchiectasis and scarring. These latter lesions have been called tumourlets [94].

All forms of carcinoid have the potential to metastasize, though this probably occurs in fewer than 10% of treated cases. Metastasis may occur to local nodes, to liver and to bone particularly; in bone the lesions tend to be osteoblastic. Metastases may present clinically many years after surgical removal of the primary tumour, although when they do so the patient may still survive several years, with or without treatment.

The carcinoid syndrome, characterized by attacks of intense flushing, tachycardia, occasionally wheeze, and hypotension, occurs in approximately 1% of patients with bronchial carcinoid [95,96]. Other features may be abdominal cramps and profuse watery diarrhoea, oedema of the face and arms, symptoms of pellagra and stenotic or regurgitant lesions of the pulmonary and tricuspid valves [97]. Pulmonary carcinoid has been reported to cause mitral valve disease on one occasion [98]. This syndrome seems to be related in part to the carcinoid cell's role in tryptophan metabolism, the amino acid being converted to 5-hydroxytryptophan and then decarboxylated to 5-hydroxytryptamine (serotonin). Release of this substance into the blood may be a cause of the wheeze and diarrhoea, while competition by the tumour for tryptophan may be responsible for the symptoms of pellagra. Subsequent conversion of serotonin to 5-hydroxyindoleacetic acid occurs in the liver; this substance is then excreted in urine where it provides the basis of a useful test for diagnosis of the syndrome. The flush does not seem to be related to serotonin but may be provoked by alcohol, excitement or intravenous norepinephrine (noradrenaline), and may be due to secretion of kinins or vasoactive peptides by the tumour [99]. These substances may also be responsible for fibrous damage to the heart valves, though how this occurs is not clear.

Carcinoid tumour of the lung has also been reported to be associated with Cushing's syndrome [96], acromegaly [100], pluriglandular adenomatosis [101] and hypercalcaemia [102]. These rare occurrences are presumably related to the potential of the APUD cell to secrete hormones or hormone precursors.

### Treatment and prognosis

Carcinoid tumours should be removed surgically [82,83]. At operation it is unusual to find metastases in nodes, although the nodes may be enlarged due to associated infection and frozen section may be advisable. If the tumour is confined to a bronchus, it may be possible to remove it by sleeve resection; otherwise lobectomy or pneumonectomy may be necessary. In general, surgery should be as conservative as possible. After successful

resection, the prognosis is very good, with a better than 90% 10-year survival rate. If endocrine symptoms are present, these are relieved by successful tumour resection. However, metastasis may present even as late as 16 years after resection.

Liver metastases may be treated, and the attendant symptoms palliated, by selective hepatic arterial embolization [82,103]. If symptoms of the carcinoid syndrome are associated with an irresectable or metastasized tumour, which is very rarely the case with lung tumours, control of diarrhoea, flushing and wheeze may be obtained with serotonin antagonists (methysergide or cyproheptadine) and  $\alpha$ -adrenergic blocking drugs. Valvular heart lesions may require surgical treatment, while pellagra may be treated with supplemental nicotinamide. Since the prognosis of carcinoid tumour is relatively prolonged, even when associated with such symptoms and metastases, control of symptoms with this treatment may be an important part of the patient's management.

### Cylindroma (adenoid cystic carcinoma)

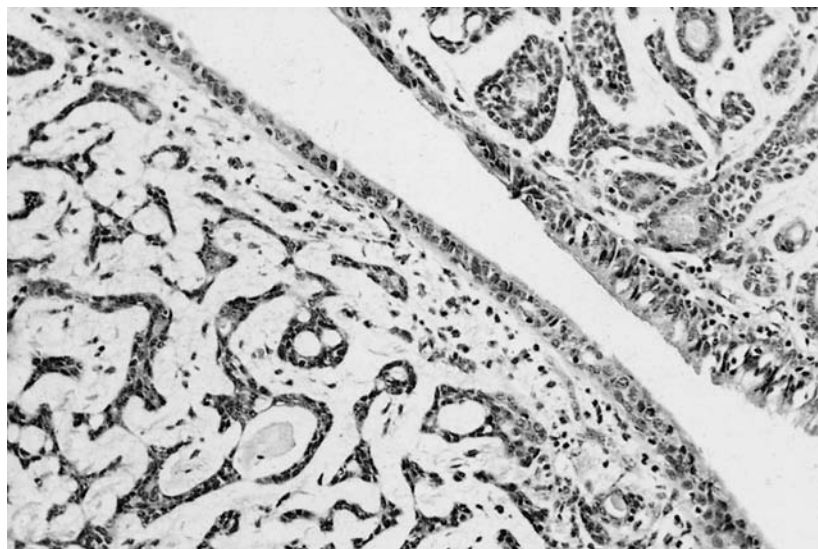
This tumour represents only about 15% of so-called bronchial adenomas [104], although it is probably the most common primary malignant tumour of the trachea [105]. Histologically, it originates from bronchial glands and is composed of small round cells with dark nuclei arranged in a cribriform manner, with larger paler cells forming clumps and pseudoacini [96] (Fig. 42.11). The bronchial mucosa usually remains intact.

### Clinical features

Cylindromas may occur at any age and cause haemoptysis and symptoms of bronchial obstruction [96,106]. They should be suspected particularly if a young or middle-aged adult presents with increasing stridor of a few weeks' or months' duration. Radiology of the chest may show a hilar tumour or distal collapse or consolidation; if the tumour arises in the trachea, the film is usually normal. Diagnosis is made by bronchial biopsy, and bronchography may be used to delineate the extent of a central tumour. The tumour may rarely metastasize to nodes and liver, but more commonly invades local structures widely.

### Treatment and prognosis

Ideally, treatment is by excision, although owing to the usually central situation of the tumour this may not be feasible. In some centres, tracheal reconstruction procedures have allowed complete removal [107]. If resection proves impossible, radiotherapy often produces prolonged remission and relief of symptoms where tracheal obstruction is threatening life [108]. The use of laser therapy holds promise of controlling the obstruction if resection is



**Fig. 42.11** Resected bronchial tumour showing bronchial lumen compressed from both sides by infiltrating submucosal adenoid cystic carcinoma (haematoxylin & eosin  $\times 150$ ).

impossible. The tumour grows slowly, but nevertheless has a considerably worse prognosis than carcinoid [109,110].

### **Mucoepidermoid tumour**

These salivary gland-type tumours are even less common than cylindromas, which they resemble in clinical features [106,111–113]. They may occur at any age, and like all slow-growing intrabronchial tumours may initially be misdiagnosed as asthma [114]. Pathologically they may be divided into high-grade and low-grade types, the former having a greater propensity to metastasize and invade locally. They arise from glandular structures, usually in trachea and major bronchi, and histologically consist of squamous elements and mucus-secreting acini. A papillary variant has been described [115]. Treatment is by surgical resection if possible [113,116].

### **Bronchial melanoma**

Malignant melanomas may metastasize to bronchi but more commonly to lung parenchyma. Very rarely, primary melanoma arises in bronchi where it is usually clinically indistinguishable from bronchial carcinoma [117], although pigmentation may be seen bronchoscopically or on sputum cytology [118]. The prognosis is poor, metastasis occurring to local nodes and by haematogenous dissemination; nevertheless, long-term survival has been reported following pneumonectomy [119]. The origin of the tumour is presumed to be from neuroectodermal melanoblasts that have migrated to the bronchial mucosa during embryonic development, since melanocytes are not a normal feature of the respiratory epithelium.

### **Bronchial papilloma**

Papillomas are quite frequently seen on the larynx, but are rare tumours of trachea and bronchi. They may occur as solitary lesions [120,121] or as multiple tracheobronchial papillomatosis [122]. The latter seem to occur predominantly in middle-aged men. All papillomas should be regarded as having the potential to undergo malignant change to squamous carcinoma [123] and should be excised. Histologically they resemble papillomas elsewhere, with a vascular stroma surrounded by stratified keratinizing squamous epithelium. They are not to be confused with inflammatory polyps that may sometimes be seen in bronchiectasis or asthma [124].

### **Clear-cell tumour**

This benign tumour is composed of sheets of cells with small nuclei and foamy or clear cytoplasm [125,126]. It usually appears as a small peripheral nodule on chest radiography. The cell of origin is not known and it has not been described as undergoing malignant change. It is not to be confused with metastatic renal carcinoma or with the clear-cell subdivision of large-cell anaplastic bronchial carcinoma.

### **True bronchial adenoma**

Benign adenomas, which may occur at any age, may arise from several different cells in bronchial glands [127]. All are exceedingly rare. Mucous gland [128], serous [129], pleomorphic (derived from myoepithelial cells) [130], oncocyctic (from a cell in the region of the collecting ducts) [131] and mixed cell types have been described. Diagnosis

is normally made after excision, which would be expected to be curative.

### **Sclerosing pneumocytoma (sclerosing haemangioma)**

This peripheral tumour occurs predominantly in women and may present at any age. It is usually small, subpleural and polypoid and may be associated with cough, haemoptysis or no symptoms [132,133]. It seems more common in Chinese women, and electron microscope studies have suggested that it is not a tumour of endothelial cells but of type II pneumocytes [134]. Malignant change has not been described.

## **Tumours of vascular tissue**

A group of rare tumours originate in vascular tissue, including capillary haemangioma and haemangiomatosis [135], haemangiopericytoma, intravascular bronchioloalveolar tumour and angiosarcoma. Sclerosing haemangioma seems to be derived from type II epithelial cells in a number of cases (see above), although variants have been thought to be of endothelial origin [134]. Two non-neoplastic vascular anomalies, arteriovenous malformation and pulmonary telangiectasia, are discussed here for convenience, as are tumours arising from lymphatic tissue.

### **Haemangiopericytoma**

This tumour arises from capillary pericytes, pluripotential cells associated with the vascular basement membrane [136]. It presents as a peripheral radiographic shadow, which may be very large and involve a whole lobe. Growth rate is very variable and it may both metastasize widely and invade locally. However, removal of a small or early lesion may be curative; if this is not possible, radiotherapy may be effective. Similar tumours may occur in other organs of the body.

### **Intravascular bronchioloalveolar tumour**

This is a multicentric lung tumour that arises in either vascular pericytes or endothelial cells and which is more common in women [137,138]. It may occur at any age, half the reported tumours having presented before the age of 40. It is usually found incidentally on chest radiography, when it appears as multiple small nodules, but may present in a form that mimics pulmonary embolic disease with pulmonary hypertension [139]. Excision of these tumours shows collections of vesicular cells with nodules of eosinophilic hyaline material. The cells protrude into alveoli and bronchioles and invade arteries and veins. There is often central necrosis. Metastasis occurs occasion-

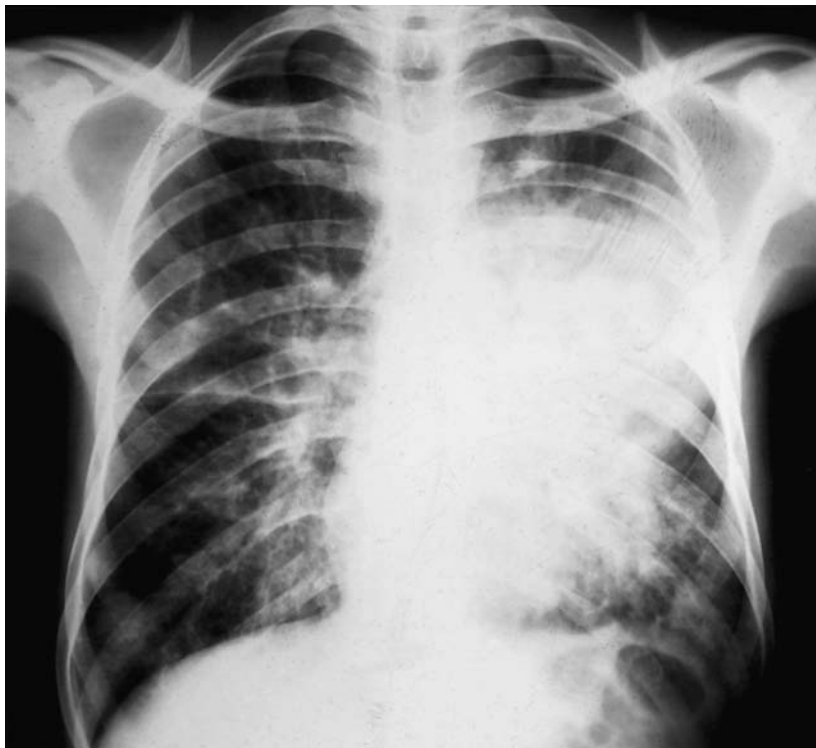
ally, but the course of the disease is usually characterized by slow extension of the tumour throughout the lungs until the patient dies in respiratory failure. No treatment has so far been shown to induce remission, although transplantation would presumably be an option.

### **Angiosarcoma (Kaposi's sarcoma)**

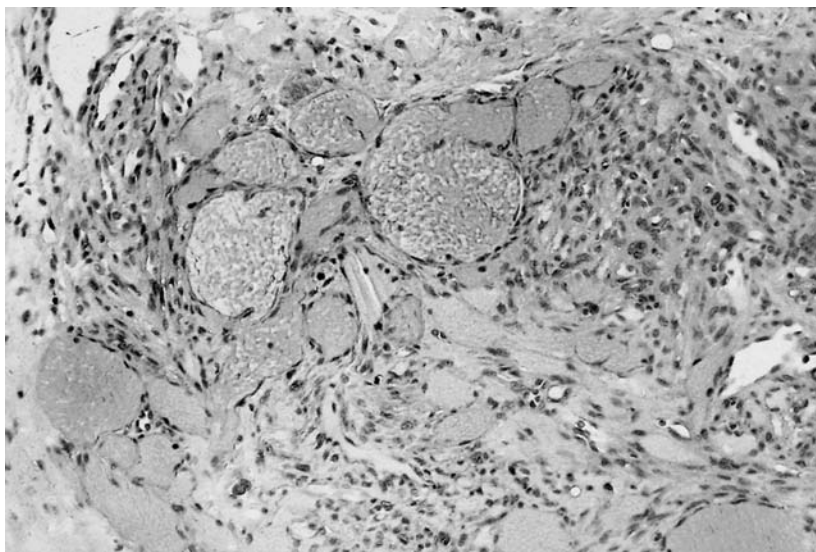
This malignant tumour is derived from vascular endothelium [140]. Its cells secrete multiple cytokines that probably sustain the tumour's growth. It was very rarely recognized in the lung prior to the arrival of AIDS in the USA but now appears commonly in subjects with sexually acquired disease; however, it is still rare in those in whom AIDS was acquired through blood transfusion or intravenous drug abuse, suggesting that another infection together with immunosuppression is necessary for its pathogenesis. Recently a new herpes virus has been found in a proportion of these tumours [141]. Previously it was more familiar as a rather indolent skin tumour in Africans [142] or occasionally as a more aggressive disseminated disease [143]. Now, however, its most frequent presentation is in people suffering from AIDS [144], in one series being present in the skin at death in 59% of patients and in the lungs in 36% [145]. The tumour presents with diffuse nodular and patchy infiltrates throughout both lungs [146,147] (Fig. 42.12); the patient has often been unwell for some time previously and may have generalized lymphadenopathy. The radiograph shows gradually increasing diffuse nodular infiltrates that have a tendency to coalesce and become more profuse over several months, although the disease may be present with a normal radiograph [148,149]. Pleural involvement with effusion may occur. The diagnosis may be made by transbronchial [150] or open lung [144] biopsy, though until there is reasonably effective treatment for the tumour the latter procedure is rarely justified. However, there is therapeutic justification for the use of bronchoscopy for differentiating Kaposi's sarcoma from other diffuse infiltrative conditions that afflict AIDS sufferers, and future treatment possibilities, such as the use of combination chemotherapy, interferon  $\alpha$  or liposomal agents [151–153], may make aggressive diagnostic procedures more worth while (see Chapter 52).

The pathological appearances are of multiple discrete haemorrhagic nodules throughout the lung parenchyma. Bronchi and vessels may be invaded. Histological appearances vary from thin fibrous septa with malignant epithelium in a lake of blood to solid sheets of spindle cells with inconspicuous vascular spaces [146] (Fig. 42.13).

Many combinations of antiviral and chemotherapeutic agents have been tried and temporary remission may be obtained [152,153]; the use of liposomal drug preparations to deliver adequate doses with minimal side-effects seems a promising approach. However, no regimen has been shown to be sufficiently effective and free of toxicity to



**Fig. 42.12** Radiograph of African patient with AIDS and extensive pulmonary infiltration by Kaposi's sarcoma. (Courtesy of Dr Dwight McLeod.)



**Fig. 42.13** Histological appearance of Kaposi's sarcoma showing ectatic vascular channels admixed with malignant spindle cells, infiltrating connective tissue stroma (haematoxylin & eosin  $\times 150$ ).

become established treatment, and usually the patient passes from having no respiratory symptoms to death from respiratory failure over the course of a few months.

### **Lymphangioliomyoma**

This is a condition affecting women [154–156], almost always of child-bearing age, though occasional cases have been described after the menopause [157]. The patient often presents initially with haemoptysis, pneumothorax and a chylous pleural effusion. Initially the chest radio-

graph may be normal, but subsequently there is often a fine reticulonodular shadowing, sometimes associated with septal lines. The changes are more marked at the bases and are seldom profuse. In addition, or sometimes alternatively, there is evidence of overinflation or frank emphysema and this combination in a premenopausal woman should always raise the possibility of lymphangioliomyomatosis. The patient may often have other manifestations of systemic disease, such as lymphoedema and leiomyomas of kidney or uterus.

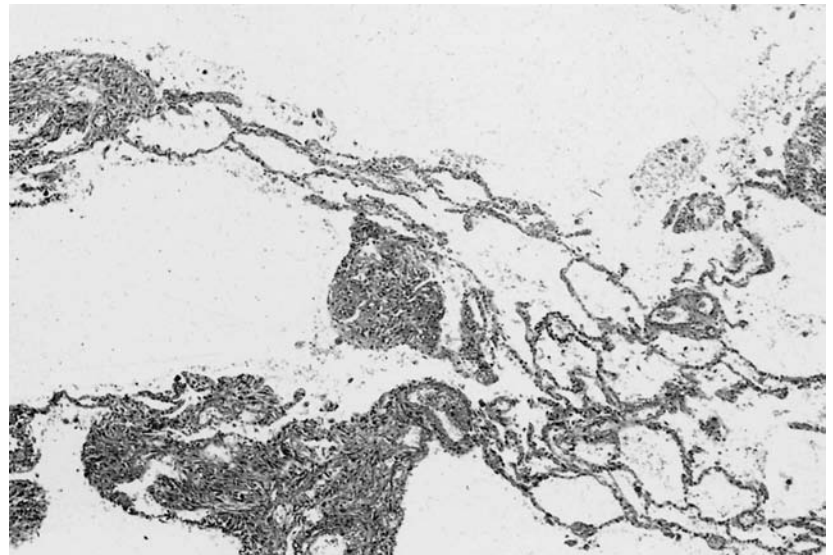
Unlike many conditions where the radiograph shows a

fine infiltrate, lung function testing usually shows an obstructive pattern and hyperinflation. Sometimes there may be a considerably higher thoracic gas volume (measured by plethysmography) than total lung capacity (measured by helium dilution); this probably represents air trapped in cysts by peribronchiolar muscle hypertrophy.

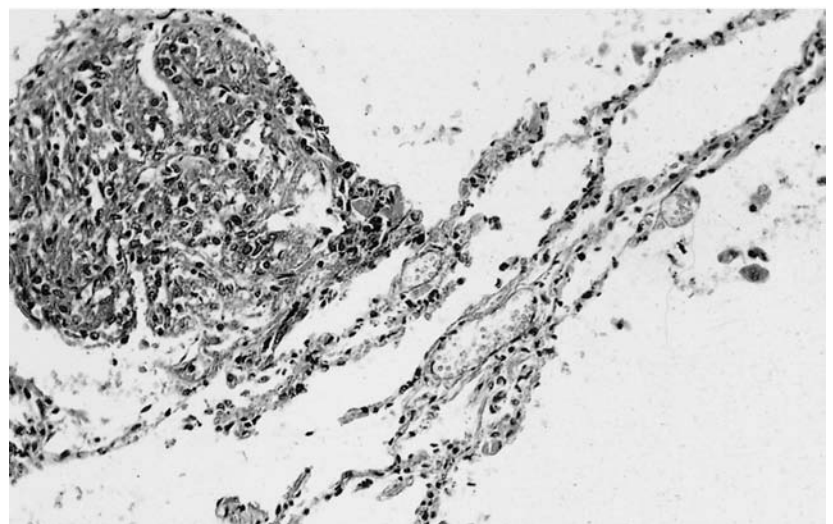
It is easy to miss the diagnosis of lymphangioleiomyomatosis because of the way it mimics emphysema. Chylous effusion and recurrent pneumothorax are clues, as is irreversible airways obstruction in a non-smoking woman. Lung biopsy shows the characteristic histology [158,159]; the lungs show diffuse cystic change with apparent intervening fibrosis. Microscopically, there is proliferation of spindle-shaped primitive smooth muscle cells around lymphatics throughout the lungs and pleura (Fig. 42.14). The airways obstruction is probably related to smooth muscle proliferation around bronchioles, leading

to air trapping and cyst formation. Rupture of these cysts causes pneumothorax, while haemoptysis is probably explained by capillary congestion due to perivenular muscle hypertrophy.

The course of the disease is one of progressive increase in dyspnoea over about 10 years, culminating in death from respiratory failure. In postmenopausal women it may be more slowly progressive, suggesting that it is hormone-dependent [157]; indeed progesterone and oestrogen receptors have been demonstrated on lung biopsy material [160]. The condition may deteriorate in response to oral contraceptives, and remit or progress less rapidly after oophorectomy [161] or treatment with progesterone [162]. Because of this hormone dependence, it has been suggested that the use of oral contraceptives may be an aetiological factor, although a case-control study has not supported this hypothesis [163]. If the diagnosis is



(a)



(b)

**Fig. 42.14** Necropsy specimen from lung of a woman who died apparently of emphysema but who proved to have lymphangioleiomyoma. (a) Dilated airspaces with proliferating smooth muscle in remaining alveolar walls (haematoxylin & eosin  $\times 50$ ). (b) A higher-power view showing the proliferating smooth muscle cells (haematoxylin & eosin  $\times 150$ ).

made in life, progesterone or oophorectomy would be appropriate treatment, especially if instituted at an early stage of the condition, and lung transplantation would now be an option.

### **Tuberous sclerosis**

This inherited disorder usually presents with mental retardation or slowly progressive dementia, associated with epilepsy and skin changes comprising patchy depigmentation, warty elevations on the face (adenoma sebaceum) and patches of elevated rough yellowish skin on the back (shagreen patch) [164]. It affects males and females equally. It may be associated with a nodular infiltrate on chest radiography that leads to cystic change. Pathologically the lesions are multiple leiomyomas, though probably based on blood vessels rather than lymphatics. Similar smooth muscle tumours are found in other organs. Sometimes the tumours are described as being angiomyolipomas, and this lesion has also been described in the lung in the absence of other evidence of tuberous sclerosis [165]. The pulmonary condition may be complicated by recurrent pneumothorax [166] or by pleural effusion [167]. The pathological condition overlaps with that of lymphangiioleiomyomatosis and airflow obstruction with reduced diffusing capacity are physiological features also [168]. In view of this, hormonal treatment has been tried in female patients with some limited evidence of response.

### **Arteriovenous malformations and telangiectasia**

(see also Chapter 50)

These lesions represent a developmental anomaly rather than a tumour and consist of abnormal connections between pulmonary artery and vein, probably due to persistence of the short fetal capillary anastomoses. Pathologically they appear as a thin-walled labyrinth of vessels connecting a rather dilated artery and vein [169,170]. Occasionally they may be supplied by more than one artery and there may be associated anomalies of pulmonary venous drainage.

#### **Clinical features**

Patients with this condition may present with one or several rounded radiological opacities [171]. In some cases there may be a fine diffuse nodularity of the lower zones, when the condition is known as pulmonary telangiectasia [172,173]. Discrete lesions, which may be single or multiple, are not necessarily associated with symptoms or signs [174]; the presence of these depends on the size of the shunt. If it is large, finger clubbing and cyanosis may be apparent and a systolic bruit, sometimes accentuated by inspiration, may be heard over the lesion [175]. In up to

half of all cases, evidence of hereditary telangiectasia (Osler-Weber-Rendu disease) elsewhere may be present [176], the patient having had nose or gastrointestinal bleeds and showing small telangiectases on tongue, face and lips (see Fig. 50.14). In pulmonary telangiectasia, the patient presents with cyanosis, finger clubbing and increasing breathlessness [172]. Faints or fits due to cerebral hypoxaemia may occur.

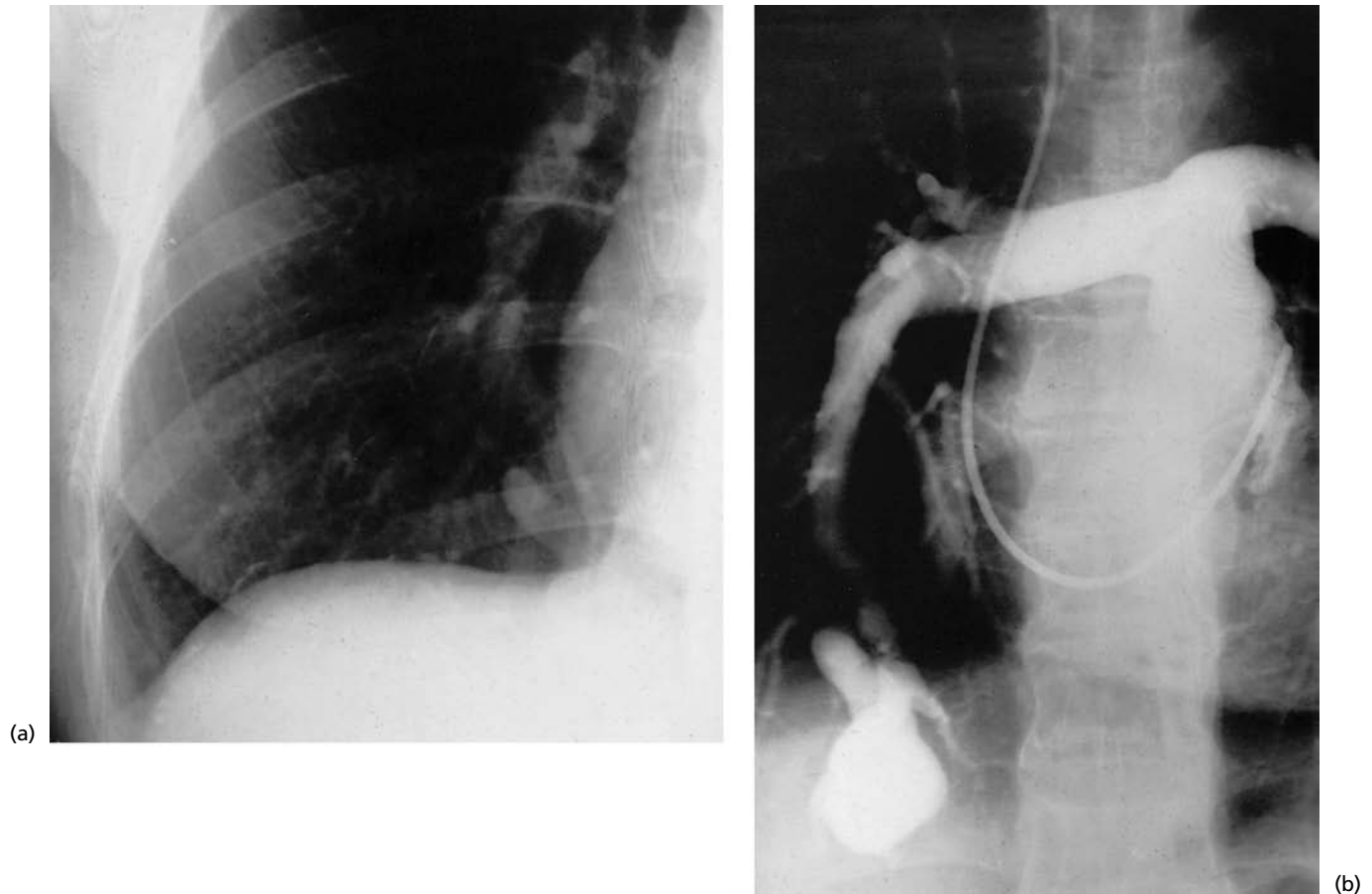
The discrete type of arteriovenous malformation may present at almost any age but is most frequent in the third decade and after. Telangiectasia is more frequently seen in young children, since it always causes cyanosis and symptoms, although the diagnosis may not be made until adult life. The radiological appearances of the discrete lesions are of rounded or lobulated shadows, usually in lower zones. The feeding and draining vessels may be apparent on the radiograph; if not, they can usually be demonstrated by tomography (Fig. 42.15). They gradually increase in size over several years. The diagnosis should be confirmed by pulmonary angiography, especially if removal is planned, as smaller lesions not seen on chest radiography may then become apparent [171]. Pulmonary hypertension is not normally present, because of low vascular resistance, but has been described [177]. In pulmonary telangiectasia the chest radiograph shows a diffuse lower zone nodularity that may be easily mistaken for pulmonary fibrosis (Fig. 42.16). The associated marked cyanosis and relative lack of breathlessness (relative to that of a patient with cyanosis at rest with pulmonary fibrosis) should alert the physician to the correct diagnosis. The nodular shadows may be quite small but tend to increase in size as time goes by. Pulmonary angiography demonstrates the lesions if they are large enough, although minute ones may not be seen.

The only physiological abnormality in patients with the discrete lesions may be slight hypoxaemia and failure of the arterial blood fully to saturate on breathing oxygen. With multiple lesions, a low carbon monoxide diffusing capacity is usual, due to diversion of blood from the pulmonary capillary bed. Paradoxically, in diffuse telangiectasia, breathing of 100% oxygen may lead to full saturation because oxygen is able to diffuse into the small abnormal vessels sufficiently rapidly [172]. On catheterization, dye curves do not show the two peaks of an intracardiac shunt but a decreased transit time with rapid reappearance of dye. Radiolabelled macroaggregates of albumin may be used to confirm the diagnosis in telangiectasia [173,178].

#### **Management and prognosis**

The solitary lesion should generally be removed [179,180], since the shunt increases progressively and complications such as brain abscess or bacterial infection of the angioma itself may occur. Before removal, angiography should be carried out to look for additional smaller lesions. Even if





**Fig. 42.15** (a) Penetrated film showing arteriovenous malformation in right lower lobe, in cardiophrenic angle. (b) Pulmonary arteriogram of the same patient.

these are undetected, there is a risk that other shunts may gradually become apparent after the operation and these in turn may need removal [172]. For this reason, surgery should if possible avoid resection of lung. If the lesions are multiple, as is the case in about 20% of patients, it may not be practicable to remove them and in such patients embolization with detachable balloons or coils passed through a catheter is now the treatment of choice (see Chapter 50) [172]. In the absence of such treatment these patients become progressively more cyanosed and breathless, eventually dying of the effects of hypoxaemia and high-output cardiac failure. Transplantation may be necessary in patients with telangiectasia [181]. While most such patients do not survive their fourth decade, the author has made the diagnosis for the first time in a patient of 58 whose symptoms dated back to childhood [182].

#### **Pulmonary capillary haemangiomatosis**

This is an exceedingly rare locally invasive tumour pre-

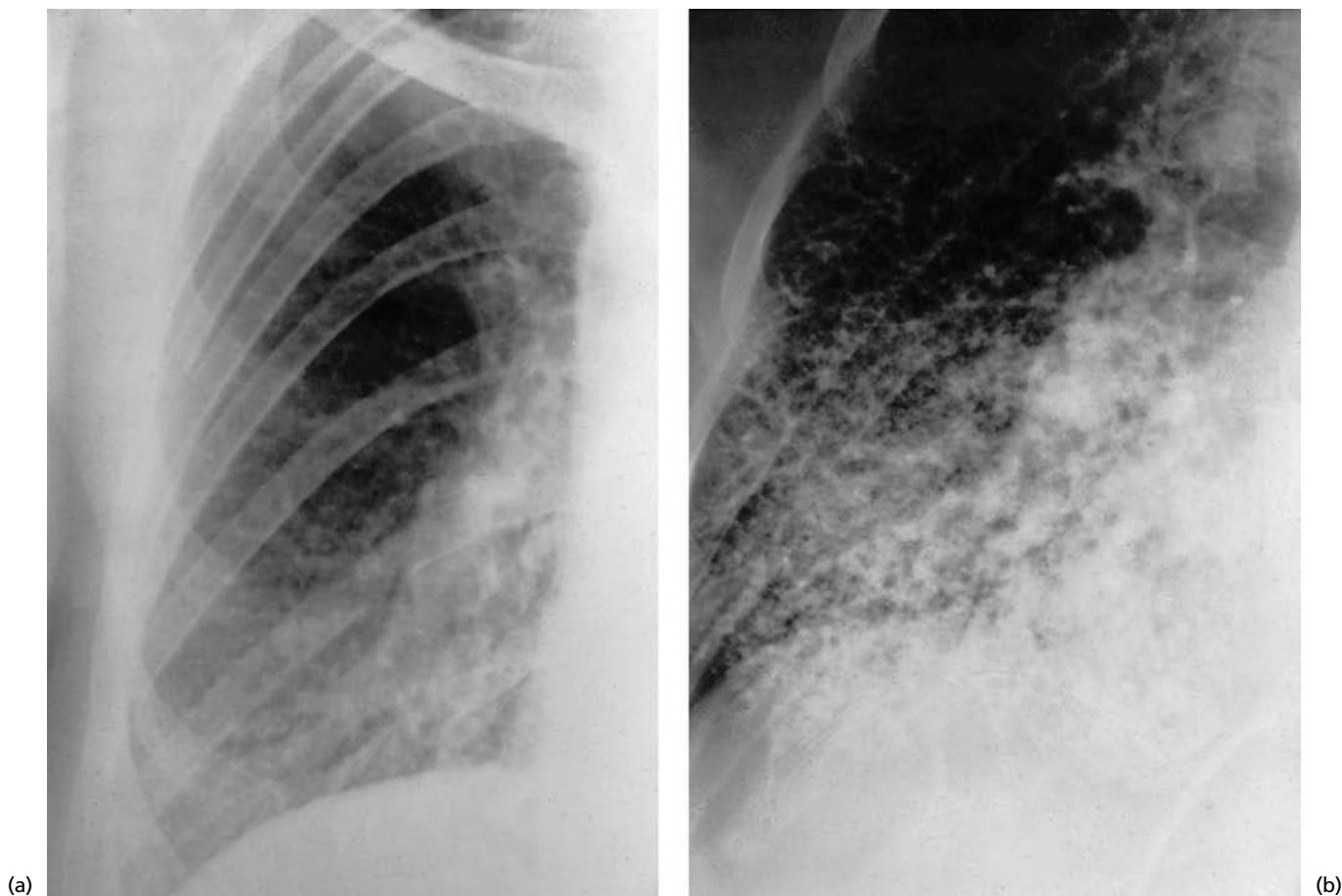
sented with progressive pulmonary hypertension, characterized pathologically by proliferation of thin-walled capillaries throughout the lungs [183]. It is progressive and fatal unless transplantation can be carried out.

#### **Pulmonary lymphangiectasis**

Primary cystic dilatation of pulmonary lymphatics may occur in children, either as part of a generalized disease of lymphatics or as a lesion confined to the lungs [184,185]. It may occur throughout the lungs, presenting as multiple cystic shadows on chest radiography, or be localized to one or several lobes. In this latter case, it may present as a hilar or intrapulmonary solid shadow or may mimic bronchiectasis. After surgical removal it can be seen to consist of dilated very thin-walled cysts filled with lymph. The cysts are adjacent to bronchi, veins, pleura and in interlobar septa and represent grossly dilated lymphatics. The cause of this congenital abnormality is not known.

#### **Pulmonary lymphangiomatosis**

This condition, analogous to capillary haemangiomatosis but characterized by overgrowth of anastomosing lymphatic vessels throughout the lungs, presents with breath-



**Fig. 42.16** (a) Chest film of right lower zone of cyanosed 58-year-old woman showing diffuse lower zone nodularity. (b) Angiogram of the same patient showing multiple minute arteriovenous malformations.

lessness in childhood, obstructive lung function, radiographic infiltrates and pleural effusions [186]. It runs a progressive course.

## **Tumours of muscle and connective tissue**

### **Leiomyoma and leiomyosarcoma**

The very rare leiomyoma originates in airway smooth muscle [187,188]. It may present as a peripheral tumour, when it has no specific features, or as a central bronchial or tracheal lesion, often polypoid or pedunculated. It tends to occur in children and young adults. Occasionally it has been removed by endoscopy [189], although surgical sleeve or wedge resection is to be preferred. Pathologically it consists of interlacing whorled smooth muscle cells and fibroblasts. On biopsy it may be difficult to distinguish from leiomyosarcoma, which is characterized by more mitotic figures and whose prognosis is related to the number of these [190]. Leiomyosarcomas present similarly

to benign leiomyomas, as incidental radiological findings when peripheral or with symptoms and signs of bronchial block when central. They may be removed surgically; in general, the larger they are at presentation, the worse the prognosis [190], although long-term cure has been reported in about 50% of cases after radical resection [187]. They appear not to be radiosensitive. Metastases occur and the prognosis is usually poor if the tumour cannot be resected. In assessing patients for surgery, care should be taken that the pulmonary tumour is not one of several metastases from a primary uterine sarcoma. Both leiomyoma and leiomyosarcoma have been reported in the trachea, presenting with signs of respiratory obstruction. They may be misdiagnosed as asthma. Resection with end-to-end tracheal anastomosis or with tracheal reconstruction with myocutaneous flaps has been associated with reported cures [191,192].

### **Rhabdomyosarcoma**

This rare tumour has been reported in bronchi, trachea and peripheral lung [193–195]. Its apparent striated muscle origin is presumably from either primitive pluripotential mesenchymal cells or displaced teratomatous muscle cells. It presents no specific clinical features and should be removed by radical resection where possible.

### **Fibroma and fibrosarcoma**

Benign fibroma of bronchus or lung is also an exceedingly rare tumour with no special clinical features [190,196]. Pleural fibroma, which is a benign mesothelioma, is discussed in Chapter 43. Fibrosarcoma has also been described, arising in bronchus, lung or pulmonary artery [197]. It may be difficult to distinguish pathologically from leiomyosarcoma.

### **Lipoma and liposarcoma**

Lipomas are very rare tumours that may occur in trachea or bronchi [198,199]. They may be pedunculated and produce obstruction or arise deep in the bronchial wall and present as radiological shadows. They consist of mature lipocytes surrounded by fibrous trabeculae. Liposarcoma is a highly malignant tumour, usually derived from soft tissues, and has been reported in the mediastinum [200], pericardium [201] and trachea [199] but not so far in bronchus. It commonly metastasizes to the lung from elsewhere. It may consist of a mixture of well-differentiated fat cells and poorly differentiated lipoblasts in a myxoid stroma, or of anaplastic bizarre giant cells with some lipoblastic differentiation. It invades locally and spreads by metastasis.

### **Other connective tissue tumours**

Other tumours have been described occasionally in the literature. These include benign chondromas [202], which may be confused with chondromatous hamartomas, chondrosarcomas [203] and myxoma [204]. Fibroma and myxoma may calcify.

Carney's triad is the name given to the coincidence of pulmonary fibromas, leiomyosarcoma of stomach and functioning paraganglionoma [205,206]. The lung lesions are benign, and may be single or multiple. If one is unaware of the syndrome, as is probably the case with most doctors, the lung lesions may be mistaken for metastases from the stomach. If the lung and stomach tumours are found, tests should be carried out for the third component, which may cause problems during anaesthesia. Removal of the stomach tumour, sometimes together with metastases, has been attended by prolonged remission so a radical surgical approach seems justified [207]. Patients have been described in whom only two of the three components of the triad have been found, and one patient where the sarcoma was in the duodenum [208]. The syndrome appears to occur predominantly in young females.

### **Tumours of neural tissue**

Neural tumours may be classified as neurilemmoma (arising from the Schwann cell), neurofibroma (from the

nerve sheath), ganglioneuroma (from the neurone) and their malignant counterparts neurosarcoma and neuroblastoma. Mixed forms occur and tumours may show transitional features between benign and malignant types; histopathological diagnosis may therefore be difficult. In addition, tumours may arise in paraganglion cells, i.e. pheochromocytoma and chemodectoma.

Neurilemmoma, neurofibroma and neurosarcoma are exceedingly rare tumours in the trachea and bronchi [209,210], though they are the commonest tumours of the posterior mediastinum (see Chapter 49). Neurofibroma may be seen as part of von Recklinghausen's syndrome of multiple neurofibromatosis. Chemodectomas or paragangliomas occur in the posterior mediastinum and may be responsible for causing hypertension [211]. They have been described occasionally as occurring within the lung in association with the pulmonary artery [212]. Multiple minute (0.2 cm) tumours, similar on light microscopy to chemodectomas, have been seen within the lung as an incidental finding at postmortem, although their significance and histogenesis is unclear [213].

## **Tumours of mixed-cell origin**

### **Teratoma**

Intrathoracic teratomas are usually seen in the mediastinum (see Chapter 49). They are tumours derived from the three primitive germ layers and may contain a variety of tissues, including hair, skin, bone, muscle and teeth. Glandular tissue may actively secrete hormones. The benign type is often called a dermoid cyst. Malignant change occurs in up to 20% of teratomas, when one or more cell lines show poor differentiation and pleomorphism. Often trophoblastic tissue is predominant, the tumour taking on the characteristics of a choriocarcinoma.

Both benign and malignant teratomas have been described in the lung and, very occasionally, in the bronchus [214,215]. Their clinical characteristics are those of any slow-growing pulmonary tumour [216], with the additional possibilities of complications such as necrosis due to pancreatic hormone secretion or expectoration of components such as hair. Because of their potential for malignant change, and also because diagnosis is rarely made before excision, treatment is surgical removal. Malignant tumours in the mediastinum have also shown good response to chemotherapy in combination with surgery [217].

### **Hamartoma**

Hamartoma has usually been regarded as a developmental anomaly [218–221]; however, recent genetic analysis of a series of such lesions has shown an abnormal karyotype, suggesting that they are neoplastic [222]. It is a lesion in

which the normal components of the organ are combined in a disorganized manner. Pathologically, pulmonary hamartomas are usually small 1–3 cm lesions containing predominantly cartilage, with epithelium, fibrous tissue and fat. Calcification occurs frequently and on radiography they appear as well-demarcated, dense, round peripheral shadows often with a central dot of calcium (Fig. 42.17). Though usually single, multiple hamartomas may occur and give rise to diagnostic difficulties [223]. Multiple lesions may also be a feature of tuberous sclerosis and have been described in the trachea as an incidental finding at autopsy [224]. Cystic appearances may be due to deposits of fat within the lesion [225], and multiple cavitating tumours have been described that mimic metastases [226]. They may grow slowly and very occasionally reach a large size. They occur predominantly in the fourth decade, although they may be seen at any age, and are more common in males than females [219,227].

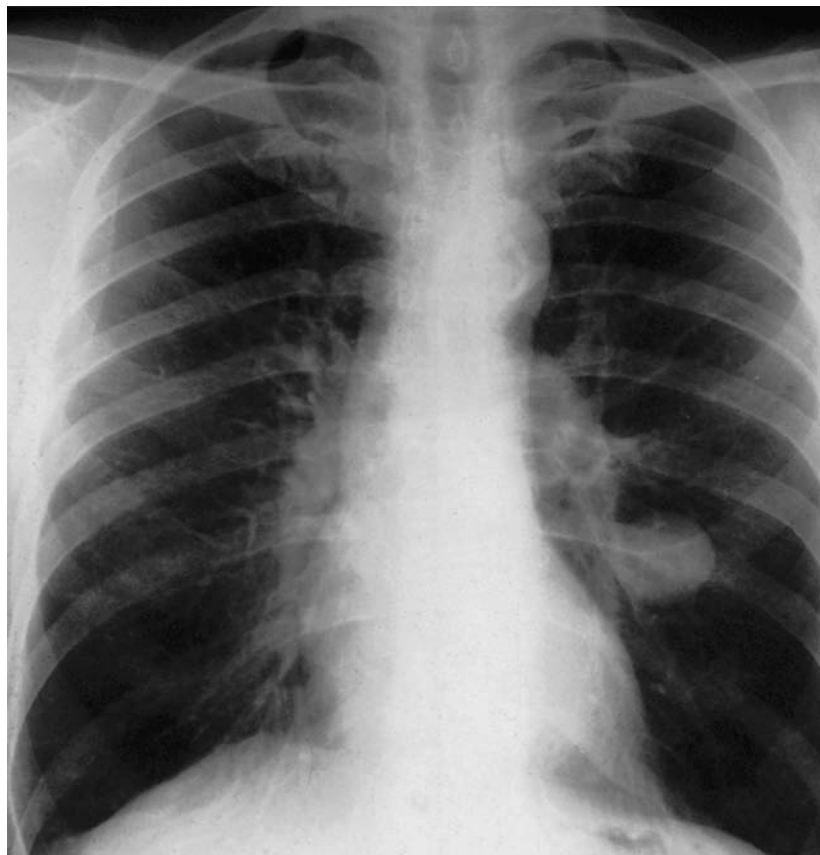
Less commonly, the predominant tissue in a hamartoma is smooth muscle [225,228,229]. These fibroleiomyomatous hamartomas may occur as a diffuse pulmonary infiltrate, giving the appearance of honeycomb lung, or as a localized lesion; the latter usually presents radiologically as an ill-defined subpleural shadow. The tumour may be intrabronchial, giving rise to collapse or distal infection. In

contrast to the chondromatous type, fibroleiomyomatous hamartomas are more common in women [220].

If a hamartoma is diagnosed with confidence, on the basis of its presence on old radiographs, slow growth and central calcification, the patient may be spared surgery since malignant change has been described only rarely [230]. Indeed there is some doubt that it ever occurs in true hamartomas [1]. More usually, however, there is sufficient clinical doubt for surgery to be justified; the tumour has a characteristic hard feel and can often be removed without resection of lung tissue. The finding of a fibromatous hamartoma should bring to mind the possibility of Carney's triad; in one series of 65 resections this was found in two, while in eight an associated carcinoma was found [231].

### Carcinosarcoma and blastoma

These tumours contain malignant cells derived from both epithelial and connective tissue [232,233]. Their histogenesis is obscure. Blastomas are regarded as tumours that contain cells of fetal type, whereas carcinosarcomas are derived from adult cells. In children the tumour is regarded as highly malignant but responsive, at least in the short term, to combination chemotherapy [234,235]. Their histological features are of interest to pathologists



**Fig. 42.17** Typical smoothly outlined, dense, spherical appearance of hamartoma.

[236], while from a clinical point of view they behave like other bronchial carcinomas; metastasis occurs and may be of single or both cell types. Treatment is by surgery if possible, usually combined with chemotherapy.

### Metastatic tumours in the lung

Any malignant tumour, including bronchial carcinoma, may metastasize to the lung. Clinically, it is helpful to recognize several different patterns of metastasis, as this may be of assistance in differential diagnosis or planning treatment. These patterns include solitary metastasis, multiple cannonball lesions, diffuse nodular infiltration, lymphangitic carcinomatosis, endobronchial metastasis and carcinomatous embolization. Metastasis to hilar nodes bilaterally may also be seen.

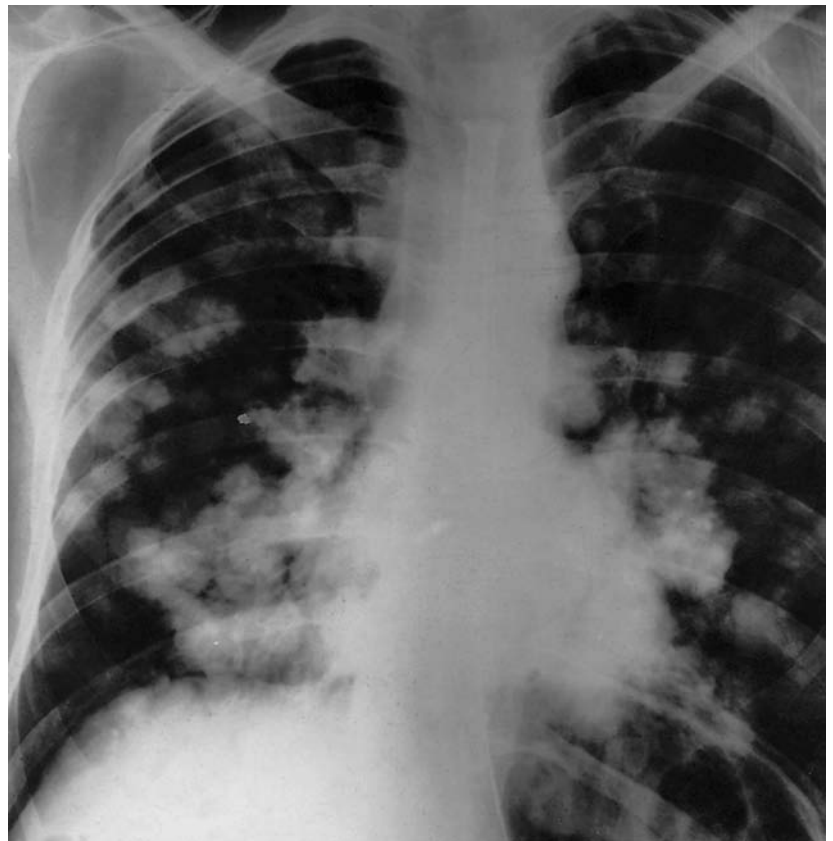
#### Solitary metastasis

This lesion presents as a peripheral tumour, usually spherical and well demarcated from surrounding lung [237]. It may cavitate and clinical differentiation from primary tumour is difficult, especially as it may be the presenting feature of an occult neoplasm elsewhere. The most common sites of origin of the tumour are large bowel, breast, cervix, kidney and sarcomas. In the absence of metastases elsewhere, and if the primary tumour is

resectable, there may be a case for surgical removal [237,238], although it is never certain whether reported long-term survival following this procedure owes more to the surgery or the biological nature of the tumour. Other tumours may respond to radiotherapy or chemotherapy.

#### Multiple cannonball tumours

Multiple spherical lesions of many different sizes are characteristic of metastatic deposits (Fig. 42.18), though similar appearances may occur occasionally in sarcoidosis, tuberculosis, hydatid and fungal disease, multiple hamartomas and Wegener's granulomatosis. Cannonball metastases originate particularly from hypernephroma, seminoma, sarcoma, colon carcinoma, choriocarcinoma and breast carcinoma. Cavitation, calcification or haemorrhage may occasionally occur in these metastases; when necrosis occurs in them adjacent to pleura, they may cause pneumothorax. It is not normally necessary to take further diagnostic steps, since the primary tumour is usually clinically evident. If it is not, care should be taken to exclude seminoma, and prostatic and breast carcinoma, which may respond to appropriate combinations of chemotherapy, hormone treatment and radiotherapy. In patients where there is no obvious primary tumour, biopsy of a lesion is justified in order to exclude rare granulomatous and infective causes.



**Fig. 42.18** Multiple cannonball metastases from oesophageal carcinoma. Note the oesophageal tube.

### Diffuse nodular infiltration

Multiple small nodules, usually less than 5 mm in size but varying from pin-point size upwards (Fig. 42.19), occasionally occur as a manifestation of metastatic spread, particularly from breast, stomach, thyroid and colonic carcinomas. A similar appearance may occur in diffuse alveolar cell or pulmonary adenocarcinoma. The patient may present with shortness of breath, although this is initially not so severe as with lymphangitic spread. Again, it is desirable to exclude those primary sites that may be responsive to chemotherapy or hormone treatment. Spontaneous regression after removal of the primary tumour or temporary regression after corticosteroid treatment may occur very occasionally.

### Lymphangitic carcinomatosis

Lymphangitic spread of carcinoma occurs particularly from breast, stomach, pancreas and prostate, as well as from bronchial carcinoma itself. The patient presents with increasingly severe dyspnoea, cough and evidence of general ill-health. Auscultation of the lungs may be normal or show repetitive inspiratory crackles. The radiograph shows multiple small nodular and linear shadows and Kerley's lines, particularly in the lower zones (Fig. 42.20). The course is usually rapidly downhill, though

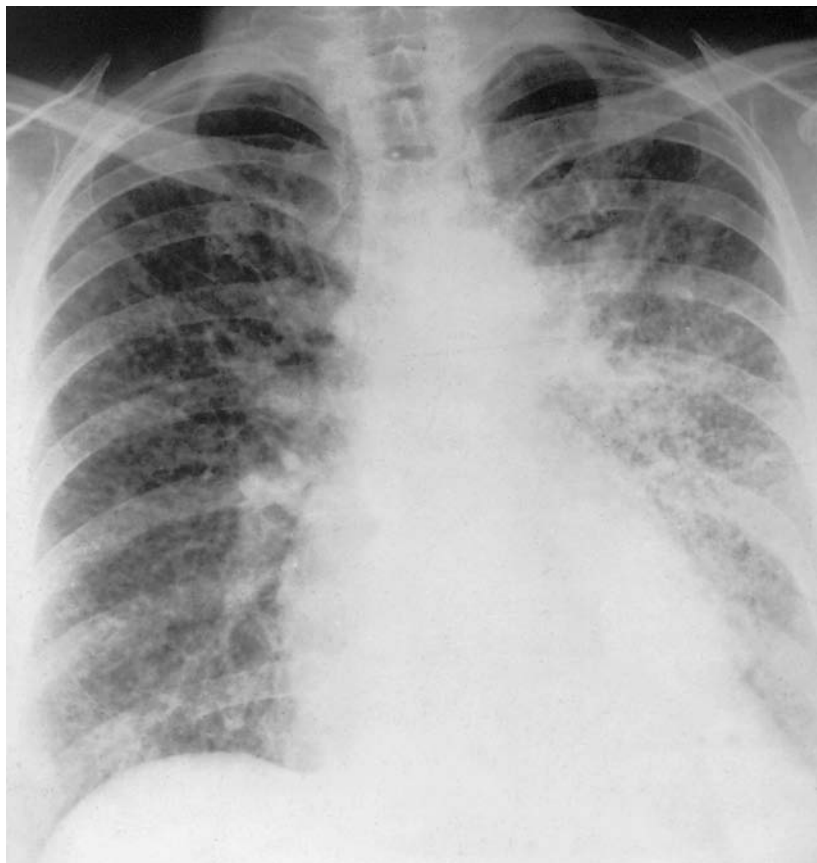
remission has been described with chemosensitive or hormone-dependent tumours [239]. Partial relief of symptoms may occur on treatment with corticosteroids, diazepam or opiates.

### Endobronchial metastases

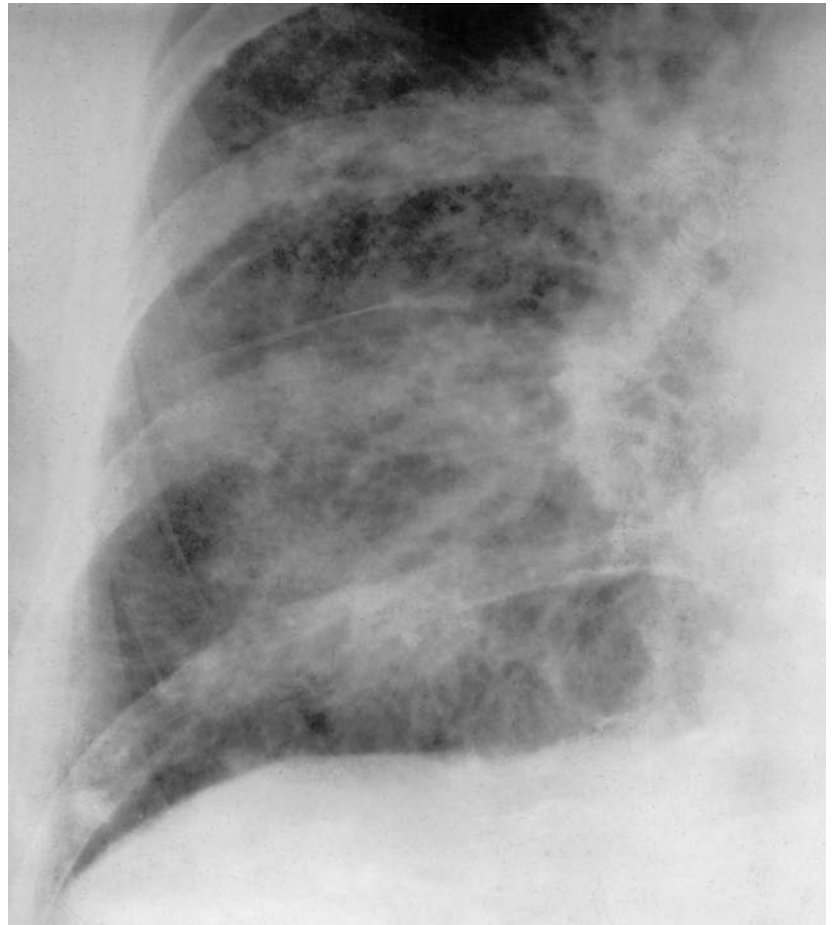
Endobronchial metastasis is much less common than the patterns described above. It occurs particularly in breast, kidney, colon and cervical cancer [240]. In its mode of presentation it mimics primary bronchial carcinoma [241,242] and most cases described in the literature are of patients subjected to lobectomy or pneumonectomy on this account. The finding of clear-cell tumour on bronchial biopsy or cytology should always arouse suspicion of a renal primary. Indeed, endobronchial renal metastases may be expectorated by the patient [242]. The prognosis depends on the biological behaviour of the tumour, although long-term survival with or without resection may occasionally occur.

### Carcinomatous embolization

Very rarely a patient may present with increasing dyspnoea, a clear chest radiograph and reduction in  $PaO_2$  and diffusing capacity. In such circumstances, multiple pulmonary emboli should be considered; occasionally these



**Fig. 42.19** Diffuse fine nodular infiltrate due to metastatic breast adenocarcinoma.



**Fig. 42.20** Lymphangitic spread of breast carcinoma. Note irregular pulmonary infiltration and Kerley B lines.

are due to blood-borne tumour cells rather than thrombi. This syndrome has been described with prostatic, breast, stomach, colonic, pancreatic, hepatic and cervical cancers and with choriocarcinoma [243,244]. The lung scan shows features typical of multiple emboli. The diagnosis is usually made at postmortem, but would probably require open lung biopsy in life.

### Bilateral hilar node metastasis

The common causes of bilateral hilar node enlargement are sarcoidosis, tuberculosis in Asians, and lymphoma. Oat-cell carcinoma of bronchus may metastasize bilaterally, and this may also be an occasional feature of cancers of kidney, head and neck, testicle and breast, and of malignant melanoma [245,246].

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# DISEASES OF THE PLEURA

ANTHONY SEATON

The two layers of the pleura (visceral and parietal) that surround the lung are described in Chapter 1. Only the parietal layer has a somatic nerve supply, derived from intercostal and diaphragmatic nerves, and is therefore sensitive to painful stimuli. In almost all instances of disease of the pleural membranes and of the potential cavity that they enclose, the cause is in the lung or elsewhere in the body, although in a few instances primary pleural disease may occur. This chapter discusses the main diseases that affect the pleura, with the exception of empyema (see Chapter 14) and pneumothorax (see Chapter 44).

## Physiology of the pleura

The pleura transmits the force generated by the respiratory muscles to the lungs [1]. During normal respiration there is therefore a pressure negative to atmosphere (about  $-0.66$  kPa at functional residual capacity) within the pleural space. This would tend to suck capillary fluid and gas from surrounding tissue into the space if it were not for other balancing factors. In the case of fluid, there is a hydrostatic pressure difference between parietal pleural capillaries, supplied by systemic arterial vessels (about 4 kPa), and visceral pleural capillaries, supplied by pulmonary arterial vessels (about 1.5 kPa). Plasma oncotic pressure is the same in both sets of capillaries (about 4.66 kPa), while pleural osmotic pressure is only about 0.8 kPa, since little protein is able to escape from the adjacent healthy capillaries. Thus there is a net force that drives fluid from parietal capillaries to pleural space ( $-0.66 - 4 - 0.8 + 4.66 = -0.8$  kPa); similarly, a net force drives pleural fluid into visceral capillaries and lymphatics ( $-0.66 - 1.5 - 0.8 + 4.66 = +1.7$  kPa). There is therefore a regular transfer of low-protein fluid from parietal to pleural space, although recent evidence suggests that reabsorption is not, as was thought, via the visceral pleura but through lymphatic vessels opening into the parietal pleura. In the case of gas, any that gains access to the pleural space is at atmospheric minus pleural pressure, i.e.

$101.1 - 0.66 = 100.44$  kPa. In contrast, the partial pressure of gas within the pleural capillary blood is some 5.3–6.6 kPa below atmospheric pressure, and thus there is a driving force of about 5.3 kPa available to resolve any pneumothorax.

The pleural fluid is in a dynamic state, 30–75% of the water being turned over every hour [2]. This is accelerated by increased lung movements, such as during exercise. Protein and particles are turned over much less rapidly, being absorbed by lymphatics only [3,4]; stomata leading into lymphatics have been demonstrated over the lower mediastinal, chest wall and diaphragmatic parietal pleura [5]. These, together with the valves of the lymphatic vessels, ensure transport of protein and particle-containing fluid from the pleural space. Any disease that causes inflammatory or neoplastic change in the parietal pleura is likely to decrease protein reabsorption and therefore alter the fluid hydrodynamics in such a way as to increase the size of the effusion.

It has generally been assumed that the pleural space is lubricated by a thin film of serous fluid, and it has been shown that a few millilitres of this fluid can be obtained from the normal space. However, it has been suggested on physical grounds that this would be unlikely to provide adequate lubrication and that a surfactant would be more efficient; such surface-active phospholipids have been identified in pleural fluid [6].

## Dry or fibrinous pleurisy

### Clinical features

Pleural pain is characteristically sharp and associated with inspiration, coughing and movements of the chest wall. When it is severe the patient breathes in short grunts and may attempt to splint the appropriate part of the chest by holding it or lying on it. The site of pain can usually be localized quite closely and is most frequently in the lower posterolateral parts of the chest. As the pleurisy improves, or sometimes from the beginning when the upper chest is

involved, the pain may be more of an ache though still associated with movement and breathing.

The diagnostic sign of pleurisy is a rub, of a creaking superficial nature, usually localized closely to the site of the pain. At its most marked this is unmistakable and heard in inspiration and expiration; however, it may be confined to part of the inspiratory cycle and at times may be difficult to distinguish from pulmonary crackles. As the pleurisy improves, it tends to become less obvious but may persist after the pain has gone and in occasional patients a loud rub may be present indefinitely. Indeed, pleural rub may sometimes be heard in patients with no pain and pleural pain may occasionally occur without a rub.

Because of the innervation of the pleura, pleuritic pain may be referred to the shoulder tip via the phrenic nerve when the area over the central tendon of the diaphragm is involved or to the upper abdomen when the area over the peripheral diaphragm is affected. In the latter case this may cause diagnostic difficulties unless the relationship to respiration is recognized, especially as a rub is usually not audible. The pain of pleurisy is due to inflammation of the parietal pleura and is presumably provoked by stretching. The rub arises from friction between the two pleural surfaces when their normal lubricating mechanism is impaired by the inflammatory exudate.

### Causes

Dry pleurisy may be due to chest trauma, usually associated with rib fracture. Apart from this, the most common cause is infection of the underlying lung; recurrent pleurisy is usually associated with recurrent infection of bronchiectatic lung. Bornholm disease, collagen diseases (especially rheumatoid and systemic lupus) and pulmonary infarction are other not infrequent causes. Tumours invading the chest usually cause a persistent, continuous pain but may occasionally present with pleurisy. Rarely dry pleurisy may be associated with asbestos exposure (see below), tuberculosis and subdiaphragmatic abscess.

### Bornholm disease

Bornholm disease is named after the Danish island where an early epidemic was described and is also known as epidemic pleurodynia, epidemic myalgia or, colloquially, the devil's grip [7]. It is caused by an enterovirus, usually Coxsackie B but occasionally Coxsackie A or an echovirus [8]. In one study of an outbreak in an American football team it has been suggested that spread may have been due to contamination of a common drinking source by one of the players [9]. It has a short incubation period (3–5 days) and may occur in late summer and autumn epidemics, although sporadic cases are frequent. The disease is most

common in children and young adults, usually starting with fever and upper respiratory symptoms followed by the characteristic pain. Typically this occurs in the chest or upper abdomen and may be very severe. It is worsened by movement and respiration and associated with tenderness of intercostal muscles. Pleurisy, sometimes referred to the shoulder, is common and a pleural rub is sometimes audible. Pericarditis with rub may also be present. Fever and a raised erythrocyte sedimentation rate are occasionally present at this stage but there are no characteristic haematological changes. The chest radiograph is usually normal, though a blunted costophrenic angle may be present. There may be diagnostic confusion with early herpes zoster and the eosinophilia–myalgia syndrome associated with L-tryptophan therapy.

The illness usually lasts about a week, the pain gradually subsiding. Other organs, such as the heart, central nervous system or testes, may occasionally be involved, resulting in a more prolonged course. The disease has a tendency to relapse, usually in a milder form, over several weeks. The diagnosis is made from the characteristic clinical features and may be confirmed by viral culture of stools or throat swabs and by a rise in the appropriate viral antibodies. There is no specific treatment but analgesics are often needed to control the pain.

### Recurrent polyserositis

This condition, also known as periodic disease or familial Mediterranean fever, is an autosomal recessive genetic disease afflicting predominantly people of Jewish, Arabic, Armenian and Turkish origins [10,11]. The genetic defect has been shown in several families to be on the short arm of chromosome 16 [12,13], although the biochemical defect remains unknown. The disease is characterized by recurrent fever and inflammation of serous membranes. Attacks occur at irregular intervals, from several days to several years. The disease almost always manifests itself in childhood and very rarely after the age of 40, and there is often a history of similar illness in other members of the family, especially siblings. It presents most commonly with peritoneal inflammation that mimics a ruptured appendix, and the patient has often been subjected to laparotomy. Pleurisy mimicking Bornholm disease is another common presentation, as is acute inflammation of one or two large joints. The pain is accompanied by fever, tachycardia and often chills, and there is often a moderate neutrophil leucocytosis during attacks. Effusions into large joints and erysipelas-like rashes on the legs may occur. A similar periodic syndrome associated with hyperimmunoglobulinaemia D has been described in European families in which prolonged myositis is more frequent and serositis and amyloidosis rarer [14]. There is no diagnostic test, though immunological changes such as circulating immune complexes and raised immunoglobulins have

been described; amyloidosis of the kidneys is the most serious complication, occurring in 0–20% in different series, and may lead to renal failure. Acute attacks of the syndrome resolve spontaneously within 12–48 h in almost all cases, and apart from the renal complication the condition is generally regarded as having a benign course.

Treatment of the acute attack relies on the use of analgesics. Recurrent episodes may be prevented by regular use of colchicine [15] and there is some anecdotal evidence that this may help to prevent the long-term renal complication of amyloidosis [16].

### Diagnosis and management

The pain of pleurisy needs to be differentiated from that due to chest wall causes, such as rib fracture, intercostal muscle pain and Tietze's syndrome, and that due to neurogenic causes, such as herpes zoster and root compression. The presence of a pleural rub is helpful, although this may be heard sometimes following rib fractures. A chest radiograph is frequently useful in showing the primary lung condition. If this is normal, or if it only shows a small amount of fluid in the costophrenic angle, it is important to consider the possibility of pulmonary embolism, and further examination of the legs together with isotopic scanning may help in coming to a therapeutic decision (see Chapter 25). If this diagnosis is considered unlikely, it is reasonable to treat the patient with adequate analgesics and await developments; in most such cases, the pleurisy settles within a week. Paired blood samples taken in the acute and convalescent phases may be tested for viral antibodies. When the chest film is abnormal, further investigation or treatment may be necessary; for example pneumonic change would indicate bacteriological investigation and antibiotic treatment, while evidence of bronchiectasis may lead to consideration for surgery if it is giving rise to recurrent episodes of infection and pleurisy.

The pain of pleurisy is usually controlled by simple analgesia and the patient adopting a comfortable posture (often lying on the affected side). Severe pain may require opiates, although dramatic relief may often be obtained by raising intradermal wheals of local anaesthetic in four or five places around the site of maximum pain. This relief is often prolonged and the procedure, if successful, may be repeated periodically; it is particularly useful when the patient's respiratory condition makes the use of opiates inadvisable.

## Pleural effusion

### Clinical features

The effects of accumulation of fluid in the pleural space depend on the cause and on the amount of fluid. Small

effusions are often symptomless; even very large effusions, if they accumulate slowly, may cause little or no discomfort to the patient. If the effusion is due to inflammatory disease, it often starts with pleuritic pain that may be relieved as the fluid accumulates. The usual symptom of a large effusion is shortness of breath, often accompanied by a dull ache on the affected side; this is especially likely if the effusion is due to malignant disease of the pleura. Recurrent dry cough is frequently present, especially if the fluid has accumulated quickly.

The findings on physical examination are also dependent on the size and site of the effusion. Since most effusions are in the dependent part of the pleural space, the signs of diminished movements, dull percussion note and distant or absent breath sounds are found here. Bronchial breath sounds or aegophony (a nasal or bleating quality of transmitted voice sounds) may be heard immediately above an effusion. Large effusions displace the mediastinum to the opposite side unless there is underlying pulmonary collapse or associated pleural fibrosis. Although the signs of a large effusion are very characteristic, those of a smaller one may be mimicked by lobar collapse, pleural tumour or pleural fibrosis, and it is often difficult to assess the presence or absence of collapse or consolidation beneath an effusion. Careful clinical examination of the mediastinal position may help, as may asking the patient to change position in order to test whether the effusion moves.

### Radiological features

Free pleural fluid in small amounts (about 100 mL) may be seen as blunting of the costophrenic angle on posteroanterior or lateral films. Larger effusions are most dense at the base, obscure the diaphragm and show decreasing density towards the top. As the fluid rides up around the edges of the lung, attenuation of the X-rays decreases and the radiographic appearances suggest that the effusion is higher in the axilla than anteriorly or posteriorly (Fig. 43.1). However lateral films show the level to appear higher posteriorly and anteriorly, indicating that in fact the top of the effusion is horizontal, only showing radiographically where the X-rays have to traverse sufficient depth of fluid [17]. If there is doubt about the presence of fluid radiographically, a lateral decubitus film may be taken to show the shift of the effusion to the mediastinum or lateral chest wall. This may help particularly in differentiating a small effusion from pleural thickening.

Sometimes effusions may be encysted and cause diagnostic difficulties. Interlobar effusions may mimic tumour (Fig. 43.2); they occur particularly in cardiac failure and their clearance following diuretic treatment has given rise to the term 'vanishing pulmonary tumour' [18]. Subpulmonary effusions may not appear to rise into the axilla and may look like an elevated diaphragm. On the left, the





**Fig. 43.1** Chest film showing left pleural effusion.

stomach air bubble allows the distinction to be made, but on the right it may be more difficult. A lateral decubitus film or ultrasound investigation may be necessary. Other encysted effusions may occur anywhere in the pleural space, especially following pleural infection or pulmonary surgery, and may look like tumours. Serial radiographs often allow the diagnosis to be made and ultrasound may be helpful [19]. Fluid together with air (hydropneumothorax) shows the characteristic fluid level (Fig. 43.3). This appearance may be mimicked by fluid in a lung cyst or bulla, especially as hydropneumothorax may often be encysted following partial resolution of the pneumothorax.

### Causes

It is convenient to differentiate transudates from exudates when discussing the causes of pleural effusion.

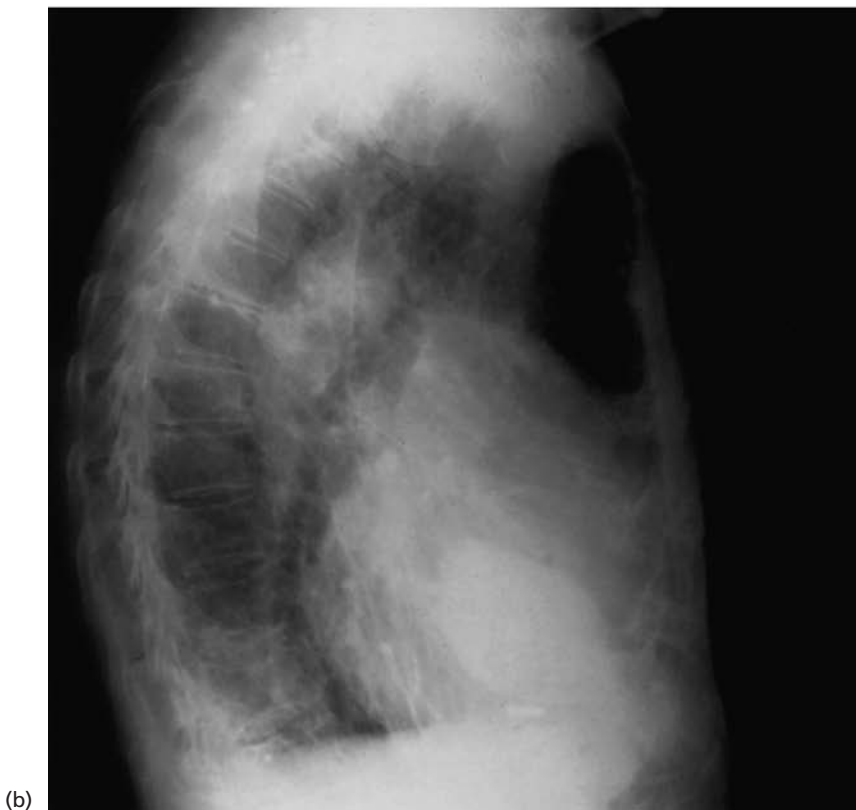
### Pleural transudates

The causes of these are given in Table 43.1. By far the most common is congestive cardiac failure [20]; this effusion is often unilateral initially, usually on the right side. In severe failure it is usually bilateral, cardiac failure being the most frequent cause of bilateral effusions. The mechanism is increased transudation of fluid from the lung, partly as a result of increased capillary pressure but also because of increased pulmonary interstitial

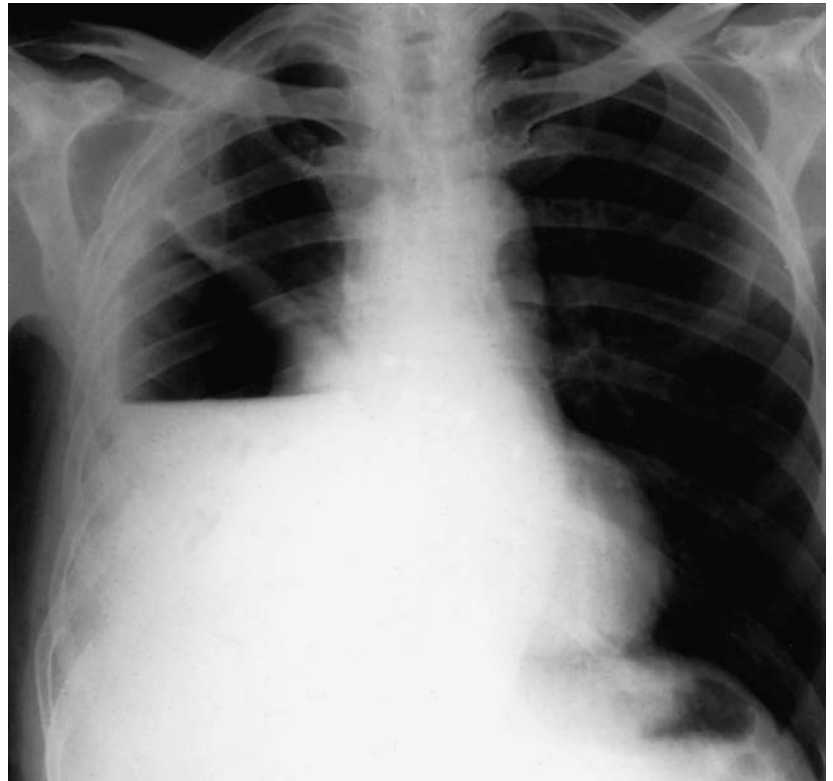
**Table 43.1** Causes of pleural transudates.

<i>Increased hydrostatic pressure</i>
Congestive cardiac failure
Constrictive pericarditis
Pericardial effusion
Constrictive cardiomyopathy
Massive pulmonary embolism
<i>Decreased capillary oncotic pressure</i>
Cirrhosis
Nephrotic syndrome
Malnutrition
Protein-losing enteritis
Small bowel disease
<i>Transmission from peritoneum</i>
Any cause of ascites
Peritoneal dialysis
Liver transplantation
<i>Increased capillary permeability</i>
Small pulmonary emboli
Myxoedema
<i>Obstructed lung lymphatics</i>
Lung transplantation

pressure [21]. The diagnosis is usually obvious from associated clinical features, this being one situation when diagnostic aspiration may be avoided, at least until after a trial of diuretic treatment. An important point



**Fig. 43.2** (a) Rounded right lower zone lesion in patient with congestive heart failure. (b) Lateral view shows the lesion to be fluid in the oblique fissure.



**Fig. 43.3** Right hydropneumothorax in patient with mesothelioma. The tumour can be seen under the ribs above the fluid level.

in radiological diagnosis is that bilateral effusions are rarely due to cardiac failure if the cardiac size is not increased (constrictive pericarditis being an exception), in which case other causes such as pulmonary embolism, neoplasm and occasionally hypoalbuminaemia need to be considered.

Pulmonary embolism may cause pleural transudates, although blood-staining occurs in about one-quarter of cases and exudates are found in about two-thirds [22]. Again, these effusions are often bilateral but usually quite small [23]. They may be associated with typical dome-shaped or linear (not, as is commonly believed, wedge-shaped) pulmonary shadows, although the radiological appearances are often quite non-specific and further investigations are usually necessary. Transudates due to hypoproteinaemia occur in cirrhosis, nephrotic syndrome and protein malnutrition. They may be diagnosed by their associated features. Constrictive pericarditis, due to old tuberculosis, rheumatoid disease or malignant infiltration of the pericardium, and constrictive cardiomyopathies are usually also associated with ascites; often this fluid tracks up into the right pleural space through small defects in the diaphragm [24,25], producing a large unilateral effusion. Indeed, a left-sided pleural effusion in hypoproteinaemia is usually due to some other cause and should be investigated accordingly. This same mechanism is responsible for the occasional right pleural effusion occurring during peritoneal dialysis [26].

Meigs' syndrome is the rare association of a benign ovarian fibroma with ascites and accompanying, usually right-sided, pleural effusion [27]. In fact ovarian fibroma is rarely associated with serous transudates and the finding of effusions in association with ovarian disease usually leads to the realization that they are exudates and that the tumour is malignant. In Meigs' syndrome it is likely that the pleural effusion has tracked through the diaphragm from the peritoneum.

Finally, myxoedema may cause pleural effusion, either as a consequence of ascites or pericardial effusion or, very rarely, as a direct effect on pleural capillary permeability [28]. This condition responds to replacement thyroxine therapy; the metabolic basis of the alteration in permeability of the capillaries of the serous membranes is unclear.

### **Pleural exudates**

The main causes are given in Table 43.2. Of these, the most common are metastatic tumour, infections and pulmonary embolism.

### **Neoplasms**

A primary pleural tumour is almost always a mesothelioma. Metastasis occurs commonly from bronchial, breast, stomach and ovarian carcinoma [29]. Almost any

**Table 43.2** Causes of pleural exudates.

<i>Neoplasms</i>
Mesothelioma, very rarely pleural sarcoma
Metastases
Lymphoma
<i>Infections</i>
Pneumonia, abscess
Tuberculosis
AIDS
Hantavirus syndrome
Fungal and actinomycotic disease
Subphrenic abscess
Hepatic amoebiasis
<i>Immune disorders</i>
Post-myocardial infarct/cardiectomy syndrome
Rheumatoid disease
Systemic lupus erythematosus
Wegener's granulomatosis
Rheumatic fever
<i>Abdominal diseases</i>
Pancreatitis
Uraemia
Other causes of peritoneal exudates
<i>Pulmonary embolism and infarction</i>
<i>Other causes</i>
Sarcoidosis
Drug reactions
Radiation therapy
Asbestos exposure
Recurrent polyserositis
Yellow nails syndrome
Oesophageal rupture

other malignant neoplasm may occasionally metastasize to pleura, while lymphoma may cause effusion without necessarily causing pleural infiltration [30]. Malignant pleural effusions are usually, though not always, blood-stained and recur after aspiration.

**Infections**

Bacterial pneumonia is associated with pleural effusion in about 40% of cases [31]. Initially the effusion may be amber-coloured, containing predominantly polymorphs, but may progress to increasing turbidity with a high white cell count (empyema; see Chapter 14). Viral and mycoplasmal pneumonias rarely cause effusion, although tuberculosis remains an important cause. Recently, infection with hantavirus, an often fatal syndrome occurring particularly in North American Indians, has been shown to cause non-cardiogenic pulmonary oedema and pleural effusion [32].

The effusion associated with bacterial pneumonia is initially sterile. However, it may frequently be invaded by

the causative organism, leading to empyema or eventual healing by fibrosis. For this reason, aspiration to dryness (or as near as possible) is necessary at the time of presentation; it is unwise to wait in the hope of resolution of the effusion with antibiotic treatment of the original pneumonia.

Pleural effusion may occur as a complication of tuberculosis in four situations. In all cases the disease is due to actual infection of the pleura by tubercle bacilli, though tuberculin hypersensitivity probably plays a part in potentiating the reaction.

1 Effusion may occur as part of primary tuberculosis in children, when the peripheral focus or a caseating lymph node ruptures into the pleura [33]. This disease is now relatively uncommon in developed countries but typically presented between the age of 5 and puberty and occurred in about 7% of patients with primary tuberculosis [34]. The effusion usually occurs 3–6 months after infection, and is associated with general malaise, fever and pleuritic pain [35]. In the era before chemotherapy, it would usually resolve without treatment in 3–4 months, leaving only some blunting of the costophrenic angle and evidence of the primary complex. Nowadays this syndrome is seen more frequently in middle-aged and elderly subjects who may have lost their tuberculin sensitivity. At presentation they may have negative tuberculin tests though these invariably become positive within a few weeks [36].

2 Pleural effusion may present in adolescents or young adults, often after a few weeks of malaise, with acute pleuritic pain and fever. This presentation became much less common after the introduction of bacille Calmette–Guérin (BCG) inoculation in the UK, though it is not prevented by this altogether. The illness may initially manifest with recurrent dry pleurisy and all evidence of disease may disappear without treatment over a few months. However, up to two-thirds of these patients develop active pulmonary tuberculosis within the ensuing 5 years [37,38]. Moreover, a proportion of patients in whom treatment is started late or withheld because of diagnostic uncertainty progress to pleural fibrosis, which may cause serious restrictive impairment of lung function; these individuals ultimately require surgical pleurectomy. Early diagnosis and treatment is therefore important.

3 This type of tuberculous effusion, also now seen relatively rarely in the West, occurs when a tuberculous cavity in a patient with extensive postprimary disease ruptures into the pleura. This usually causes a tuberculous pyopneumothorax, the patient becoming breathless and complaining of pleuritic pain and increased malaise and fever (Fig. 43.4). Bronchopleural fistula may result and causes considerable management problems [39]. A fatal outcome is not infrequent in these circumstances. When resolution takes place, chronic fibrothorax is almost always the result, with extensive calcification [40] (Fig. 43.5). Before the modern era of antibiotics, this was also often the



**Fig. 43.4** Fatal left pyopneumothorax due to extensive pulmonary tuberculosis in an alcoholic woman.



**Fig. 43.5** Extensive right pleural calcification following tuberculosis effusion.

outcome of pleural effusion complicating artificial pneumothorax treatment for tuberculosis.

**4** Pleural effusion as a manifestation of disseminated tuberculosis in patients with AIDS is becoming increasingly common. These patients are usually very ill and deteriorate rapidly. The effusion may contain large numbers of bacilli, although the typical granulomatous histological changes are often absent [41].

The effusion in tuberculosis is rarely massive but often occupies about one-third to half the hemithorax [34]. The

fluid is usually serous and contains more than 50 g/L protein with a predominant lymphocytosis [35]. In immunocompetent people, the tuberculin test is almost always positive, save in the early stages when it may occasionally be negative; if so, it should be repeated 1 month later, when it has usually converted. The initial negativity may be due to the presence of circulating lymphocytes that suppress the activity of tuberculin-sensitized T lymphocytes [42]. Culture of pleural fluid is often negative, the chances of a positive result being increased in propor-

tion to the amount of fluid sent to the laboratory. However, pleural biopsies show granulomas in about two-thirds of patients; repeating the biopsies and culturing them may increase the rate of diagnosis to 90% [43].

Infection with the other pathogenic mycobacteria (*Mycobacterium kansasii* and *M. avium-intracellulare*) has been recognized more frequently as the incidence of tuberculosis has declined in the West, and these organisms are a well-recognized problem in the immunosuppressed. These conditions are discussed in Chapters 20 and 52. Pleural effusion occurs in about 5% of cases, usually in association with radiological evidence of intrapulmonary disease [44]. The clinical and radiographic features of the disease in the immunocompetent are usually indistinguishable from those of tuberculosis, the diagnosis being made bacteriologically from pleural fluid and biopsies.

Fungal infections of the lung are relatively uncommon in the UK, being seen mainly in immunosuppressed patients. However they are seen more often in the USA, where they are endemic in certain areas (see Chapter 21). Pleural effusion may occur in any pulmonary fungal infection and usually mimics tuberculosis clinically, radiographically and in the features of the pleural fluid. It may occur as a self-limiting process, together with fever and malaise, in the primary infection, or as a more intractable illness in association with rupture of a lung focus in post-primary or disseminated disease. It has been described in about 7% of patients with coccidioidomycosis [45], 10% of patients with blastomycosis [46] and rarely in histoplasmosis [47], cryptococcosis [48] and other fungal infections. It is an occasional complication of invasive or disseminated aspergillosis [49] and has been described very rarely in allergic aspergillosis [50].

*Actinomyces* and *Nocardia* sp., filamentous branching bacteria (see Chapter 21), may infect the lung and spread to the pleura. Either parapneumonic or infected effusions may occur, almost always in association with cavitating pneumonic changes in the ipsilateral lung [51–54].

Subphrenic infection, usually due to a perforated abdominal viscus, may spread up through the diaphragm. The effusion initially contains polymorphs but no organisms; untreated it progresses to empyema [55]. Diagnosis is aided by the presence radiologically of gas under the diaphragm [56]. The usual organisms are coliforms, streptococci and clostridia.

Hepatic amoebiasis may be complicated by serous pleural effusion, usually on the right side [57]. Hepatic abscess may rupture into the pleura causing empyema; occasionally a hepatobronchial fistula forms and the so-called 'anchovy sauce' sputum is expectorated (see Chapter 22). Hydatid disease, of either liver or lung, may also rupture into the pleura, in some instances causing an anaphylactic reaction, in others leading to hepatobronchial fistula [58,59].

### Immune disorders

Rheumatic fever, still quite uncommon in the West despite an apparent rise in incidence in the western USA, occurs frequently in the tropics and India, where it has an annual incidence of about 0.5 per 1000 among rural children [60]. It may be associated with pleurisy (usually accompanied by pericarditis). Pleural effusion apparently occurred in the past in about 10% of cases of acute rheumatic fever [61], although recent reviews do not mention this as a complication.

Rheumatoid arthritis may be accompanied by effusion in about 15% of males with the disease but only 2% of females. Typically the effusion occurs within about 5 years of the start of the disease, in patients with severe arthritis and subcutaneous nodules [62–64]. The effusion may be an incidental finding or may accompany worsening arthritis and increased systemic symptoms. The fluid is straw-coloured, often turbid and typically has a low glucose and pH and a high lactate dehydrogenase. Rheumatoid factor and immune complexes may be found in pleural fluid, often at higher titres than in blood [65,66]. Biopsies of pleura may show typical rheumatoid histology. Thoracoscopy shows a highly characteristic granular appearance to the parietal pleura, with some associated inflammatory changes on the visceral pleura [67]. The granular change is due to palisaded epithelioid cells and occasional giant cells, resembling an opened-out rheumatoid nodule. These nodules may be responsible for the production of the immune complexes often found in the fluid. The condition usually regresses gradually and eventually clears over several months. Corticosteroid treatment may be of value if started early but this has not been clearly established. Chronic persistence of the effusion or progressive pleural fibrosis may lead eventually to the need for pleurectomy. Occasionally the condition may be bilateral and associated with other pulmonary manifestations of rheumatoid disease. There also appears to be a risk of infection of these effusions, leading to empyema [68].

Systemic lupus erythematosus presents not infrequently with pleurisy and, in contrast to rheumatoid pleurisy, is more common in women than men [69–71]. The usual presentation is bilateral small effusions, though unilateral ones are not unusual. Some 40% of patients have pleural effusion at some stage [69,71]. Lupus cells may be demonstrated in the fluid as well as the blood and a high titre of antinuclear antibodies in the fluid is diagnostic [72]. The fluid is often blood-stained and tends to have a normal glucose and low lactate dehydrogenase. Effusions may of course occur in lupus secondary to other complications of the disease, such as uraemia or pneumonia, in which case these antibodies may be absent from the fluid. The lupoid effusion is unlikely to resolve spontaneously, but usually does so in response to corticosteroid treat-

ment. If this fails, cyclophosphamide or azathioprine may be necessary.

Other collagen diseases seem rarely to be associated with pleural effusion unless associated with lupoid features or as a complication of renal or cardiac failure or of pulmonary infection. Wegener's granulomatosis of the lung may be complicated by pleural effusion [73,74], though this is usually small and responds to treatment with cyclophosphamide.

The post-cardiac injury syndrome, a relatively uncommon complication of myocardial infarction or cardiac surgery, is characterized by malaise, fever and pleural and pericardial pain, usually coming on about 3 weeks after the cardiac injury. Effusions may occur in pericardium and pleura, and pulmonary infiltrates may be seen; the fluid is usually bloody with high glucose and pH, and difficulty is often experienced in differentiating the condition from pulmonary infarction. It usually responds to corticosteroid treatment.

### *Abdominal diseases*

Pleural effusion may occur as a complication of a number of non-infective abdominal conditions, apart from the infective ones mentioned above. Acute pancreatitis may lead to pleural exudate, probably by transmission of inflammation through the adjacent diaphragm and of fluid through diaphragmatic lymphatics [75]. The fluid is characterized by high amylase levels, often higher than in serum. Chronic pancreatitis may also cause pseudocyst formation, with a sinus developing between cyst and pleura [76]. Again the fluid shows high amylase levels. Pleural transudates may occur as a complication of ascites due to ovarian fibroma, Meigs' syndrome [27], but more commonly exudates are seen in relation to gastrointestinal or pelvic carcinomas. The late stages of renal failure may be accompanied by pleural and pericardial pain and effusions [77].

### *Pulmonary embolism and infarction*

This condition is described in Chapter 25. As stated above, massive embolism may lead to right-sided heart failure and pleural transudation, although two-thirds of effusions associated with infarction are exudates, sometimes blood-stained [22,23]. The fluid may contain a high proportion of eosinophils.

### *Other causes*

Pleural exudates are an unusual occurrence in patients with sarcoidosis, usually presenting when the disease involves the lungs and often other organs as well [78–81]. The effusions are usually small and contain lymphocytes predominantly [81]. The pleura contains sarcoid granulo-

mas that may be found on biopsy, sometimes leading to confusion with tuberculosis. Usually the tuberculin test is negative and the Kveim test or biopsy of other tissues confirms the diagnosis.

Occasional patients working with asbestos develop pleuritic pain and an effusion, which may be recurrent [82,83]. While this may be the first evidence of mesothelioma, it may be benign asbestos pleurisy. This condition is the most common asbestos-related disease during the first two decades of exposure at work, but may occur for the first time long after exposure has ceased. The effusion is sometimes blood-stained and shows no specific cytological features. It may be an incidental finding on chest radiography, and it is likely that this is the event that leads to diffuse pleural fibrotic changes in a proportion of asbestos workers (Fig. 43.6). The effusion is usually of small or moderate size and may be bilateral. It tends to recur after aspiration but eventually disappears, sometimes leading to pleural fibrosis [83,84].

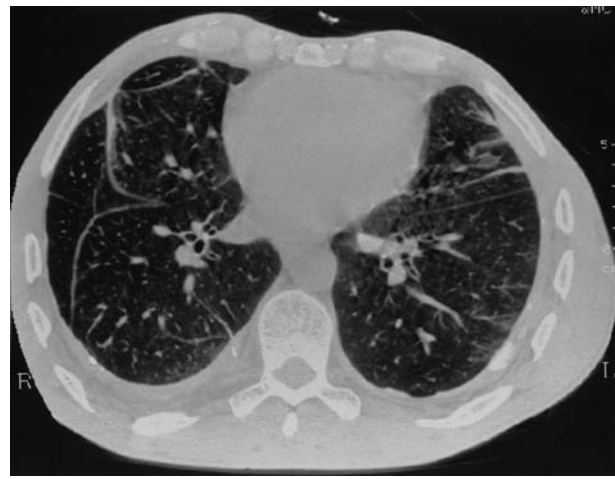
The yellow nails syndrome is a condition of hypoplasia of lymphatic vessels, leading to lymphoedema of the limbs, dystrophic changes in the nails and, sometimes, intractable pleural effusions [85–87]. The nail changes, which are not always present, take the form of thickening, increased curvature in both long and transverse axes, transverse ridging and a yellow-brown pigmentation (Fig. 43.7). They also grow more slowly than normal. The condition usually presents in adult life and is distributed equally between the sexes. In some cases it appears to be inherited as a dominant characteristic [88]. The cause of the nail changes is not known but the lymphoedema and pleural effusions are related to lymphatic vessel hypoplasia, which may be demonstrated in the limbs by lymphangiography. The condition may be complicated by bronchiectasis, sinusitis or protein-losing enteropathy [89,90] and patients have an increased risk of neoplasms, especially lymphomas and sarcomas [87]. The effusions may not require treatment but can result in pleural fibrosis. If they are sufficiently large to cause symptoms, it may be necessary to carry out pleurodesis or pleuroperitoneal shunt [91]; occasionally pleurectomy has been carried out, and on one occasion the surgical specimen showed abnormal pleural lymphatic vessels [92]. It is assumed that this abnormality hinders the reabsorption of proteins in the fluid, thus leading to effusion [93]. Effusions may occasionally be chylous and have been managed by dietary reduction of fat intake [94].

Certain drugs may provoke pleural effusions as a side-effect (see also Chapter 55). Practolol and methysergide may have a direct effect on serous membranes, leading to effusion and fibrosis [95,96]. In addition, pleural effusion may be associated with eosinophilic reactions induced by such drugs as nitrofurantoin, sulphonamides, salicylates,  $\beta$ -blockers and para-aminosalicylic acid [97]. The eosinophilia-myalgia syndrome is associated with the use





(a)



(c)



(b)

**Fig. 43.6** (a) Chest film of patient who presented with pain and weight loss showing a left-sided pleural effusion. He had a 10-year history of asbestos exposure until 10 years previously, and mesothelioma was suspected. (b) Chest film 4 months later showing resolution of the effusion leaving pleural fibrosis. Pleural fibrosis is present on the right side also. (c) CT scan after resolution showing bilateral diffuse pleural fibrosis. The patient remained well 3 years later.



(a)



(b)

**Fig. 43.7** (a) Transversely ridged curved nails of the yellow nails syndrome. (b) Chronic lymphoedema of the legs in the same patient, who presented with pleural effusion.

of L-tryptophan [98]. As mentioned above, the lupus syndrome may be associated with pleural effusion and this may also be caused by drugs such as hydralazine, procainamide, phenytoin and isoniazid [99]. Effusion occasionally follows several months after a course of radiotherapy, though this is rarely large and usually resolves after aspiration [100]. It may also occur when pericardial effusion develops as a complication of mediastinal irradiation [101,102].

The syndrome of recurrent polyserositis, discussed previously, may cause effusions as well as pleural and peritoneal pain [10,11]. Finally, oesophageal rupture leads to mediastinitis with infection of the pleura and effusions containing a high level of salivary amylase, epithelial cells and often food particles [103–105]. It may be associated with mediastinal emphysema and usually follows oesophageal instrumentation, though spontaneous rupture does occur. It is important to recognize this condition early, as it is usually fatal if surgical repair and mediastinal drainage are not instituted promptly [106].

### Investigation

A pleural effusion is normally diagnosed by chest radiography, although loculated effusions may require confirmation by ultrasound. However, the radiograph does not usually provide diagnostic information on the cause of the effusion, although evidence of a proximal or pleural tumour or of tuberculosis may be seen. Similarly, the history and clinical examination may sometimes provide clues but do not often give a clear indication of the cause, except in the case of hydrothorax. When taking the history, special attention should be paid to previous illnesses, drug or radiation treatment and symptoms not directly related to the effusion. It should be apparent from the foregoing that pleural fluid often accumulates as a consequence of systemic disease.

If the history and examination indicate a clear cause, no further investigation is necessary though therapeutic aspiration may be desirable. Thus, evidence of congestive heart failure is sufficient to justify a trial of diuretic therapy prior to aspiration of a right-sided or bilateral effusion and evidence of venous thrombosis often leads to treatment with anticoagulants rather than aspiration. In most patients, however, pleural fluid needs to be aspirated.

### Pleural aspiration and biopsy

Pleural aspiration should normally be combined with pleural biopsy during the one procedure. The best method is to seat the patient on a stool leaning forward over the side of the bed, with arms folded under the chin. The site is chosen carefully, taking account of the likely position of the diaphragm and the top of the effusion as judged by

percussion. Simple M-mode ultrasound may be very helpful in aspirating loculated effusion [107,108]. Local anaesthetic is infiltrated intradermally, subcutaneously and into muscle and parietal pleura, infiltration continuing until fluid is aspirated. If the pleura is felt to be much thickened, a long lumbar puncture needle may be used. Careful attention to anaesthetic technique, together with a reassuring explanation of the procedure, makes the aspiration less of an ordeal for both patient and doctor.

Care should be taken to insert all needles immediately above the lower rib in order to avoid damage to intercostal nerve and vessels, which lie immediately below each rib. After finding the fluid it is sensible to take some specimens for chemistry, cytology and culture immediately, and to follow this by pleural biopsy. If tuberculosis is suspected, as much fluid as possible should be sent to the microbiology laboratory. Biopsy is usually carried out with an Abrams punch [109], which is inserted along the anaesthetic needle track after its enlargement with a fine-pointed scalpel blade. Biopsies should be taken first laterally and the punch should then be rotated inferiorly and through 180°, avoiding the region of the intercostal bundle. Four or five bites should be taken to increase the chances of a positive finding [110].

Having collected specimens for diagnosis, it may be desirable to remove fluid in order to relieve symptoms. This should be done by aspiration into a large syringe equipped with a three-way tap rather than by insertion of a tube, although tube drainage is often necessary if the fluid is infected. The syringe may be connected to a wide-bore needle (and, after biopsy, to the Abrams needle for convenience) or to a plastic cannula introduced through a needle; the latter method is more comfortable for the patient and involves less risk of puncturing the lung. Aspiration should take place relatively slowly (hence the disadvantage of a tube) since rapid removal of fluid may result in unilateral pulmonary oedema, a complication that may be fatal and which is probably due to increased microvascular permeability in the reinflated lung [111,112]. Removal of large amounts of fluid may also cause hypoxaemia, which can be alleviated by administration of oxygen [113]. It is probable that these complications are related to the generation of excessively negative intrapleural pressures and can be prevented by careful and slow aspiration [114]. If the patient complains of shortness of breath, pain in the chest or general unease during the procedure, it is wise to stop immediately and to take a chest radiograph to exclude pneumothorax or pulmonary oedema.

A fortunately rare complication, though seen occasionally, is air embolism when air is introduced into the pulmonary venous circulation. This may be immediately fatal or attended by loss of consciousness. The patient should immediately be laid down on the left side with head below feet; if a hyperbaric chamber is available its use may be

life-saving. Air embolism was a complication of the old artificial pneumothorax treatment of tuberculosis and thus was more familiar to an earlier generation of chest physicians. Pneumothorax is a more frequent complication of pleural aspiration, especially when done by the inexperienced. It is usually due to puncture of the lung, though a careless technique may allow introduction of air through needles or the chest incision. It may require tube drainage. Sometimes the introduction of a small amount of air is useful in a diagnostic sense, since it may demonstrate pleural tumour separate from the effusion. Other occasional complications attendant on careless technique include the introduction of infection and the inadvertent biopsy of lung, liver, spleen or even kidney.

### Examination of the fluid

#### *Macroscopic appearances*

The fluid of a transudate is clear and pale straw-coloured. Exudates tend to be more amber-coloured and may be turbid if the cell count is high. A fresh exudate often clots on standing, while an older one has often been defibrinated and, like a transudate, remains fluid. Blood in the fluid may be due to damage to a vessel during insertion of the needle or biopsy. If this is the case, the fluid withdrawn into the local anaesthetic syringe is usually clear and later aspirates tend to be less blood-stained than the initial ones. Uniform blood-staining, of a red or brown colour, frequently indicates pleural tumour, although infarction, rheumatoid, leukaemic and tuberculous effusions may be haemorrhagic. Milky fluid is usually due to chyle (see below), though chronic effusions can mimic this appearance due to the presence of fat globules derived from degenerating cells. Purulent fluid in cases of frank empyema is easily recognized, but lesser degrees of infection give the fluid an increased turbidity indistinguishable from that due to a high cell content. A fluid with a shimmering sheen may contain high levels of cholesterol [115], another indication that the effusion is chronic but of no further significance.

#### *Microscopic appearances*

A citrated specimen of the fluid should be examined for differential cell count and for malignant cells. The polymorph is predominant when there is an infective cause in lung or pleura, other than tuberculosis, while the lymphocyte is the characteristic cell in tuberculous effusions [116,117]. It is also frequently the predominant cell in malignant effusions. An eosinophilic effusion (with >10% of white cells being eosinophils) is a non-specific finding [118,119] that occurs in association with other diseases characterized by blood eosinophilia, such as pulmonary eosinophilia, polyarteritis nodosa, tropical eosinophilia,

filariasis and Hodgkin's disease, and also in the absence of blood eosinophilia when blood has been introduced into the serous cavity [120]. It is thus seen following trauma, pulmonary infarction and infection. It is relatively unusual in carcinomatous effusions [120]. Eosinophilic effusion has also been described in response to fungal and viral infections. It may be that the common factor is the escape into the pleural fluid of eosinophil chemotactic factor derived from white cells in blood.

The examination of pleural fluid for malignant cells may lead to the diagnosis. However, caution should be exercised in interpreting positive results, since desquamated mesothelial cells may easily be mistaken for malignant cells, even by experienced pathologists [20]. Nevertheless, a high diagnostic yield following careful cytological examination has been reported from specialized laboratories [121,122], and it is likely that the use of newer cell marker techniques will improve the reliability of these diagnostic tests.

#### *Bacteriological culture*

Culture of effusions should be carried out as a routine in order to guide therapy if infection is found. If tuberculosis is thought a possibility, several large specimens of fluid should be cultured, since the chances of a positive result increase with the amount of fluid examined.

#### *Biochemical tests*

It is usual to measure the protein content of pleural fluid, 30 g/L being taken as the dividing line between transudate and exudate [20,123]. In addition the pleural fluid-serum ratios of lactate dehydrogenase and cholesterol have been found useful in differentiation. Pleural fluid cholesterol is usually less than 55 mg/dL and the fluid-blood ratio is 0.3 or below in transudates [124]. The glucose level may be helpful because it is characteristically low (<1.7 mmol/L or 30 mg/dL) in rheumatoid disease. It may also be low in infected effusions or whenever there is a high cell count [125,126]. Lactate dehydrogenase is raised in exudates above the serum level, but otherwise is a non-specific finding [127]. Amylase levels may be very high (>1000 u/L) in effusions due to pancreatitis and oesophageal rupture [126,128]. The fluid pH is reduced (acid) in pleural inflammatory disease and has been used by some as guide to the use of tube drainage in empyema [129]. In general, however, biochemical tests are not very helpful in a diagnostic sense.

#### *Further diagnostic tests*

Ultrasound and CT are now standard investigations in most centres prior to biopsy and aspiration in order to detect evidence of malignant disease, either primary or

secondary [130,131]. These investigations are a particularly useful guide to the best site to biopsy, although it should be remembered that they cannot be relied on absolutely in the diagnosis of tumour and tissue diagnosis is necessary in most cases [132]. If clinical examination, aspiration and biopsy fail to give the diagnosis, further tests may be necessary. According to the surgeon's preference, thoracoscopy can be carried out using a rigid thoracoscope or video-assisted techniques with biopsy of any pleural lesions seen [133–135]. This has a high success rate in experienced hands. If it fails, a limited thoracotomy may be necessary for appropriate biopsies to be taken.

### Management

The management of pleural effusion depends on the cause. In many cases aspiration is sufficient to cure the problem, although some effusions do recur, especially malignant ones. Infective effusions should be treated with the appropriate antibiotics (see Chapter 14) and tube drainage may be necessary. Tuberculous effusions require antituberculosis chemotherapy along standard lines and it is usual to add corticosteroids (prednisolone 20 mg daily for 2–3 weeks, reducing over a further 2–4 weeks) as there is evidence that this speeds reabsorption and prevents pleural fibrosis [136,137]. Corticosteroids also speed the resolution of effusions due to sarcoidosis, systemic lupus erythematosus, the post-cardiac injury syndrome and possibly rheumatoid disease.

In general, recurrent exudates eventually heal themselves by causing pleural fibrosis; however, since this may cause serious restriction of lung movements the aim of treatment is to prevent it happening by early aspiration and appropriate drugs. However, if there is no specific treatment for the underlying disease and if the effusion is large enough to cause symptoms due to lung compression, treatment may be aimed at producing pleural obliteration by fibrosis. This is the case with malignant effusions, which rarely resolve spontaneously. Several methods have been used to promote pleurodesis, including instillation of nitrogen mustard [138], radioactive colloidal gold [139], tetracycline [140], doxorubicin [141] and quinacrine [142], all of which show a success rate of up to 60%. A suspension of killed *Corynebacterium parvum* has also been used and has been shown to be more effective than nitrogen mustard in controlled trials [143–145], causing less nausea than the former and producing pleurodesis in more than 90% of subjects. There is also some evidence that it lengthens survival in some of the patients [146]. The technique is to aspirate the pleural space until no more fluid is obtained and to inject 7 mg of heat-killed, freeze-dried *C. parvum* in 20 mL saline into the pleural cavity. The patient is then tilted in the bed and placed in series of different positions for 15 min each to ensure generalized distribution of the material over the pleural surface. The

usual side-effect is fever associated with malaise for 2–3 days. A brisk pleural reaction occurs that may cause widespread radiological shadowing before the space is obliterated. Reaspiration and a second instillation is sometimes necessary. The mechanism of action of *C. parvum* is not known, but it clearly excites a brisk fibrotic reaction and produces a thick rind round the lung. It may also have an indirect antitumour action, possibly by activating macrophages or natural killer cells [147].

Pleurodesis with *C. parvum* has been so successful in our hands that more aggressive treatment, with insufflation of kaolin or talc through a thoracoscope or intercostal tube or surgical pleurectomy, is now rarely necessary to prevent recurrent effusions. These techniques have been used widely, are effective [148–150] and there is still an occasional need for them, though thoracotomy should only be used as a last resort in patients with pleural tumour. In particular, when using talc for non-malignant effusions care should be taken to ensure that it is not contaminated with tremolite asbestos, the two minerals often occurring together in the same geological formations. Fortunately, one survey of patients many years after talc pleurodesis failed to show any case of mesothelioma developing to the time of the survey [151], and personal investigation of talc BP as used in the UK has shown no contamination.

## Chylothorax

### Anatomy and physiology

In general, the thoracic duct receives the lymph from both sides of the body below the diaphragm and from the left side above it. The lymph from the right side of the head and neck and right arm is drained into the right lymphatic duct, while that from the right hemithorax is drained into the right bronchomediastinal trunk. The thoracic duct begins in the abdomen as a dilatation called the cisterna chyli, which lies on the front of the upper two lumbar vertebrae between the aorta and the right crus of the diaphragm. The duct passes upwards through the aortic opening of the diaphragm, ascends in the posterior mediastinum behind the diaphragm and then the oesophagus, inclining to the left at the fifth thoracic vertebra to ascend in the superior mediastinum closely applied to the left side of the oesophagus. Entering the root of the neck, it turns laterally between the carotid sheath and the vertebral artery, then downwards in front of the subclavian artery and enters the venous system at the junction of the left internal jugular and subclavian veins. In rather fewer than 50% of subjects there are variations in the anatomy of the thoracic duct, two or more ducts frequently being present at some point in the course.

The right lymphatic duct is usually quite short, about 1 cm long, starting at the medial margin of the scalenus

anterior muscle above the subclavian artery where it is formed by the junction of right jugular and subclavian lymph trunks. The right bronchomediastinal trunk runs up the right side of the oesophagus into the neck. Both trunks end in the innominate vein, either separately or as a common trunk. Many anastomoses occur between the bronchomediastinal trunk, thoracic duct and the azygos, intercostal and lumbar veins, so that the thoracic duct may be ligated at any point in its thoracic course without causing problems of lymph drainage [152,153]. This is important in the management of chylothorax.

The chyle that drains up the thoracic duct is an alkaline fluid which may be milky or almost serous in appearance depending on the nutritional state of the subject. On standing it separates into a creamy upper layer rich in chylomicrons, a milky middle layer and a lower layer containing lymphocytes. It has a protein content of 20–60 g/L and a fat content of up to 60 g/L. The amount of chyle produced daily may be as much as 2.5 L [154], again depending on the subject's nutritional status and especially the fat content of the food. Thus the rate of accumulation of a chylothorax may be controlled by dietary measures [94].

### Clinical features and aetiology

There are no specific clinical features associated with chylothorax, which presents as does any other pleural effusion. It may be bilateral or unilateral, with a tendency to be right-sided with lesions of the thoracic duct below the fifth dorsal vertebra and left-sided with lesions above that level [155]. It is usually not associated with pleural pain, and infection does not occur because of the antibacterial properties of chyle. The diagnosis is made on aspiration of the fluid, although this is not always obviously milky; it may require biochemical analysis of triglycerides and chylomicrons to confirm the diagnosis [156]. Alternatively, detection of dye or radioactivity in pleural fluid after the patient has eaten butter containing a lipophilic dye or radioiodine-labelled triglyceride also allows confirmation [155,157].

If the effusion is milky, the only possible cause of confusion is the so-called chyliform, pseudochylous or cholesterol effusion [158]. This is usually readily distinguished because it is due to fat globules from degenerating cells in long-standing encysted effusions, usually secondary to tuberculosis or rheumatoid disease. The history and features of the primary condition should allow the distinction to be made without difficulty; if not, the presence of cholesterol crystals and negative dye or radioiodine tests settle the matter.

Chylothorax is uncommon. The most frequent cause is tumour [159], especially lymphoma and metastases from stomach and gastric carcinoma to mediastinal nodes. Occasionally radiotherapy to these tumours may provoke

the chylothorax. Extensive blockage or invasion of the duct, with fistula formation, or invasion of the left subclavian vein is responsible. Some 50% of cases are due to tumour, while about 25% are due to trauma [159]. Half of these are the result of damage to the duct at surgery [160,161], especially in the region of the left subclavian vein, though many cervical and thoracic operations may cause this, from neck dissection, cervical sympathectomy and oesophagectomy to coronary bypass, high lumbar aortography and diaphragmatic hernia repair. The other half are due to knife and bullet wounds or stretching and bending injuries to the spine; sometimes these may be surprisingly minor, such as coughing, straining or vomiting [162,163]. Of the remaining 25% a few may be due to tuberculous mediastinal nodes, filariasis, left subclavian vein thrombosis, thoracic aortic aneurysm, lymphangioma and thoracic duct lymphangioma, sometimes associated with generalized lymphangioma and lymphoedema [164,165]. Finally, a proportion of cases seem to have no obvious cause. This is particularly so with the neonatal type [166], which presents within a day or two of birth and, though rare, is the most common cause of pleural effusion at that early stage of life.

Traumatic chylothorax usually presents 2–10 days after the injury, the interval being the time taken for a mediastinal chylous cyst to rupture into the pleura [167]. Drainage is only required to relieve the symptom of increasing dyspnoea; however, since recurrent aspirations are almost always necessary, this leads to the important complication of nutritional deficiency. Thus emaciation and dehydration occur quickly without appropriate treatment, death ensuing.

### Management

If the patient's nutritional status can be maintained, spontaneous or traumatic damage to the thoracic duct may heal. Thus, in such cases, a trial of conservative treatment is justified [168]. This means tube drainage of the pleural space, reduction of chyle formation by cessation of oral feeding and total parenteral nutrition. Assuming the patient's nutritional status is maintained, it is reasonable to wait about a week to see if the drainage of chyle is ceasing. If it is not, surgical treatment is indicated [169]. The surgeon usually attempts to locate the tear, using an injection of Evans blue dye into a leg as a marker, and suture the duct above and below it [155]. Alternatively, active attempts at talc, kaolin or tetracycline pleurodesis, combined with tube drainage, may be used at an early stage and have been reported to be successful [170,171].

In the case of non-traumatic chylothorax, the treatment is planned in the light of the primary disease, bearing in mind the principles of maintaining nutrition and preventing chyle leaking into the pleura. Thus, lymphoma may

well respond to radiotherapy or chemotherapy, although pleurodesis and tube drainage as above may be necessary as well. Symptomatic relief in the case of metastatic carcinoma may also be provided by radiotherapy, though pleurodesis or low thoracic duct ligation may also be necessary. In some cases of terminal disease, it may be kinder to avoid all such measures and simply palliate the patient's symptoms with appropriate drugs.

## Pleural plaques

### Clinical features

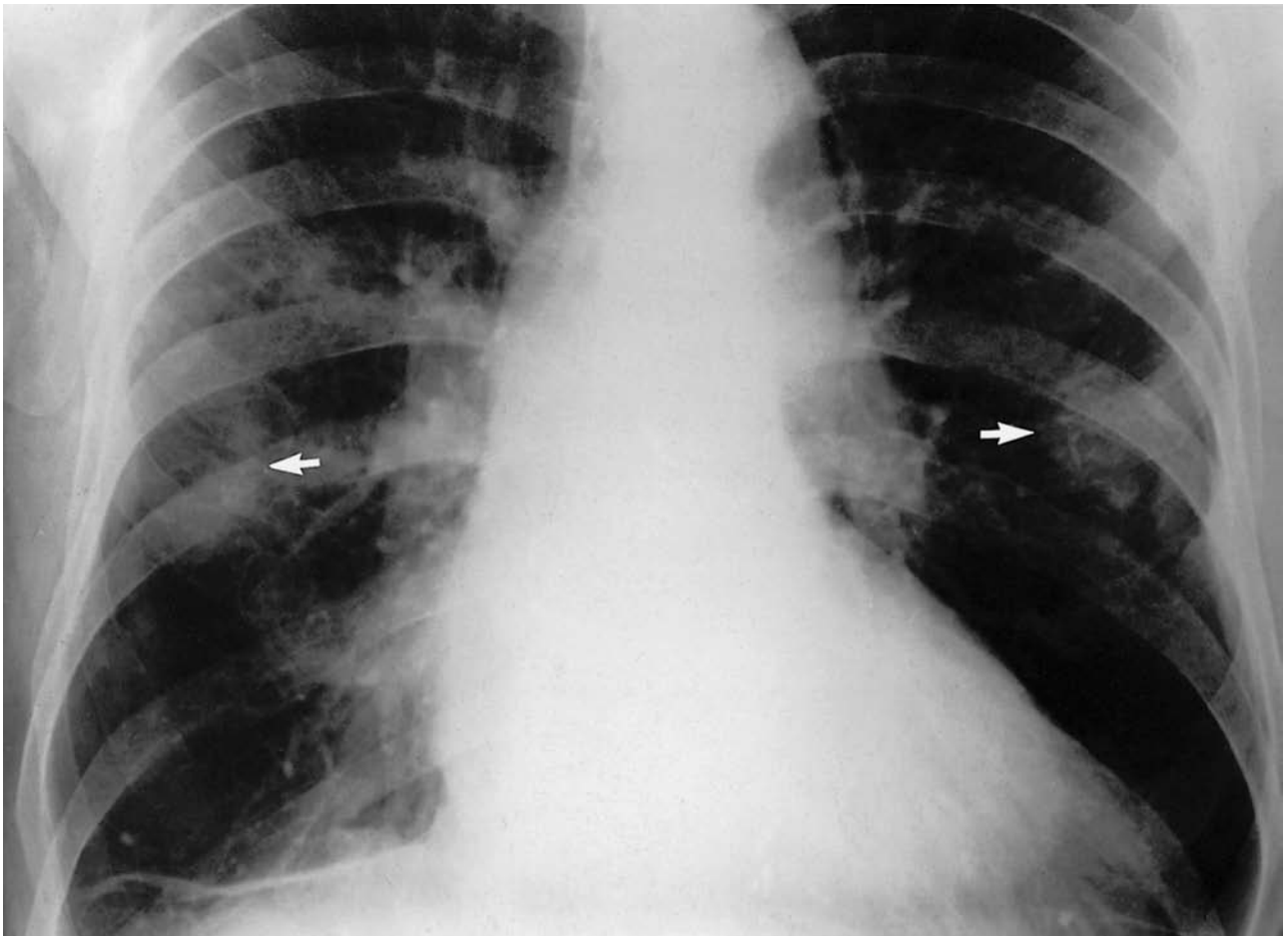
Pleural plaques are benign fibrous lesions of the parietal pleura that occur as a result of exposure to asbestos; however, they may frequently be found at postmortem in people in whom such exposure was not known. Radiologically they present as indistinct elevations of the pleura [172], which may easily be missed unless they are large

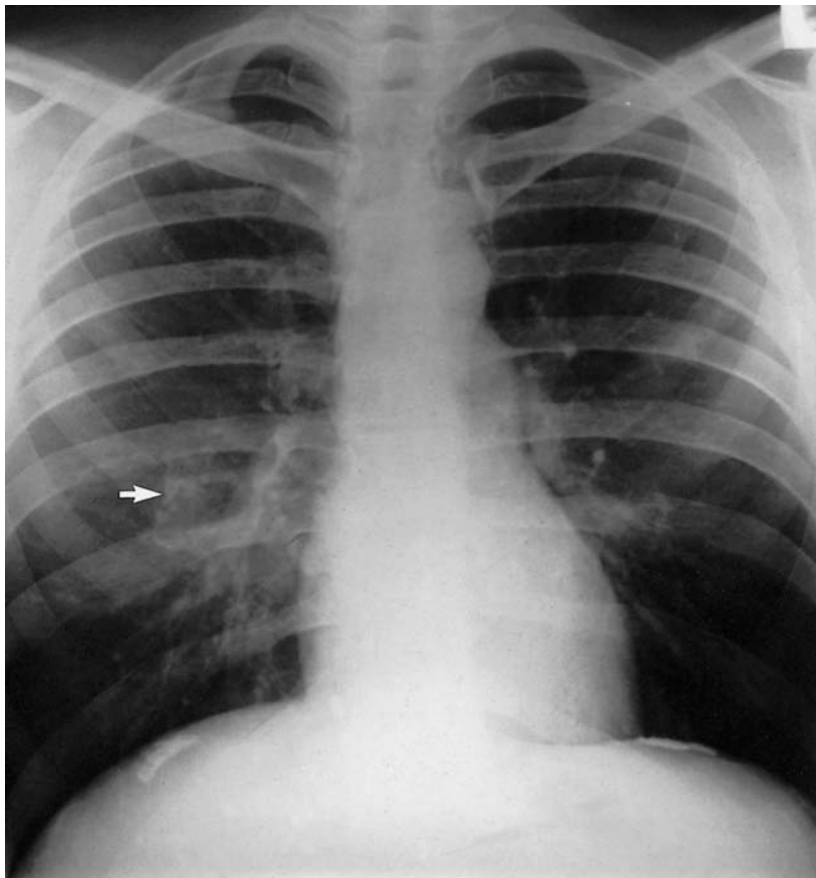
and multiple (Fig. 43.8); indeed one autopsy series has shown only a 15% ante-mortem diagnosis rate [173]. Moreover, pleural fat pads and companion shadows may easily be mistaken for plaques, leading to a tendency to false-positive diagnoses. Thus diagnosis of fibrous plaques by routine chest radiography is unreliable. However, most long-standing plaques calcify and this leads to characteristic radiological shadows, often seen most distinctly as elongated 2–3 mm wide calcifications on the lateral chest wall, diaphragm and pericardium but also *en face* as 'holly leaf' shadows (Fig. 43.9). In cases of doubt, and where the additional radiation is considered justified, CT proves a reliable means of diagnosing and defining the extent of plaques [174]. Parietal pleural plaques would not be expected to cause any detectable lung functional impairment; studies demonstrating abnormalities in such subjects are likely due to the effects of asbestos exposure or some confounder, usually cigarette smoking, on the lungs.

### Pathological features

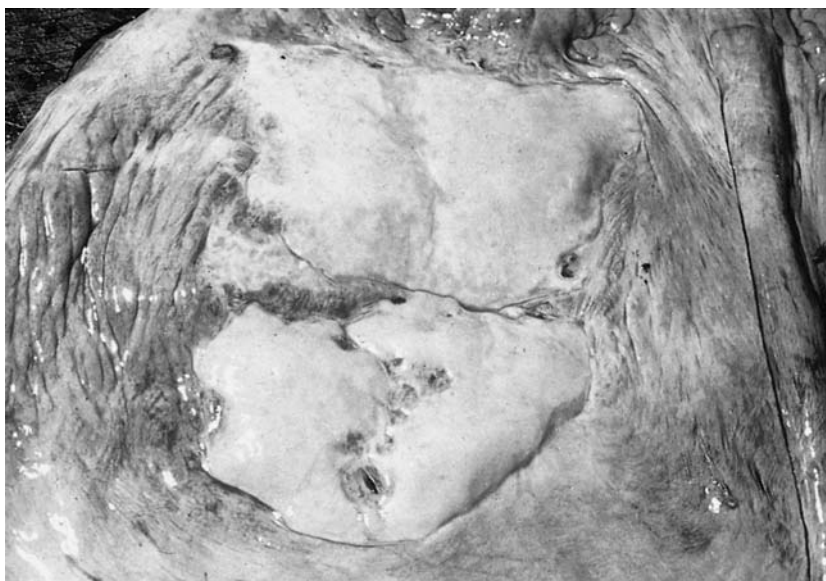
Pathologically, pleural plaques are smooth, whitish-

**Fig. 43.8** Fibrous pleural plaques (arrowed) in retired asbestos worker, best seen in left mid zone and under lateral chest wall.





**Fig. 43.9** Calcified plaques on diaphragm and, *en face*, in right mid zone (arrowed).



**Fig. 43.10** Diaphragmatic pleural plaques as seen at necropsy.

yellow elevations of the parietal pleura, separated distinctly from surrounding mesothelium and having their centres usually over a rib or over the central tendon of the diaphragm (Fig. 43.10). They vary in size from pin-head to

that of a hand and are almost always multiple. Histologically, they consist of collagen arranged in a basket-weave pattern and covered by an intact and non-metaplastic mesothelial layer [175]. In their deeper layers there may be



small collections of lymphocytes and plasma cells. Asbestos fibres may be found in plaques by electron microscopy but are usually too small and sparse to be seen by light microscopy. Electron microscopy has shown these to be predominantly short chrysotile fibres [176]. Asbestos bodies are not present in plaques, although they may be found in the subject's lung.

### Aetiology

It is well established that plaques occur most frequently in populations exposed industrially to asbestos, although exposure does not have to be heavy or prolonged [177]. Usually plaques only make their radiological appearance about 10 years, and calcification usually only 20 years, or more after first exposure. They have also been found in populations exposed to the non-asbestos fibrous mineral erionite present in the environment in certain parts of Turkey [178,179], and in people exposed environmentally, rather than occupationally, to naturally occurring soil or rock asbestos in parts of Finland, central Europe, Turkey and Greece [180,181].

It is likely that pleural plaques are a benign reaction to an individual fibre or a very small number of fibres that have lodged in the parietal pleura, probably being transferred via pleural lymphatics. Their site, centred over ribs and diaphragmatic tendon, suggests that the fibre's progress through the lung, as a result of forces exerted by lung movement, has been arrested by impenetrable tissue. There is no evidence that the plaque is in any way premalignant, although a subject with plaques has been exposed to asbestos and may be at increased risk of lung cancer or mesothelioma in relation to the intensity and duration of such exposure.

### Management

Pleural plaques are of no account save as a marker of asbestos exposure. Since they are benign, reassurance should be given to the individual in whom they are found and he or she should not be followed up in clinic. The risk of mesothelioma in such an individual is likely to be greater than in someone without plaques, and depends upon their exposure to asbestos rather than the presence of the plaques (see Chapter 54). In any case, the risk cannot be reduced further by any action other than by ensuring no future exposure to asbestos. However, a number of people with plaques and no other disease have received compensation for having these wholly benign lesions, thus increasing anxiety and public misconceptions about their nature. The sensible physician recognizes and attempts to allay the natural anxiety of a patient in whom these plaques have been found, and is now able to provide a sensible risk estimate based on likely past exposure to asbestos (see Chapter 54).

### Pleural fibrosis

Distinction should be made between pleural plaques, which are well-demarcated lesions of the parietal pleura, and pleural fibrosis, which is a diffuse process involving both layers of pleura and not infrequently extending into the surface of the lung.

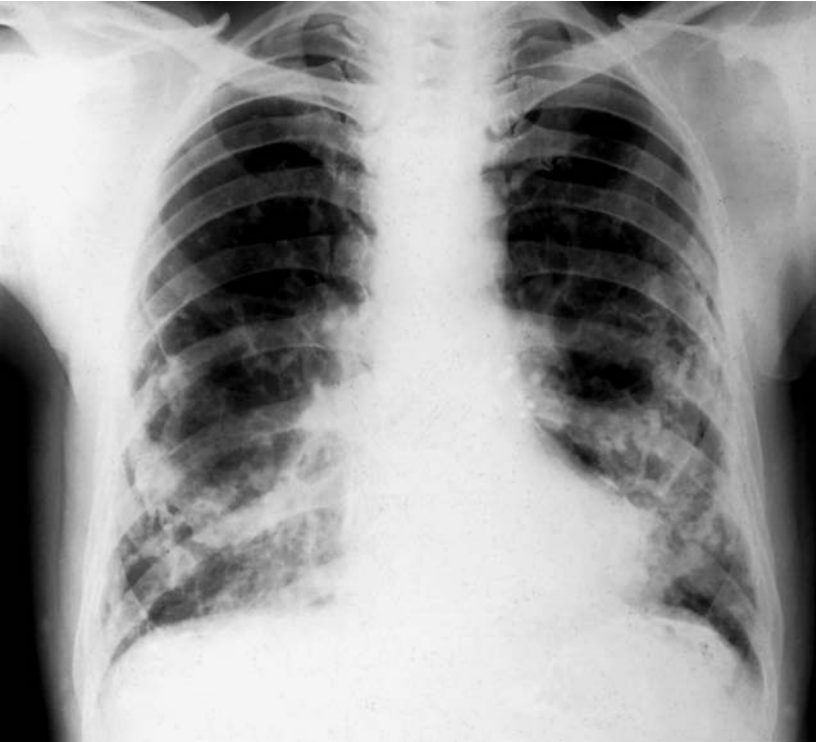
### Clinical features

Pleural fibrosis is usually the sequel of an unabsorbed pleural effusion, although the presence of the effusion may not have been recognized clinically (see Fig. 43.6). Thus it may present in a patient with a recent history of effusion or episode of pleural pain, or it may be found incidentally on chest radiographs. The lesion may be unilateral or bilateral. Whether it is associated with symptoms depends on its extent and on the health of the underlying lung; in general, bilateral thickening has to be quite extensive before it interferes seriously with lung expansion, while unilateral thickening is unlikely to cause symptoms unless associated with other lung disease. The physiological effects of pleural fibrosis are decreased lung volumes, without reduction in transfer coefficient, and decreased compliance. These features may be associated with exertional dyspnoea. Chest pain is not usually a feature and when it is present it should always lead the physician to suspect that the pleural thickening is due to tumour rather than fibrosis. However, it is apparent that some patients with asbestos pleural fibrosis present to their doctors with pleuritic pain or with a persistent chest wall ache [182].

The radiological features vary according to the cause. There may be localized lower zone thickening with obliteration of the costophrenic angle following an unresolved effusion, or more generalized changes. These may have the appearance of 'crow's feet', irregular streaky shadows, diffuse thickening of pleura or a combination. Calcification may be present; if this is unilateral the fibrosis is likely to be due to an old haemothorax or tuberculous effusion, but if bilateral is almost certainly due to asbestos exposure (Fig. 43.11). Grossly thickened pleura with nodular changes is unlikely to be due to fibrosis alone and usually indicates pleural infiltration by carcinoma or mesothelioma.

Occasionally, pleural thickening is responsible for distortion and atelectasis of underlying lung with infolding of pleura, causing appearances resembling tumour. This appearance is sometimes called Blesovsky's syndrome [183,184]. It should be noted that it occurs with diffuse thickening and not with pleural plaques. Some patients with this syndrome may complain of persistent non-pleuritic chest pain.

The clinical course of pleural thickening is varied. In many cases it does not progress. However, when the cause



**Fig. 43.11** Extensive bilateral calcified pleural fibrosis in pipe lagger exposed for many years to asbestos.

is still active, as for example with collagen disease, asbestos and drug therapy, it may progress, infiltrate the peripheral lung and cause restrictive interference with lung function. Pleural thickening is often associated with physical signs. The localized type mimics pleural effusion, with local reduction in movements, percussion note and breath sounds. The generalized type may cause marked limitation of chest wall movements, retraction of intercostal spaces and flattening of the chest wall, mimicking the features of extensive pulmonary fibrosis. As stated above, in such cases lung fibrosis is often present also by extension from the pleura. It is not uncommon to be able to hear inspiratory crackles and there is evidence that these may in some cases originate in the pleura and be distinct from those due to underlying pulmonary fibrosis; in such cases there may be a mid-expiratory component [185].

**Causes**

Any cause of pleural exudate may be responsible for the subsequent development of pleural fibrosis, usually of the localized type. However there are relatively few commonly recognized causes of general pleural fibrosis (Table 43.3). If it is calcified, it is likely to be due to old empyema or haemothorax, tuberculous effusion, artificial pneumothorax treatment or asbestos exposure [186]. Bilateral, diffuse, non-calcified thickening suggests a collagen disease or therapy with  $\beta$ -blockers or methysergide [95,96] (Fig. 43.12).

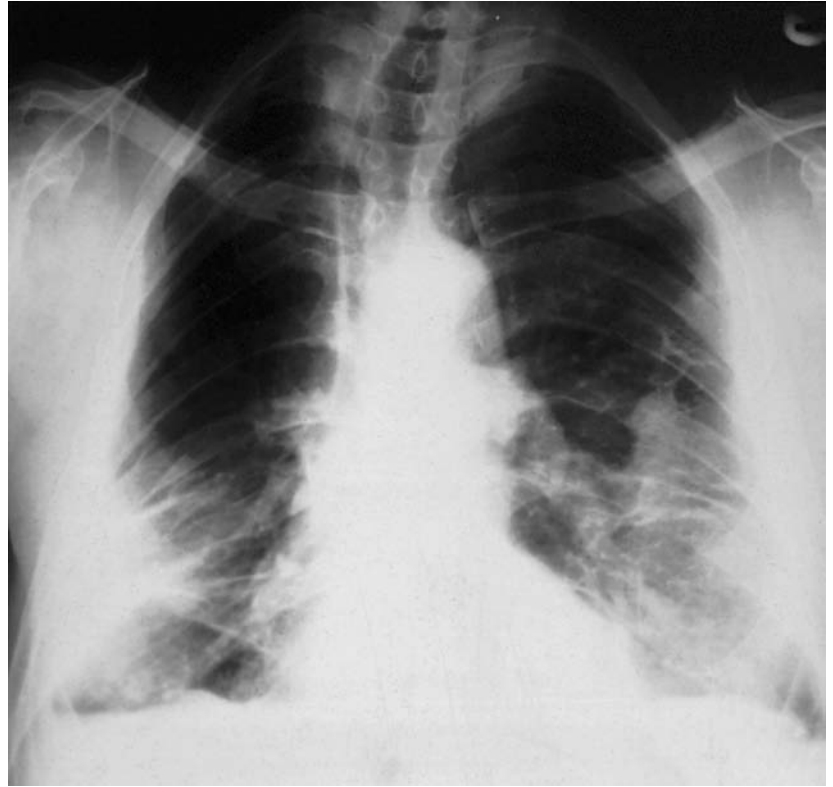
**Table 43.3** Causes of generalized pleural fibrosis.

Tuberculous effusion	Unilateral	Calcified
Old artificial pneumothorax	Unilateral	Calcified
Haemothorax	Unilateral	Calcified
Multiple rib fractures	Either	Either
Old empyema	Unilateral	Either
Thoracotomy, thoracoplasty	Unilateral	Uncalcified
Radiation therapy	Unilateral	Uncalcified
Rheumatoid disease	Bilateral	Uncalcified
Systemic lupus	Bilateral	Uncalcified
Drugs (practolol, methysergide)	Bilateral	Uncalcified
Asbestos exposure	Usually bilateral	Calcified
Silicotic massive fibrosis	Overlying the PMF	Uncalcified

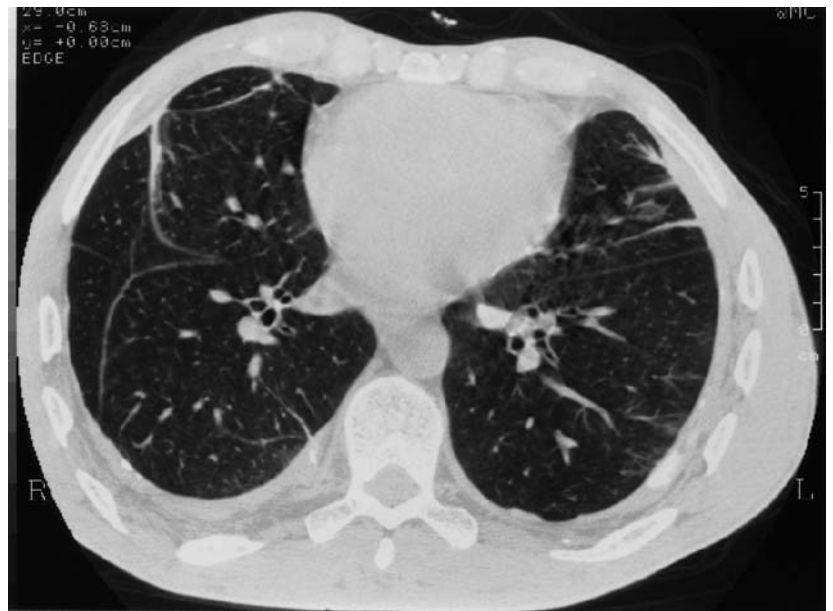
PMF, progressive massive fibrosis.

**Investigation and management**

The clinical history and chest radiograph are usually sufficient to lead to the diagnosis. Care should be taken to exclude asbestos exposure and drug therapy as causes. In the case of the former, diffuse pleural thickening should only be attributed to asbestos exposure if the patient has worked regularly with the material; occasional, incidental or non-occupational exposure to asbestos is very unlikely to cause anything other than pleural plaques. There is evidence from lung asbestos counts that diffuse pleural fibrosis occurs at exposure levels comparable to those that cause early asbestosis [187].



**Fig. 43.12** Bilateral non-calcified pleural fibrosis in patient treated for 10 years with methysergide for migraine.



**Fig. 43.13** High-resolution CT scan of asbestos worker showing diffuse pleural fibrosis with some extension into underlying lung. Calcification is visible bilaterally.

The main problem in diagnosis is differentiation of the lesion from malignant infiltration of the pleura, especially by mesothelioma. Mesothelioma is usually unilateral and associated with some nodular change. However, metastases and alveolar cell carcinoma may present with bilateral pleural involvement. If a primary tumour is not demonstrable, bronchoscopy and needle biopsy of the

pleura may be necessary, though these investigations may be avoided if the appearances are shown to have been present on previous radiographs. CT may be useful in deciding whether extension of the fibrosis into lung has occurred and when surgical treatment is being contemplated [188], and is commonly used in the assessment of asbestos disease (Fig. 43.13).

Apart from the treatment of any underlying cause, such as cessation of drugs or appropriate therapy for collagen disease, there is only one therapeutic decision: whether to seek the advice of a thoracic surgeon. Pleurectomy and 'decortication', i.e. removal of the thick fibrous peel, may release the lung and chest wall and thereby relieve the restriction to ventilation. This operation has much to offer in the case of localized fibrothorax following empyema or tuberculous effusion and surgical advice should be sought early in these situations [189]. Where fibrosis is generalized and well established, the decision should be made after consideration of the patient's disability and age and in the knowledge that the procedure may be hazardous and not produce a dramatic improvement. In particular, care should be taken to assess the underlying lung for the presence of disease such as fibrosis and bronchiectasis and for the extension of pleural disease into its surface; the former prevents a good functional result while the latter causes surgical difficulties and complications. Bronchoscopy, bronchography, CT and regional lung function testing may all be of value in coming to a decision about surgery. In general, the more recent the development of the fibrothorax, the more likely is surgical success, and the more extensive the fibrosis, the better the functional result after surgery. Patients with Blesovsky's syndrome not infrequently undergo surgery in the belief that the lesion is a tumour. Long-term results are generally satisfactory in that it does not recur, although lung function may not improve and may even deteriorate [190]. Operation for asbestos pleural fibrosis is inadvisable since the underlying lung is usually involved and results are likely to be poor.

## Tumours of the pleura

Secondary tumour of the pleura is quite common and is discussed briefly in Chapter 42. Primary pleural tumour is increasing in incidence. The most important and most common, occurring in over 1000 people annually in the UK, is malignant mesothelioma. Benign mesothelioma or fibroma and sarcoma are very uncommon primary pleural tumours.

### Localized fibrous pleural tumour (pleural fibroma, benign mesothelioma)

#### Clinical features

This tumour [191–193] may present as an incidental radiological finding or on account of symptoms; when these are present they may be due to direct pressure effects of the lesion, which cause breathlessness, or to one of the recognized indirect effects: fever and chills [194,195], hypoglycaemia [196] or hypertrophic pulmonary osteoarthropathy [197]. The patient is usually over 40,

although children have been described with the disease. Clinical signs depend on the size of the tumour, which may be very large and mimic massive pleural effusion; in one case, signs suggestive of constrictive pericarditis related to gross mediastinal displacement have been reported [195].

The radiological appearance is usually that of a spherical or lobulated peripheral mass adjacent to the pleura. Occasionally it may have a broad base (Fig. 43.14a) but more usually the pleural connection is a narrow pedicle. As it may arise from parietal or visceral pleura, it may occur anywhere on the chest film in relation to chest wall, diaphragm, mediastinum or fissures. In fissures it may have an ovoid shape. It may be complicated by pleural effusion, which is sometimes blood-stained [194,198].

Pathologically, the tumour is well encapsulated, surrounded by compressed lung, from which it can be shelled out easily. The histological appearances are predominantly of interlaced fibrous tissue with few mitotic figures and areas of myxomatous degeneration (Fig. 43.14b). However, pleomorphic types are well recognized and there may be difficulty in deciding whether the tumour has undergone sarcomatous change [191,199]. While the cell of origin may be mesothelial in some cases, in others the histology suggests submesothelial mesenchymal origin [191].

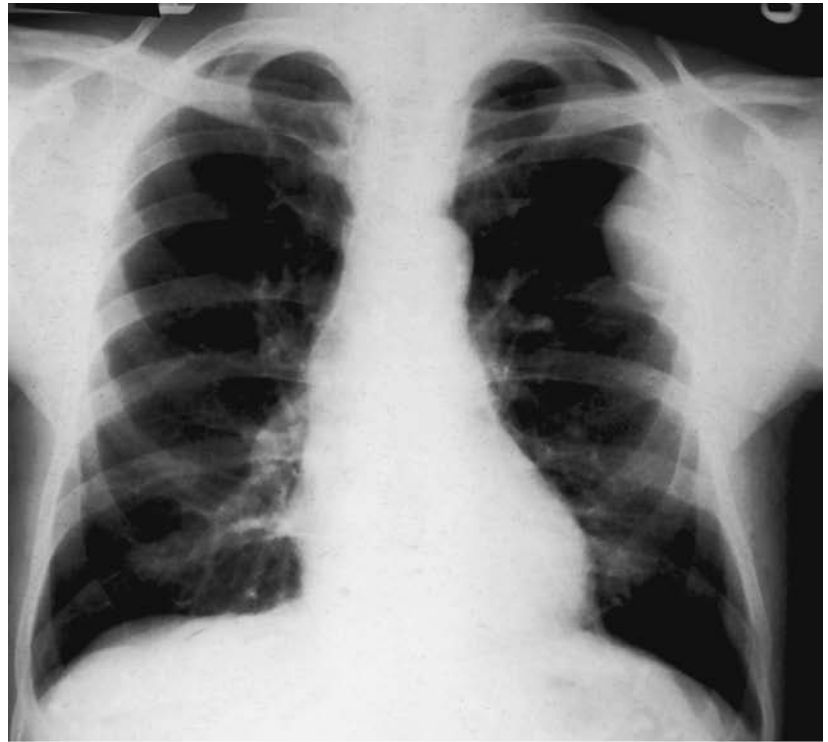
#### Investigation and management

Localized fibrous tumour can rarely be distinguished clinically from bronchial carcinoma; in any case, because of its potential for malignant change the treatment is surgical. Sometimes the presence of hypertrophic osteoarthropathy in association with a tumour adjacent to the pleura suggests the diagnosis. The presence of a haemorrhagic effusion should not prevent surgery.

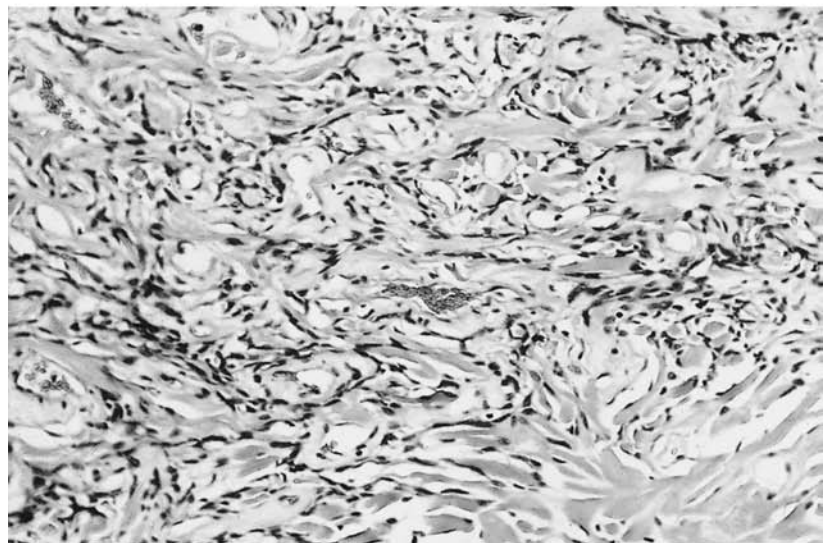
Surgical resection can usually be carried out without removing lung and is normally curative. Secondary effects of the tumour, such as fever and joint pains, disappear by the time the patient wakes from the anaesthetic, while the clubbing and swelling of the osteoarthropathy settle over a month or two. The tumour may sometimes recur and need further resection; osteoarthropathy may be the symptom that announces this. Occasionally the tumour behaves like a sarcoma and metastasizes widely.

#### Pleural sarcoma

This is a very rare and highly malignant tumour that occurs predominantly in young adults [191]. Although it may be confused histologically and radiologically with fibrous or malignant mesothelioma, it is distinguished by the age group of the patient and the tendency to metastasize early. The clinical course is characterized by local invasion of lung and chest wall as well as by blood-



(a)



(b)

**Fig. 43.14** (a) Broad-based chest wall tumour in left upper zone. At operation this proved to be a fibroma. (b) Histology of resected specimen showing admixture of spindle cells and mature collagen.

borne metastases. Histologically it has a pleomorphic appearance, with spindle and polygonal cells with many mitoses.

### **Malignant mesothelioma**

#### **Aetiology**

Before 1960, malignant mesothelioma [200] was regarded as a very rare tumour of unknown aetiology. Several classical cases were described from Glasgow in 1945 but their histological classification was not recognized [201]. In

1960, however, Wagner and colleagues [202] described a large cluster of patients with the disease in the crocidolite asbestos mining area of the North-Western Cape in South Africa. Many further studies have now confirmed the strong association between the tumour and exposure to crocidolite, especially in asbestos product manufacture, ship-breaking and gas mask production. There has been much debate about two other important matters with respect to aetiology: whether all types of asbestos cause the disease, and how large an exposure is necessary for the risk of mesothelioma to be incurred. With respect to the former, animal studies have shown that any asbestos type,

indeed many synthetic and other naturally occurring fibrous minerals, provoke mesothelioma when injected directly into the pleural or peritoneal cavity, although the frequency of this response differs with dose and with different mineral types [203]. However, studies of human populations have shown that the risks of mesothelioma are remote in people exposed only to chrysotile [204], definite in those exposed to amosite [205] and high (up to 10% after as little as a year's exposure) in those exposed to crocidolite [206]. These exposures apply to an occupational setting; para-occupational exposures, such as regular washing of a worker's overalls or close proximity to asbestos insulation work, may also involve high and prolonged dosage and may lead to mesothelioma [207]. The second, and connected, question concerns the amount of asbestos required to provoke mesothelioma. Evidence from pure exposures to crocidolite and amosite has shown that the disease may develop after exposures (almost certainly to very high fibre levels) for as little as 6 months [205,206]. However, there is no evidence associating the disease with exposures to the very low levels that may be found in buildings with undisturbed asbestos walling or insulation. Non-occupational exposures leading to mesothelioma have been described, for example children habitually playing on asbestos waste tips or people living close to a heavily polluting asbestos factory, but these levels of exposure have almost certainly been of the same order of magnitude as those of asbestos workers [207].

The apparent conflicts between the human and experimental data on aetiology are resolved by the hypothesis that chrysotile, while carcinogenic to the pleura, does not normally reach the target organ in sufficiently large doses to initiate the process. Two factors may be responsible for this: (i) its curly nature prevents sufficient being inhaled and (iii) once inhaled the fibres do not reach the pleura in sufficient numbers. Support for the hypothesis comes from the observation that in people with mixed exposures to asbestos much less chrysotile is found in the lungs at postmortem than would be expected from the exposure history, while proportionally much larger amounts of crocidolite or amosite are found [208]. It seems likely that chrysotile does not penetrate so readily into the lung because of its physical and mineralogical characteristics; once in the lung, over the years of residence it is gradually broken down into microfibrils sufficiently small to be removed by macrophages.

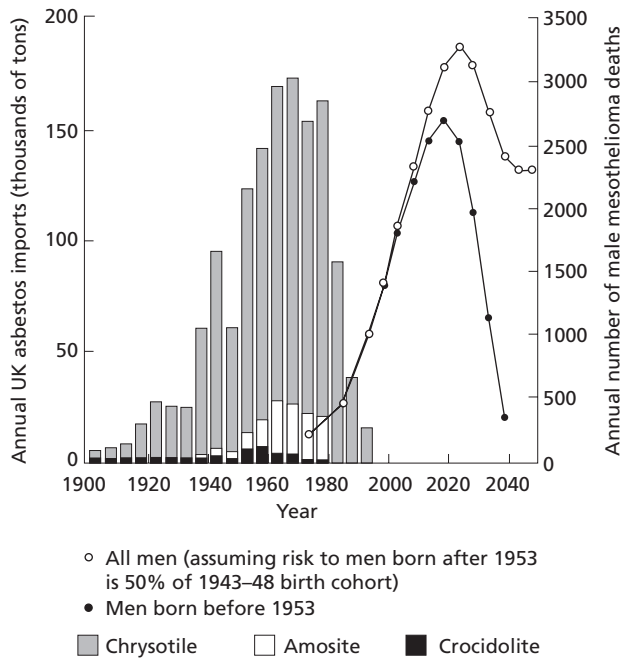
Thus it can be stated with reasonable confidence that mesothelioma is a disease that occurs in people who have been exposed to relatively high levels of crocidolite or amosite in the past, almost always as part of their occupation. In people with no known exposure to these minerals, the risk is about one in a million, since sporadic cases unassociated with any known aetiological agent do occur; in those with heavy past exposure, the risk may be as high as 15%. However, in terms of predicting risk in the

majority of patients presenting with fear of future disease, these figures are often unhelpful since people have usually had mixed exposures in the user industries and never know exactly what they have worked with. The matter of predicting risk is discussed in the section on management.

Mesothelioma has also been described in people living in parts of rural Turkey. Two endemic areas have been discovered, one where the use of naturally occurring tremolite asbestos as building material and whitewash is responsible [180] and another where a non-asbestos mineral, fibrous erionite, is thought to be the cause [178]. The importance of the latter observation is that erionite, though fibrous, is not related to asbestos, thus lending strong support to the hypothesis that the propensity of a mineral to cause mesothelioma is due to its physical rather than its chemical properties. This casts doubt over the safety of a number of other fibrous substitutes for asbestos, such as artificial glass and carbon fibres and naturally occurring vermiculite and wollastonite. So far no epidemiological or clinical evidence has implicated these substances in the causation of mesothelioma, although superfine glass fibres have caused the disease when injected directly into the peritoneum or pleura of rats [209]. It would therefore be prudent for industry to avoid the use of such very fine fibres and to confine commercial interest to those outside the respirable range.

One other intriguing clue to the aetiology of mesothelioma has come from a study that has shown DNA sequences resembling those of a monkey virus, SV40, in human mesothelioma tissue. This virus contaminated some of the injected Salk poliomyelitis vaccines used in the 1950s and, if these observations are confirmed, may be a factor predisposing some individuals to the disease, perhaps acting in synergy with asbestos [210,211].

Approximately 1000 people each year die of mesothelioma in the UK, this figure having risen annually since reliable records were first kept in the late 1960s. This rise has been related to the much increased importation of all forms of asbestos during and after the Second World War that continued almost exponentially until 1970. In that year, crocidolite was effectively banned and control of the use of all asbestos considerably tightened. By 1980, importation of amosite had ceased and that of chrysotile had reduced substantially (Fig. 43.15). Unfortunately, this continued extensive use of asbestos for at least 20 years after the association with mesothelioma was described, together with the fact that once in place the mineral remains a threat to those who are required to remove or otherwise work with it, means that the epidemic of mesothelioma is likely to continue rising for a further 20 years and ultimately may be responsible for some 3000 deaths in the UK each year [212]. Mesothelioma is now the most common of the serious dust-related diseases seen in the UK, as well as being the most fatal.



**Fig. 43.15** Importation of asbestos into the UK and predicted annual deaths of British men from mesothelioma. (From Peto *et al.* [212] with permission.)

### Clinical features

Mesothelioma may affect pleura, peritoneum or pericardium [213]. The last two sites are much less common than the first, and peritoneal mesothelioma seems to have occurred more frequently in the past, reflecting particularly high previous exposures. The tumour characteristically presents 20–40 years after first exposure to asbestos, and often the victim has forgotten that he or she worked with the mineral. However, it is usually possible to obtain a history of work likely to have entailed exposure; jobs in railway workshops, shipyards, ships' engine rooms, gas mask or asbestos manufacture, thermal insulation or building are those most frequently associated with the disease. The first symptoms of mesothelioma are those associated with pleural effusion, breathlessness and chest pain. Often the chest pain is a persistent dull ache, but it may be severe. As the disease progresses, the pain and breathlessness become more troublesome and the patient loses weight. Distant metastases rarely present clinical problems, although they are usually found at post-mortem. Local spread of disease, causing cardiac tamponade, superior caval or oesophageal obstruction, spinal cord and intercostal nerve involvement or chest wall infiltration, is a usual feature; tumour very frequently grows through thoracotomy scars and not uncommonly through needle tracks. Examination of the patient reveals the signs of pleural effusion, though mediastinal displacement to the opposite side is unusual; this combination of appar-

ently massive effusion without displacement of the heart should lead to suspicion of malignant pleural disease. Finger clubbing and hypertrophic osteoarthropathy are rare.

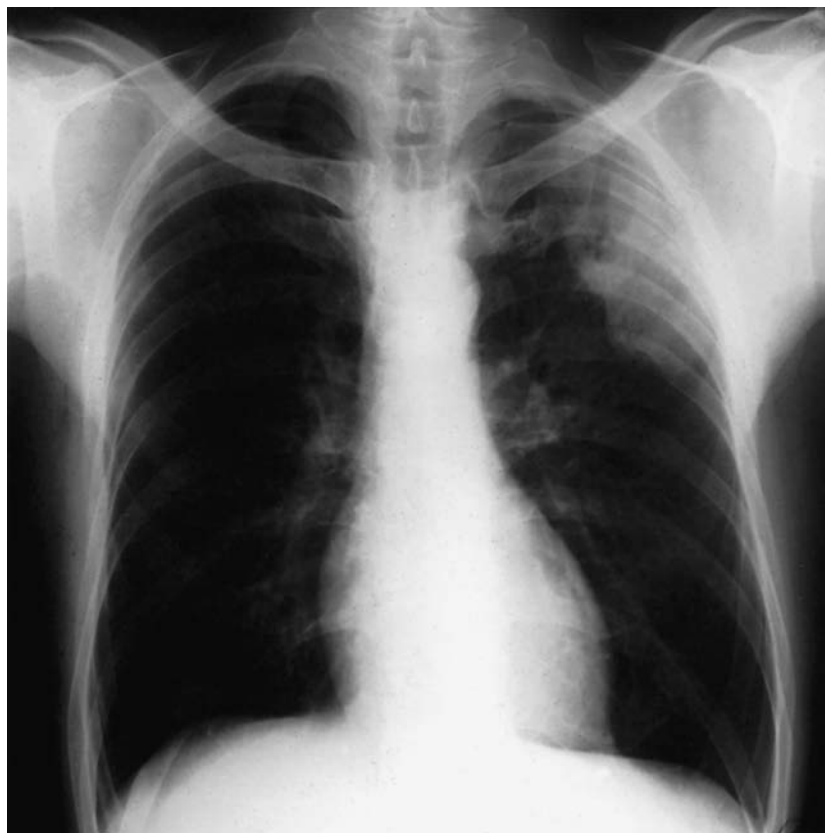
The radiographic features are usually of a large pleural effusion. If the pleura can be seen, pleural nodules may be visible (Fig. 43.16). The lesion is almost always unilateral, although spread across the mediastinum sometimes occurs. Other features of asbestos-related disease may be seen, such as pleural plaques or asbestosis in the opposite lung.

The diagnosis is made on the history and by needle biopsy of the pleura. Typically an attempt to aspirate the effusion is thwarted by encountering much-thickened pleura, and biopsy of this with a cutting needle or drill may show characteristic features. If fluid is withdrawn, it is an exudate and often haemorrhagic. Hyaluronic acid may be present in the fluid or tissue, and cytology with electron microscopy may be useful in the hands of experts [214,215]. However, often the diagnosis cannot be made on examination of the fluid. Moreover, needle biopsy specimens may provide insufficient tissue for a firm diagnosis to be made. In these circumstances, it is wise neither to repeat the procedure too frequently nor to resort to thoracotomy for diagnosis; evidence of pleural tumour, consistent with the diagnosis, is sufficient to exclude a treatable cause of the pleural disease and is also adequate evidence in the UK for industrial injuries benefit to be paid.

The only treatable condition that may mimic mesothelioma is tuberculous pleural disease, and diagnostic efforts should be directed towards excluding this. However, the usual problem in differential diagnosis is whether the condition is mesothelioma or secondary pleural carcinoma. The latter is usually bilateral, except when due to bronchial or breast carcinoma. Certain tumour markers may be helpful in differentiation if the histological appearances are equivocal. Secondary adenocarcinomas frequently stain positively for carcinoembryonic antigen or  $\beta_1$  pregnancy-specific glycoprotein, whereas mesothelioma is usually negative for these [216]. However, until satisfactory treatment becomes available for these tumours, differentiation is of no value to the patient.

The clinical course of mesothelioma is one of steady deterioration to death over 1–2 years; patients are only rarely alive more than 2 years after diagnosis, although there is some evidence that those with a predominantly epithelial histological pattern have a somewhat better prognosis, a few long-term survivals in this group having been described [200]. Death usually occurs after a prolonged period of increasing chest pain and breathlessness, and may be precipitated by terminal infection or cardiac involvement. Loss of appetite and weight are constant features.





**Fig. 43.16** Unusual presentation of mesothelioma without pleural effusion but with extensive tumour in left upper chest wall.

### Pathology

The gross appearances are of a thick rind of white or grey-yellow tissue surrounding the lung and usually involving both pleural layers [217,218] (Fig. 43.17). The pleural space may be wholly or partly obliterated; where it persists it contains mucinous or haemorrhagic fluid. The tumour infiltrates lung, chest wall and diaphragm, and is frequently present in surgical wounds and needle tracks. Although few in number, metastases are frequently present in lung, nodes and other viscera.

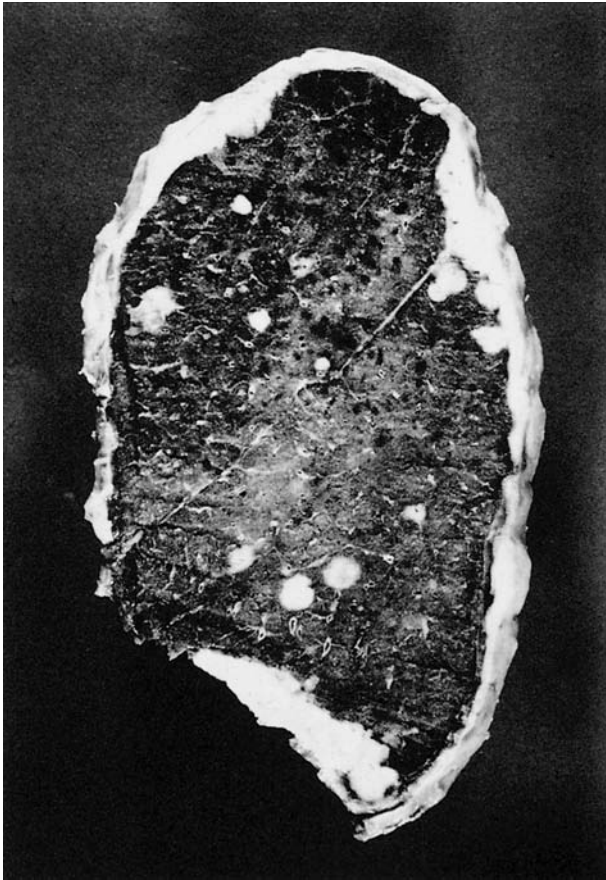
The histological appearances vary, reflecting the potential of mesothelial cells to differentiate into epithelial or mesenchymal tissue. Typically there is much collagen, often containing clefts lined by tumour cells (Fig. 43.18). The predominant histological pattern may be epithelial, consisting of cuboidal or flattened cells forming tubular and papillary structures separated by a matrix that may consist of closely packed spheroidal cells, collagen or a mixture. This type may be confused with adenocarcinoma, especially with small biopsies, and it is in these circumstances that special stains may be of value in differentiation. The other main histological type consists of diffuse spindle cells, resembling sarcoma. Frequently the two types coexist in different areas of the same tumour. There is some evidence that the epithelial type has a

slightly better prognosis than the mixed and sarcomatous types. Asbestos bodies are not usually seen in the tumour but may be found in the lungs of the patient. Analysis of lung tissue using phase-contrast optical microscopy for uncoated asbestos fibres usually reveals large numbers [219]. Electron microscopy is necessary to analyse the fibres, since it is not possible to differentiate asbestos from other fibres commonly found in lungs by light microscopy [220]. Electron microprobe analysis usually shows the asbestos present to be predominantly crocidolite or amosite, since over time chrysotile dissolves. It should be stressed that such expensive and time-consuming analyses are of great value in research into asbestos-related diseases but have no useful application in clinical diagnosis. However, they are used increasingly in litigation issues, since the very large numbers generated by these methods have an impressive effect on judges and juries.

### Management

The prospects for curative treatment are not good. Surgery, radical radiotherapy and chemotherapy have all been tried and a number of enthusiastic reports published. However, none of these has been controlled and the few long-term survivors are matched by those from untreated

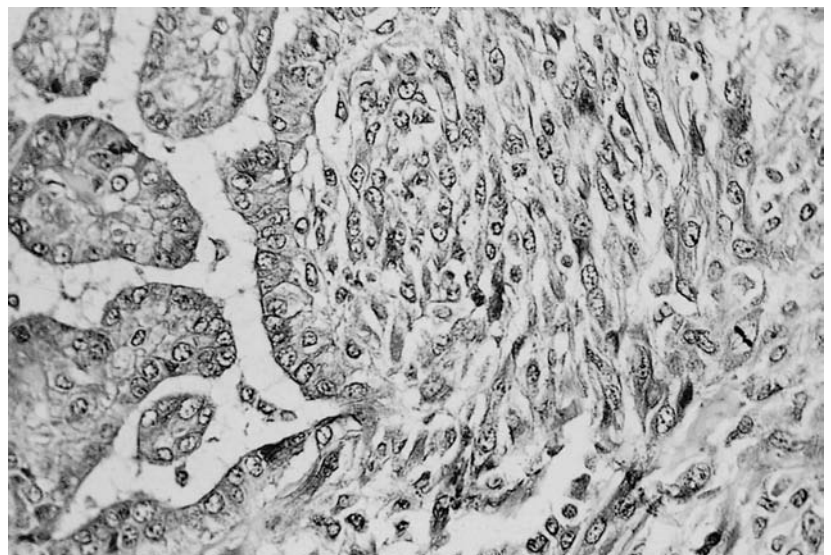
series. In particular, it is wise to be sceptical of reports of improved survival rates in people treated for 'early disease'. Clearly, the earlier intervention occurs in the natural history of a disease, the longer the apparent sur-



**Fig. 43.17** Excised lung with surrounding mesothelioma. Some metastatic deposits are also visible in the lung.

vival unless the treatment actually reduces it, and it is therefore necessary in any such research to have controls in order to demonstrate benefit convincingly. Surgery, which is popular in the USA, has a high mortality and is attended by considerable discomfort. Radiotherapy may produce some regression and prevent reaccumulation of fluid, although the author's experience suggests that it has a useful place in palliation of tumour growing through aspiration tracks or wounds and might also have a prophylactic role after aspiration or pleural biopsy. Single-agent therapy with doxorubicin, cyclophosphamide, interferon  $\gamma$  and other drugs and multiple regimens have been tried, all with anecdotal reports of improvement. Perhaps the most promising has been interferon  $\gamma$  administered intrapleurally, although in this study the response was seen only in very early cases who might well have been expected to live longer anyway [221]. There is clearly a need for multicentre controlled trials, and until then the management of individual patients must depend on the physician's judgement. Since the chances of achieving long-term remission seem as bad with treatment as without and the side-effects of treatment often add to the patient's misery, it is wise to confine treatment to palliation of symptoms with appropriate analgesics. Radiotherapy or *C. parvum* pleurodesis may be helpful in preventing recurrent effusions and the former may be useful in the relief of local bone or nerve pain or in reducing the size of subcutaneous extensions of tumour.

An increasingly frequent aspect of management related to mesothelioma is the requirement to advise patients who have been exposed to asbestos about their risks of developing the disease. This arises particularly in relation to the finding of pleural plaques on a chest radiograph, which sometimes leads to ill-considered advice to sue an employer rather than to reassurance



**Fig. 43.18** Histological appearance of a malignant mesothelioma showing tubopapillary tumour to the left and sarcomatous cells to the right. Note the mitotic figure in the mid right (haematoxylin & eosin  $\times 300$ ).

about the benign nature of this condition. It is now possible to make reasonable predictions of risk from the epidemiological study of Peto and colleagues [212]. These authors have calculated lifetime probabilities of death from mesothelioma for British males by year of birth. For those born between 1933 and 1938 the risk is about 8 per 1000, rising to about 12 per 1000 in the 1943–48 birth cohort. These estimates may be multiplied by the relative risks for different trades (e.g. 7 for metal plate and shipyard workers, 4 for plumbers and 3 for electricians) to give an estimate that can be further weighted by a detailed knowledge of the individual's exposure history within the confidence intervals given in the paper. Thus a shipyard worker, such as a shipwright or boilermaker, born in 1943 might have a lifetime risk (assuming typical exposure to asbestos in that trade) of about 8%. This can be explained

to an individual in relation to risks of other diseases such as heart attack or any type of cancer in order to put matters into some sort of perspective. It has to be said that this form of prediction has become a necessary part of the business of preparing a medicolegal report and almost inevitably causes anxiety to the patient unless explained very carefully.

## Other pleural lesions

Endometriosis may very rarely involve the pleura, causing haemopneumothorax associated with menstruation [222,223]. Transplantation of splenic tissue to the pleura, splenosis pleurae, has been described very rarely following abdominal injuries with rupture of the spleen [224]. They present as rounded pleural opacities.

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# PNEUMOTHORAX

DOUGLAS SEATON

A pneumothorax is defined as the presence of air within the pleural cavity. The term was first used in the doctoral thesis of the French physician Itard in 1803 [1], although the presence of abnormal collections of air and fluid within the chest might have been inferred as early as the fifth century BC by physicians in ancient Greece who practised so-called Hippocratic succussion of the chest [2,3].

## Classification and terminology

In health each lung is surrounded by two contiguous layers of pleura separated by the potential space known as the pleural cavity. The pressure in this space is negative with respect to the atmosphere and as a result the elastic structures comprising the lung are held in apposition to the chest wall. Should air gain entry to the pleural cavity by whatever means, intrapleural pressure becomes less negative with respect to atmospheric pressure and this permits the lung to move away from the chest wall by deflation until a point is reached at which the pressure remains sufficiently negative to prevent further collapse. Should the pressure in the pleural cavity reach that of the atmosphere then a complete, as opposed to a partial, pneumothorax is said to exist. Should intrapleural pressure exceed that of the atmosphere then as well as the pneumothorax being complete, the structures comprising the mediastinum are compressed and displaced to the opposite side producing a tension pneumothorax.

From the foregoing it is clear that a pneumothorax cannot occur unless the integrity of either the visceral or parietal layer of pleura, or both, is breached. Should the breach remain patent then a fistula exists and the pneumothorax may be described as open. More frequently the breach seals off, resulting in a closed pneumothorax. A tension pneumothorax arises when the defect is valve-like, permitting air to pass into the pleural cavity on inspiration but preventing its escape. A working classification of pneumothorax based on aetiology is given in Fig. 44.1.

## Spontaneous pneumothorax

Any pneumothorax occurring in the absence of trauma may be described as spontaneous (syn. primary simple pneumothorax, primary pneumothorax, simple pneumothorax, pneumothorax simplex, idiopathic pneumothorax). The term 'primary spontaneous pneumothorax' is used in the absence of clinical evidence of pre-existing respiratory disease, while 'secondary spontaneous pneumothorax' denotes a clinically recognizable coexisting structural or functional abnormality in the lung. In a histopathological sense this distinction is somewhat artificial as small defects in the pleura and adjacent lung (see below) have been causally related to primary spontaneous pneumothorax. However, it should be stressed that the distinction remains clinically valid, since these defects in primary spontaneous pneumothorax are of no functional significance and usually go undetected prior to the event. Some cases of secondary spontaneous pneumothorax may at first be misclassified as primary before the underlying clinical condition evolves to the point of recognition.

## Primary spontaneous pneumothorax

Spontaneous pneumothorax most commonly occurs in apparently healthy subjects with no history of pre-existing lung disease. In a series of 210 consecutive cases of spontaneous pneumothorax admitted to a teaching hospital over a 5-year period, 67% fell into this primary category [4]. Primary spontaneous pneumothorax is predominantly a disease of young adults, being rare in children [5], the peak incidence falling in the third decade [4,6,7]. One study found that spontaneous pneumothorax was primary in 81% of cases presenting at the age of 45 years or under [4]. It is also of note that the condition predominantly affects males, the male to female ratio lying somewhere between the 12:1 found in a study of 118 cases of primary spontaneous pneumothorax [8], 4:1 in a series of 400 cases [9] and 3:1 in a later Swedish community survey that included 2414 patients [10]. In a detailed community-



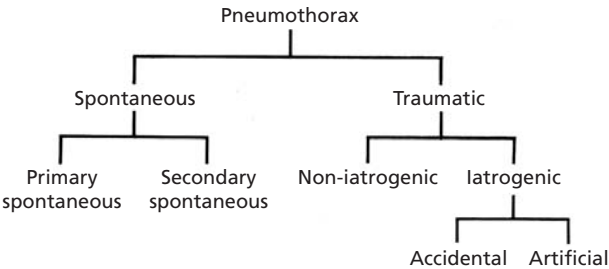


Fig. 44.1 Classification of pneumothorax.

based survey carried out in Minnesota, USA, the incidence of primary spontaneous pneumothorax was found to be 7.4 per 100 000 per year for males and 1.2 per 100 000 per year for females [11]. A similar overall incidence has been reported in the UK [6]. The annual incidence in Stockholm was found to be higher at 18 per 100 000 for men and 6 per 100 000 for women [10]. The right and left lung appear to be affected with equal frequency [12].

**Aetiology** (Table 44.1)

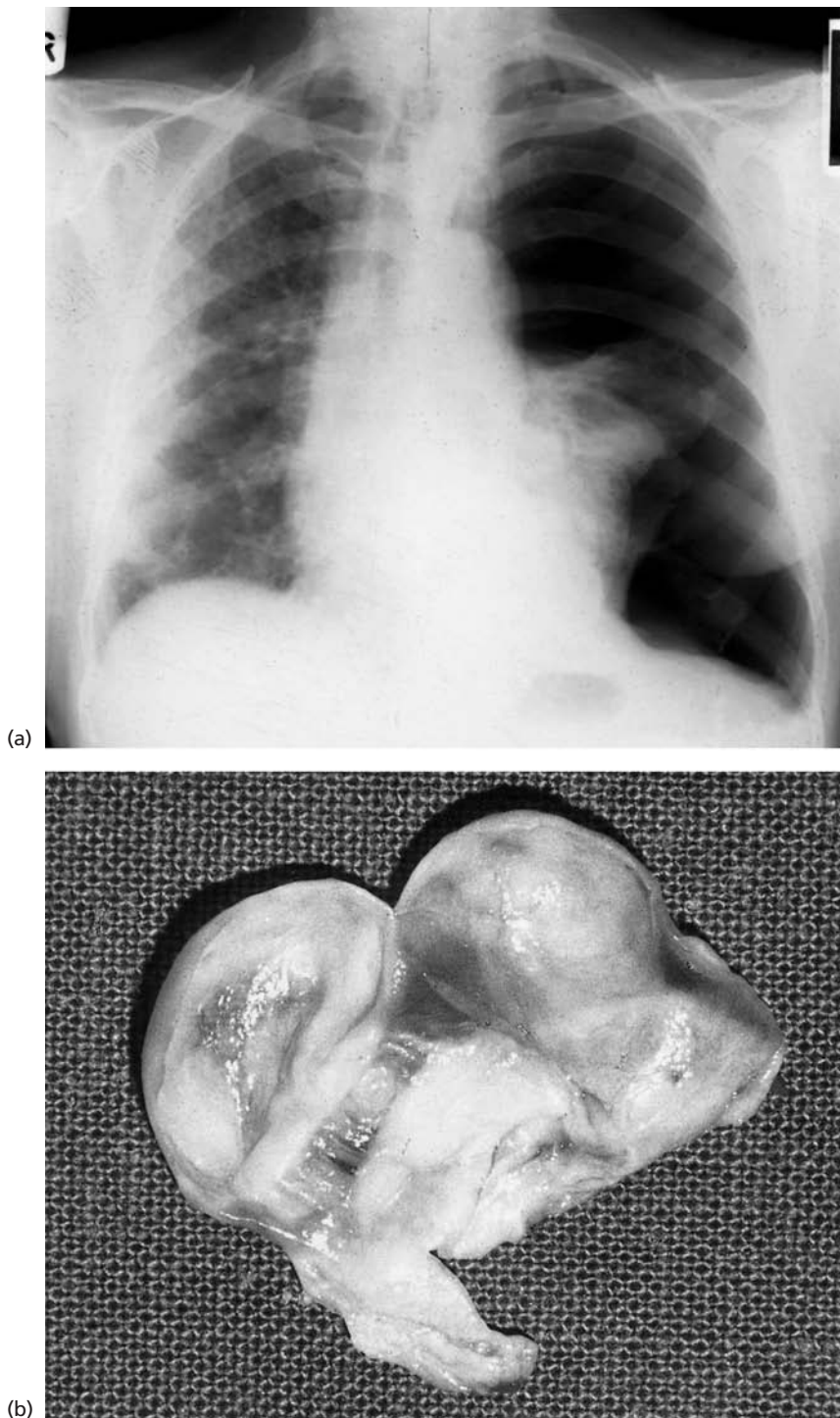
In the early part of the twentieth century spontaneous pneumothorax was, in the minds of most physicians, inextricably bound up with pulmonary tuberculosis, Biach [13] having described such an association in 79% of 918 cases of pneumothorax. A gradual realization that pneumothorax could occur in the absence of underlying lung disease subsequently emerged and Kjaergaard's monograph [14] in which he reviewed 51 cases did much to cause general acceptance of the concept of primary spontaneous pneumothorax. This results from the rupture into the pleural cavity of a small air-filled space know as a pulmonary bleb (Fig. 44.2), a localized collection of air within the cellular layers of the visceral pleura that is contiguous with the lung parenchyma [15]. Blebs may arise as a result of a congenital weakness in the connective tissue of subpleural alveoli and electron microscopic studies have demonstrated that communications exist between blebs and the adjacent alveolar spaces [16]. In cases of primary spontaneous pneumothorax coming to surgery it has been shown that blebs are very common, occurring in over 90% of patients [17], are frequently multiple, occur most commonly at the lung apices and are found in the uncollapsed contralateral lung almost as frequently as in the lung where the pneumothorax has occurred [18,19]. Blebs may occur more frequently at the lung apices as a result of the regional differences in mechanical stresses known to exist within the lungs [20]. In the upright posture a gravity-dependent gradient of negative intrapleural pressure extends along the length of each lung so that distending forces are greatest over the lung apices [21], just as a loosely coiled spring, when suspended by its uppermost coil, becomes progressively more expanded by its own

Table 44.1 Causes of pneumothorax.

<i>Spontaneous pneumothorax</i>
Primary
apical blebs
stature
Secondary
chronic bronchitis and emphysema
asthma
suppurative pneumonia
tuberculosis of the lungs
cystic fibrosis
rare causes (see text)
<i>Traumatic pneumothorax</i>
Non-iatrogenic
open and closed chest injury
barotrauma
Iatrogenic (accidental)
paracentesis thoracis
pleural biopsy
transbronchial biopsy
percutaneous lung biopsy/aspiration
central venous cannulation
barotrauma (mechanical ventilation)
rare causes (see text)
Iatrogenic (deliberate)
artificial pneumothorax

weight from bottom to top (Fig. 44.3). It has also been suggested that the relative ischaemia at the apex of the lung makes this area more susceptible to infection, so that blebs may develop as a result of inflammation occurring in a zone of maximal stress [22] and there is some histological support for this view [19]. A higher incidence of primary spontaneous pneumothorax has been recorded in individuals who have a tall and thin body habitus. In a study comprising 92 patients with primary spontaneous pneumothorax, mean height was found to be 5 cm greater and mean weight 11 kg less than predicted [23]. A study in the UK recorded a similarly increased mean height in patients with primary spontaneous pneumothorax [24]. In a Japanese study that compared patients with primary spontaneous pneumothorax with controls, those in the pneumothorax group were no taller but had significantly longer lungs and were also leaner [25]. In a detailed epidemiological study in the USA it was concluded that much of the male predominance in spontaneous pneumothorax could be explained in terms of height [11].

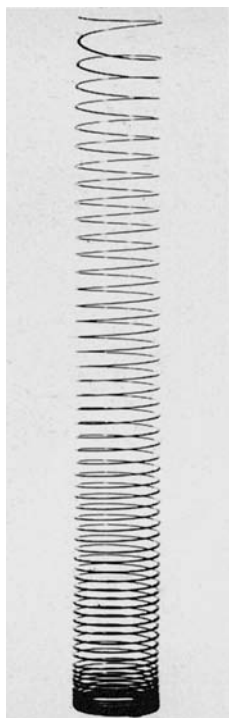
There have been several case reports of primary spontaneous pneumothorax occurring in families [26–28]. In one such report an association between spontaneous pneumothorax and specific human leucocyte antigen (HLA) and antitrypsin phenotypes was suggested but not proved conclusively [29]. In a study of 286 Israeli military personnel, a positive family history of primary spontaneous pneumothorax was obtained in 11.5% of cases [30]. The



**Fig. 44.2** (a) Left pneumothorax showing blebs at apex. (b) Operative specimen showing excised blebs.

lungs of some patients with spontaneous pneumothorax have been reported to contain high levels of soluble hydroxyproline. This substance is a degradation product of collagen and the finding was taken to imply an abnormality in the structure or biosynthesis of lung collagen resulting in its increased breakdown [31]. A high incidence of tobacco smoking has been reported in several series of primary spontaneous pneumothorax and this may be a

predisposing factor [7,11,32,33]. A Swedish study found that there was a significant dose-response relationship between smoking and the occurrence of primary spontaneous pneumothorax, the habit increasing the risk 22-fold among men and ninefold among women [10]. Data relating to the same group also showed that there was an apparent temporal relationship between tobacco consumption and changes in the incidence of primary sponta-



**Fig. 44.3** Suspended spring showing effects of increased tension in the upper coils.

neous pneumothorax in the community, a decrease in consumption being followed by a decrease in incidence within 1–2 years [34]. It is conjectured that the repeated stress imposed upon the walls of a pulmonary bleb by a smoker's cough might make it more likely to rupture. A causal relationship between the presence of a sharp inner border to the first or second ribs and primary spontaneous pneumothorax has been proposed [35]. This finding was present at thoracotomy in 49% of a series of 57 cases compared with only 8% of control subjects coming to thoracotomy for other reasons. It has been claimed that patients presenting with primary spontaneous pneumothorax are more likely to have minor bronchial anomalies at endoscopy than controls [36] and these patients are also more likely to show localized emphysema-like changes on CT, particularly in the upper zones and towards the lung periphery [37].

#### **Secondary spontaneous pneumothorax** (Table 44.1)

Spontaneous pneumothorax that occurs as a result of disease is categorized as secondary. Although it is less common than the primary form in developed countries, accounting for about one-third of cases [38], this may not be the case in those parts of the world where the prevalence of pulmonary tuberculosis remains high. With this possible exception, chronic bronchitis and emphysema are the most frequently associated conditions, accounting for

30–50% of cases in this group [4,33]. As these patients tend to be middle-aged or elderly, emphysema is the most common cause of pneumothorax in patient over 40 years of age [39]. Spontaneous pneumothorax has been recorded in 0.8% of a series of 1714 patients admitted to hospital with acute exacerbations of chronic bronchitis and emphysema [40]. Emphysematous bullae on the plain chest radiograph are frequently evident but this is by no means always the case [41]. In emphysema the leakage of trapped air through the weakened walls of dilated airspaces is probably assisted by the high intrabronchial pressures produced as a consequence of repeated coughing. It is also evident that pneumothorax may occur in association with large congenital bullae or cysts and in the absence of airflow limitation.

In one series, pneumothorax was reported to complicate 1.4% of cases of active tuberculosis [42]. Over 90% of these were cavitating and the pneumothoraces were thought to have resulted from the breakdown of tuberculous lesions situated close to the visceral pleura. It was observed that this might have been a more frequent complication had the overlying pleura not been thickened by fibrosis: when the pneumothorax did arise, the fibrosis caused it to be localized and limited in size. Before the advent of effective antituberculous chemotherapy, pneumothorax was frequently accompanied by a persistent bronchopleural fistula and tuberculous empyema with a mortality rate of 30–50% [43]. Pneumothorax has also been described in association with miliary tuberculosis but this is a rare complication [44].

Pneumothorax occasionally complicates asthma, having been found in 0.8% of 2000 adult asthmatics and 2.6% of 269 children admitted to hospital with severe asthma [45,46]. A more recent review of the chest radiographic findings of 1016 adult patients with asthma that was severe enough to require hospital admission in a large city in the UK found only one case (0.1%) of complicating pneumothorax [47].

Suppurative disease of the lungs and pleurae, particularly staphylococcal and *Klebsiella* pneumonia, is associated with pneumothorax. In the former, multiple lung abscesses may lead to the formation of cystic spaces or pneumatoceles that sometimes rupture into the pleural cavity, although such pneumatoceles are rare in adult compared with paediatric practice [48,49]. Prior to the availability of modern antibiotics, pneumothorax complicated approximately 5% of cases of staphylococcal pneumonia in adults and over 30% of cases in children [50,51]. Staphylococcal pneumonia continues to be the leading cause of pneumothorax in children and infants beyond the neonatal age group.

With the increasing prevalence of human immunodeficiency virus (HIV) infection, pneumothorax has become recognized as an important complication that occurs in approximately 2–4% of patients with AIDS, over 90%

of pneumothoraces in this condition being associated with active or previous episodes of *Pneumocystis carinii* pneumonia [52,53]. The chances of a patient with AIDS-associated *Pneumocystis* pneumonia developing a pneumothorax have been found to be about 6–9% [54]. One North American series of 120 patients with spontaneous pneumothorax referred to a surgical unit found that 27% of them had AIDS [55]. Patients with AIDS may be subject to bullous changes that have been termed ‘premature emphysema’ and *Pneumocystis* pneumonia itself has been shown to produce cystic changes on CT that persist despite clinical recovery [56]. Spontaneous pneumothoraces in AIDS are more commonly bilateral than is the case with other predisposing conditions, occurring in both lungs simultaneously in 34% according to one reported series [55]. It has been suspected that aerosolized pentamidine might predispose to spontaneous pneumothorax, although doubt remains on this score [53,57].

Patients with cystic fibrosis have a high incidence of spontaneous pneumothorax, which increases with age and which is an important cause of morbidity and mortality in this group (see Chapter 30) [58,59].

All other causes of secondary spontaneous pneumothorax may be regarded as unusual or rare. The diseases responsible include diffuse pulmonary inflammation of varying severity, which may be associated with fibrosis and cyst formation (honeycomb lung), and more localized disease processes abutting the pleural surface. Individual case reports abound and the following list is not exhaustive: cryptogenic fibrosing alveolitis [60]; occupational lung disease, particularly acute silicosis and Shaver’s disease [61,62]; granulomatous disease such as sarcoidosis, usually at a late and fibrotic stage [63] but occasionally at an early stage of active inflammation [64]; Langerhans-cell histiocytosis (histiocytosis-X) [65] and Wegener’s granulomatosis [66]; rheumatoid disease [67]; systemic sclerosis [68]; haemosiderosis [69]; lymphangioliomyomatosis [70,71]; pulmonary alveolar proteinosis [72]; inherited disorders of connective tissue such as Marfan’s syndrome [73], Ehlers–Danlos syndrome [74] and the marfanoid hypermobility syndrome [75]; other hereditary conditions, including neurofibromatosis [76] and tuberous sclerosis (which has been linked with lymphangioliomyomatosis) [77,78]; coccidioidomycosis [60,79]; parasitic infections of the lung including hydatid disease [80]; intrathoracic tumours, particularly metastatic sarcomas and germ cell tumours [81,82]; primary bronchial carcinoma [83]; malignant mesothelioma of the pleura [84]; and cavitating pulmonary infarction [85]. Pneumothorax has been seen with septic pulmonary emboli occurring as a complication of staphylococcal tricuspid endocarditis in drug addicts using intravenous heroin [86]. Infection or inflammation in the gastrointestinal tract may unusually result in pneumothorax that may complicate retropharyngeal abscess formation [87]. Fistulous communications

have also been described between benign gastric ulcers and the pleural cavity across an anatomically intact diaphragm [88] and between stomach, colon and the pleural cavity in the presence of congenital diaphragmatic herniae [89,90]. Pneumothorax has also been recorded in association with hyperinflation and cystic changes occurring distal to congenital bronchial atresia [91]. Radiotherapy used to treat Hodgkin’s disease above the diaphragm using a ‘mantle’ field may be complicated by pneumothorax [92,93].

Recurrent pneumothorax associated with menstruation was first reported by Maurer and is known as catamenial pneumothorax [94,95]. This rare condition, which is the usual way in which the thoracic endometriosis syndrome declares itself, is right-sided in about 90% of cases and is associated with multiparity, the pneumothorax occurring within 24–72 h of the onset of menstruation. Symptomatic pelvic endometriosis may be present in one-third to half of patients [96,97]. Examination of the diaphragm has occasionally revealed bluish cystic implants of endometrial tissue and there may be tiny diaphragmatic fenestrations through which it is supposed that endometrial tissue may find its way from the pelvis to the pleural cavity [98,99]. Less frequently the thoracic endometriosis syndrome presents as haemoptysis, sometimes in the presence of lung nodules consisting of islands of intrapulmonary endometrial tissue that may reach the lung by microembolization through the pelvic veins [100].

### Traumatic pneumothorax

Traumatic pneumothoraces may arise from the penetration of the pleural cavity as a result of stab or gunshot wounds or from its accidental puncture by needles or cannulae. It may also occur in closed or blunt chest injury such as may result from road traffic accidents or explosions [101,102]. In this situation, rib fractures and bronchial rupture are frequent findings, as is blood loss into the pleural cavity resulting in haemopneumothorax [103,104].

### Iatrogenic pneumothoraces

Iatrogenic pneumothoraces are common [105]. A 5-year study from a Veterans Administration medical centre in California found iatrogenic pneumothoraces to be slightly more common than the spontaneous variety; one-third were caused by transthoracic needle aspiration biopsy of suspected lung disease, 28% by thoracentesis and 22% by attempts to cannulate the subclavian vein [106].

About 12% of thoracenteses carried out on medical services result in pleural air leaks and pneumothoraces, although these are often shallow [107,108]. The frequency with which pneumothorax occurs may be increased further by closed needle biopsy of the pleura, although

rates of 8% or less are achieved as the experience of the operator increases [108]. Pneumothorax is also a common complication of the placement of intercostal tubes intended for the drainage of malignant pleural effusions. The pneumothorax rate was found to be 31% in 88 such patients when drainage of pleural fluid was being effected by a small-bore tube [109]. None of these pneumothoraces were associated with tension or respiratory distress, the tendency being for them to either resolve spontaneously or remain stable [109].

Pneumothorax is an accepted but unwelcome complication of percutaneous lung biopsy by any form of needle or trephine (see Chapter 8), occurring in 20–45% of patients. In some but not all studies, the rate of pneumothorax has been found to be greater with increasing distance of the target lesion from the chest wall and also with smaller lesions, which may require more needle passes to locate them [110–113]. Lower complication rates have been obtained when a fine-gauge needle is employed [110,114], and lower rates may also be obtained when a modern gun-actuated cutting needle is used [115,116]. These accidental pneumothoraces are generally shallow but when they do occur chest tube placement has been recorded as necessary in 10–30% of cases [111,116]. Some investigators have found that the probability of pneumothorax is increased not only by greater depth of penetration of the needle but also by the presence of an obstructive impairment of ventilatory capacity [110,117]. Others have found that an obstructive impairment of lung function does not reliably predict complicating pneumothorax, although when pneumothorax does occur the need for tube placement clearly depends on the severity of any pre-existing pulmonary impairment [110–113]. It has been claimed that if the patient breathes pure oxygen before lung biopsy, the frequency of complicating pneumothoraces is reduced [118]. However, Poe and colleagues [117] observed an unaltered risk after breathing oxygen, although the size of the pneumothorax was reduced and the rate of its absorption increased.

Subclavian vein cannulation, with location of the vein by surface landmarks, is commonly used for measurement of central venous pressure, the administration of high-dose chemotherapy and long-term antibiotics, and total parenteral nutrition. A prospective study of 821 subclavian vein catheterizations found the overall pneumothorax rate to be 1.5% [119]. The complication rate increased with the number of passes, if body mass index was greater than 30 or less than 20 and if the patient had undergone prior surgery or radiotherapy to the ipsilateral hemithorax. The complication rate was not reduced by the use of ultrasound to help localize the vein [119]. Sometimes such pneumothoraces are 'delayed' and are not evident on the radiograph taken immediately after catheterization [120].

Pneumothorax is the most common complication of transbronchial lung biopsy, occurring in about 2–5% of

cases or in a higher proportion if fluoroscopy is not used (see Chapter 8). Although pneumothorax in this situation is usually an immediate complication, it may occasionally be delayed by hours or even days [121]. The diagnostic yield of routine chest radiographs is very low in patients who have just undergone fluoroscopically guided transbronchial lung biopsy but who have no symptoms or fluoroscopic findings suggestive of pneumothorax, no unsuspected pneumothorax being found in 305 consecutive procedures in a study from the University of Virginia [122].

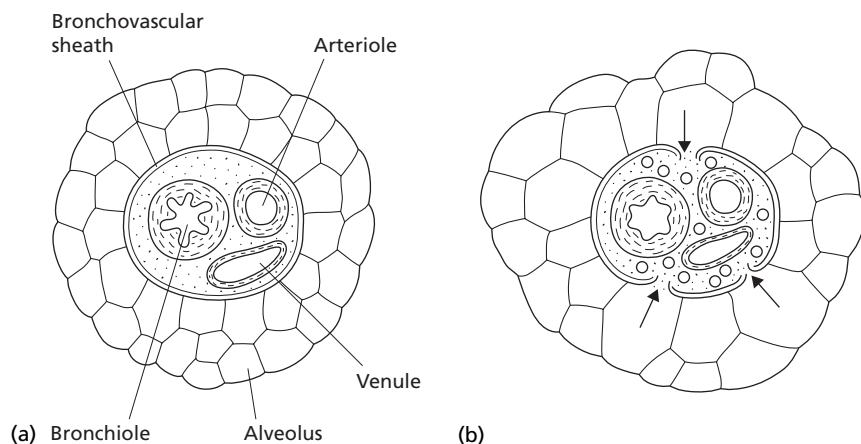
Pneumothorax may also complicate needle biopsy of the mediastinum, breast and liver [123–125], and may occur following tracheostomy [126].

Traumatic pneumothorax has also been described following a further miscellany of procedures, including acupuncture of the thoracic wall [127], the surgical use of a laser beam in the upper respiratory tract [128,129] and the misplacement of a small-bore nasogastric feeding tube in the respiratory tract [130]. Oesophageal rupture resulting from instrumental or other trauma may lead to pneumothorax in association with mediastinitis [131]. Pneumothorax may be self-inflicted by drug addicts who, having used all accessible veins in the arms, may resort to the practice of internal jugular or subclavian vein injection ('pocket shooting') [132,133]. The author has also seen traumatic pneumothorax occurring as a form of deliberate self-injury in a patient with psychological problems and access to hypodermic needles.

### Pulmonary barotrauma

Since the volume of a given mass of gas at a constant temperature is inversely proportional to its pressure (Boyle's law), so a given volume of air, saturated at 37°C, expands to approximately 1.5 times the volume it would have occupied at sea level if it is placed at an altitude of 3050 m. Should the air in question be trapped in a pleural bleb, the expansive force may cause that bleb to rupture into the pleural cavity resulting in a pneumothorax. Individuals who may be subject to such decompression occurring suddenly and by accident include aircrew, in whom radiographic screening procedures have been employed to exclude blebs prior to acceptance for flight training [134].

Considerable pressure changes may also occur underwater (see Chapter 57). The atmospheric pressure on the surface of the sea is 101 kPa (760 mmHg) but this increases linearly and doubles with every 10 m of descent. During scuba (self-contained underwater breathing apparatus) diving, in which compressed air is delivered to the lungs from a cylinder via a demand regulator, it is during ascent that barotrauma may occur: as ambient pressure falls rapidly, so gas contained in the lungs expands and serious damage may occur [135]. Such injury can be avoided if the diver is taught never to breath-hold and to ascend slowly,



**Fig. 44.4** Barotrauma resulting in pneumomediastinum: (a) normal situation; (b) distended gas-containing spaces with air tracking from ruptured alveoli into the connective tissue plane of the bronchovascular bundle from which it may travel to the mediastinum and beyond. (After Maunder *et al.* [138].)

giving time for the expanding gas to escape by exhalation. Similarly, submariners who have to surface rapidly in submarine escape tank training must never do so with the glottis closed but must be taught to exhale continuously during ascent in order to allow the expanding intrathoracic gas to vent [136,137]. Caisson workers are at similar risk from rapid decompression.

Under all these circumstances expanding gas may break through both alveoli and subsequent anatomical barriers: 1 the visceral pleura to produce pneumothorax (which may be bilateral);

2 the bronchovascular bundle (Fig. 44.4) to produce mediastinum;

3 the connective tissue continuum leading from the mediastinum to the neck and beyond, producing subcutaneous emphysema; and

4 the diaphragmatic hiatus, entering the peritoneal cavity and more rarely tracking between the diaphragm and the parietal pleura to produce encysted pockets of gas at the lung bases.

Much more seriously, rapidly expanding gas that has escaped from ruptured alveoli may track back into torn pulmonary veins, resulting in systemic arterial air embolism [139].

Pneumothorax due to barotrauma may also occur in patients who require positive-pressure mechanical ventilation, although this correlates most closely with the nature of the underlying disease. This is a particular problem in patients with adult respiratory distress syndrome (ARDS) [140,141]; 17% of 41 patients with ARDS receiving high-level ( $>15\text{ cmH}_2\text{O}$ ) positive end-expiratory pressure ventilation developed radiographic signs of barotrauma including pneumothorax in one recent series [142]. Barotrauma may also occur as a result of attempted cardiopulmonary resuscitation [143]. Endotracheal tube misplacement, which is common, may also increase the chance of barotrauma by directing an excessive blast of air to one lung [144]. Systemic arterial air embolism has also occurred as a result of ventilator-associated barotrauma in

association with ARDS and necrotizing pneumonia, but is rare [145].

There have been a number of reports of spontaneous pneumothorax occurring during the inhalation of recreational drugs, such as crystalline free base cocaine ('crack') and cannabis (marijuana, hashish, 'dope', 'pot', 'grass', 'ganja', 'hash'). The former, which looks like small crystals ('rocks'), may be smoked in a pipe or the vapour may be inhaled from a piece of heated tin foil, in contrast to cocaine powder which is taken like snuff. Cannabis is usually smoked mixed with tobacco in a rolled cigarette. Those pneumothoraces that have been described may result from a form of barotrauma, in both cases possibly being related to coughing or straining while the user is breath-holding after a deep inhalation near total lung capacity [146,147]. Pneumothorax due to presumed barotrauma has also been reported with the use of tracheo-oesophageal voice prostheses by patients who have had a total laryngectomy for carcinoma of the larynx [148].

### Artificial pneumothorax

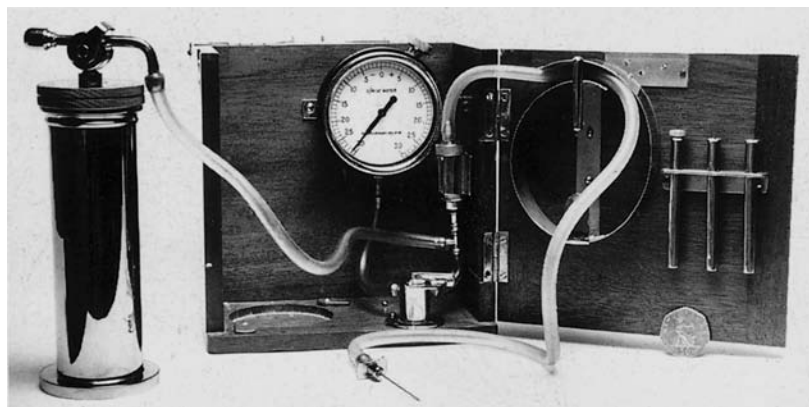
This term refers to the deliberate introduction of a measured volume of air into the pleural cavity by needle, using a device such as that illustrated in Fig. 44.5. Devised by Forlanini in the nineteenth century, this procedure became a popular method of treatment for pulmonary tuberculosis in the era before antibiotics but is now obsolete, although the technique is still employed diagnostically in order to enable the thoracoscopist to visualize the surface of the lung and postoperatively in order to test whether a chemical or surgical pleurodesis has been effective [149].

### Physiological disturbance

When pneumothorax occurs in a previously healthy subject, a restrictive impairment of ventilatory capacity is produced with a reduction in vital capacity, functional



**Fig. 44.5** Maxwell box used to induce artificial pneumothorax for the treatment of tuberculosis before the introduction of chemotherapy.



residual capacity and total lung capacity commensurate with the size of the pneumothorax [150]. There may also be a small reduction in diffusing capacity for carbon monoxide ( $DL_{CO}$ ) and increase in the transfer coefficient ( $K_{CO}$ ) [151]. If the pneumothorax is large, with greater than 20% collapse, then  $PaO_2$  falls immediately before returning to normal over the space of a few hours, despite the fact that the size of the pneumothorax may remain the same [152,153]. The initial hypoxaemia results from the shunting of blood through deaerated lung. The subsequent return to normoxaemia despite persisting lung collapse results from compensatory vasoconstriction that abolishes gross ventilation-perfusion mismatching in the affected lung [154]. Pulmonary function almost always returns to normal following re-expansion of the collapsed lung and although minor defects of gas distribution and reduced pulmonary compliance have been recorded, they appear to be of no clinical significance [155].

In tension pneumothorax the physiological disturbance may be severe and life-threatening. A valve-like tear in the visceral pleura permits air to progressively fill the pleural cavity during each inspiratory effort. As the intrapleural pressure builds up, hypoxaemia results from compression of both the ipsilateral and contralateral lung and the mediastinal structures are displaced across the midline. This mediastinal displacement and compression may cause a fall in cardiac output leading to hypotension and syncope.

Experiments with dogs have shown that the induction of pneumothorax in the conscious animal results in hyperventilation with arterial normoxaemia and hypocapnia. The belief that this behaviour is in part neuronally mediated is supported by the observation that when the same procedure is carried out in the vagotomized dog, hyperventilation does not occur and hypoxaemia ensues. General anaesthesia also impairs this adaptive response [156]. The relevance of these findings to the physiological consequences of pneumothorax in humans is unclear.

A study of regional lung function in spontaneous pneumothorax showed uniform airway closure on the affected side at low lung volumes, leading to the suggestion that

this was the chief cause of ventilation-perfusion mismatch [157].

## Clinical features

### Symptoms

The most common mode of presentation is for a previously fit young man to develop sharp unilateral chest pain. This is frequently accompanied by shortness of breath, although pain may be the sole presenting symptom in two-thirds of patients [158]. The pain may be continuous but tends to be exacerbated by deep inspiration and postural change. It is often of moderately severe intensity but is sometimes insufficiently troublesome to cause the patient to seek medical advice for several days [159]. It is common for the pain to settle within a day or so, despite the persistence of the pneumothorax on the chest radiograph. Very occasionally a pneumothorax may be found unexpectedly on a chest film taken for routine reasons in a symptom-free individual. This suggests that spontaneous pneumothorax may occur more frequently in the population than is realized and that it may resolve unnoticed. The majority of cases of spontaneous pneumothorax are unassociated with physical exertion [33,160,161].

Extreme dyspnoea in a previously healthy subject is unusual and implies that the pneumothorax is under tension. In this situation the patient is anxious, restless and tachypnoeic, struggling for breath. Unless tension is relieved the patient may worsen, developing a rapid low-volume pulse and hypotension. Dyspnoea may be equally extreme with only a small pneumothorax; when this occurs in patients whose lung function is already impaired by underlying disease and in order that serious and unnecessary mishaps may be avoided, it is essential for clinicians to be alert to the possibility of pneumothorax when assessing a deteriorating patient with known asthma or chronic obstructive airways disease.

In the majority of patients the pneumothorax is small;



when this is the case, the presenting symptoms subside within a few hours even though there has been little or no radiographic improvement. Cough is not a prominent feature unless related to coincidental disease and when present is usually dry [17].

Spontaneous bilateral pneumothorax is rare [38,162,163], occurring in subjects who rupture bilateral apical blebs simultaneously or in patients with extensive bilateral emphysema or other cystic lung disease. It may be rapidly fatal [164].

### Physical signs

A small pneumothorax may be impossible to detect on physical examination. If a sufficient volume of air enters the pleural cavity it insulates the lung from the stethoscope, producing the classical diagnostic signs described by Laënnec, comprising unilateral absent or diminished breath and voice sounds in the presence of a normal or hyperresonant percussion note [165]. Other signs are less important but complementary. Chest movement may be diminished on the affected side. When tension is present the chest may appear larger ipsilaterally and the mediastinum may be pushed to the opposite side, resulting in displacement of the trachea and apex beat. Similarly if the pneumothorax is right-sided, the liver may be displaced downwards so that the upper level of hepatic dullness moves caudally. There may be jugular venous engorgement.

A crepitous sound may be heard over the precordium and is sometimes even noticed by the patient. This noise is referred to as a 'mediastinal crunch' and may occur throughout the cardiac cycle, being influenced in its intensity by posture and the phase of respiration. It was described by Lister [166] in association with left-sided pneumothorax and later by Hamman [167], who considered it to result from free air in the mediastinum (Hamman's sign). In fact it may occur in both conditions, resulting from the close proximity of trapped air to moving heart muscle, and is not pathognomonic of pneumomediastinum. It has also given rise to the terms 'noisy' or 'clicking' pneumothorax [168,169]. Leakage of air into the mediastinum may spread to the subcutaneous tissues of the neck and beyond producing the characteristic palpable crepitus of 'surgical' emphysema, which may spread further to involve the face, anterior chest wall and beyond, sometimes alarming both onlookers and the patient who may quite suddenly come to resemble the 'Michelin man' of advertisement fame. Both may be reassured since this impressive sign is of no particular prognostic significance.

The signs of an associated pleural effusion or haemothorax are likely to be overlooked unless it is of moderate size, in which case in addition to the more usual physical signs devotees of medical history may perform Hippocratic

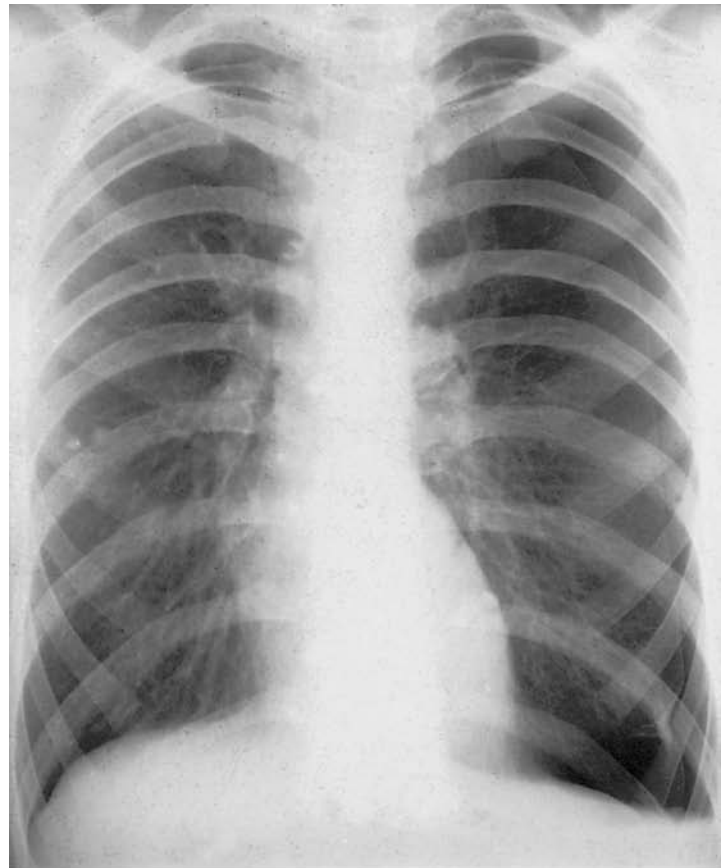
succussion, in which a splashing sound is produced by rocking the patient to and fro [170]. The coin test is another obsolete manoeuvre, although the 'scratch sign' is sometimes usefully employed. In this test the stethoscope is placed in the mid-point of the sternum and the surface of the chest wall scratched with the finger at points equidistant to the left and right of the instrument. The sound heard is louder when the side of the pneumothorax is scratched [171].

The occurrence of pneumothorax in a mechanically ventilated patient may be suggested by (i) the sudden onset of tachycardia and hypotension, caused by a tension pneumothorax impeding venous return; (ii) an increase in peak airway pressure, resulting from external lung compression; (iii) a sudden decline in oxygen saturation; or (iv) the distressed patient appearing to 'fight the ventilator'.

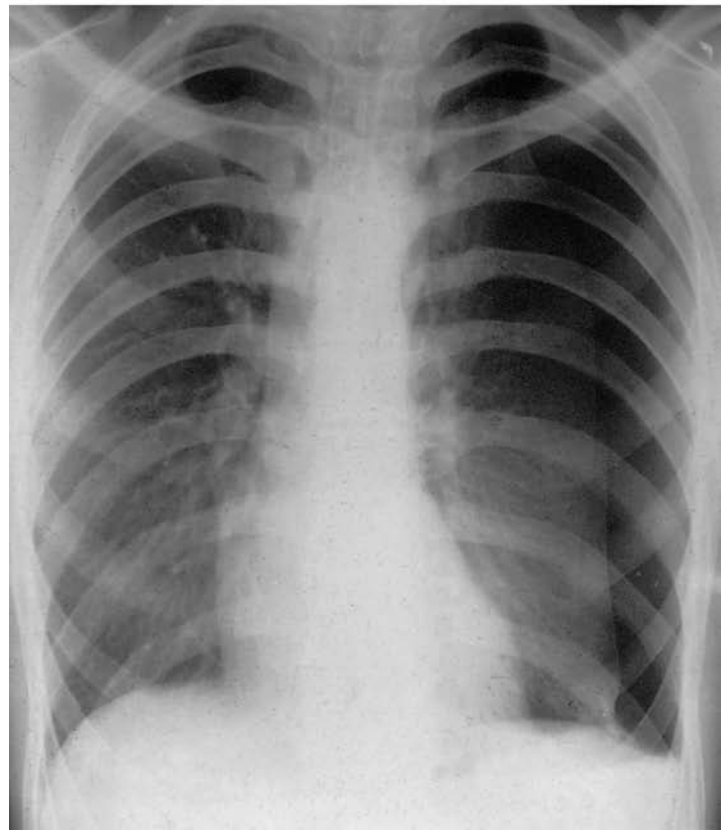
### Radiographic appearances

The characteristic finding is a sharply defined lung edge that is convex outwards and separated from the chest wall by a lucent zone entirely devoid of lung markings (Fig. 44.6). The thin white line representing the lung margin may be overlooked if the pneumothorax is shallow, in which case it may be hidden by bony shadows particularly if it is apical, as it may well be on an erect posteroanterior chest radiograph. If a pneumothorax is suspected clinically but cannot be detected on a standard inspiratory film, then two procedures may be used to confirm or refute the diagnosis. In the first the chest radiograph is taken in full expiration. This has the effect of reducing the volume of both the thorax and the partially deaerated lung. As the volume of gas contained within the pleural cavity is incompressible at physiological pressures, it remains the same on expiration and the pneumothorax therefore appears to enlarge in relation to the smaller thoracic volume (Fig. 44.6). In the second method the chest radiograph is taken in the lateral decubitus position with the side on which the pneumothorax is suspected uppermost [172]. Even a small pneumothorax is revealed by this technique as the air-lung interface becomes clearly visible beneath the lateral chest wall. This is also the preferred view for demonstrating pneumothorax in infants. In complete pneumothorax the lung appears as a dense globular shadow at the hilum (Figs 44.2 & 44.7). However, with lesser degrees of collapse the density of the lung may vary little from that of the fully expanded viscus. This finding is probably the result of a commensurate reduction in pulmonary blood flow [173]. Sometimes increased blood flow to the opposite lung may produce exaggerated vascular markings that may be mistaken for pneumonic shadowing.

In a tension pneumothorax the lung may be compressed into a shapeless shadow or even displaced across the

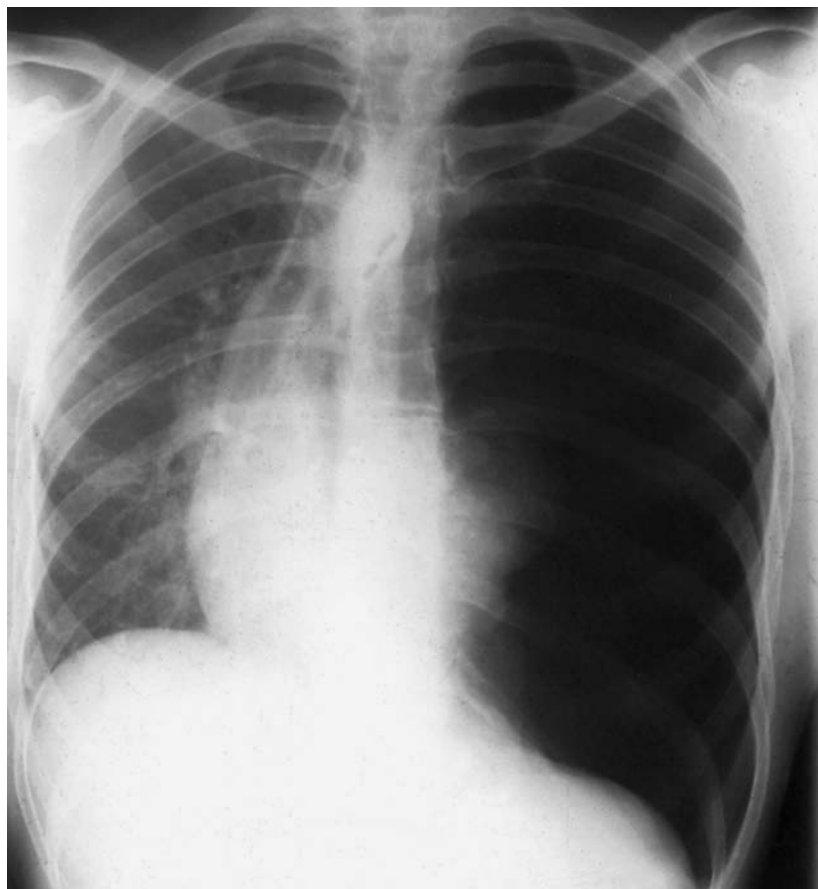


(a)



(b)

**Fig. 44.6** (a) Respiratory and (b) expiratory films showing apparent enlargement of left pneumothorax on expiration.



**Fig. 44.7** Tension pneumothorax showing small dense shadow of collapsed left lung and deviation of mediastinum to the right. There is gross overdistension of the left thoracic cavity.

midline along with the mediastinal structures (Fig. 44.7). In addition, the diaphragm may be depressed so that its costal attachments become clearly visible. It should be noted that some degree of mediastinal displacement is to be expected on an expiratory film and that this does not indicate tension. Some mediastinal displacement is also commonly seen in large pneumothoraces in the absence of *clinical* signs of tension such as tachypnoea and hypotension. When there is also fluid as well as air in the pleural cavity it appears as a completely horizontal line with no meniscus where it abuts the lateral chest wall (Fig. 44.8) and this finding may draw the observer's attention to the presence of a small pneumothorax that might otherwise have been missed.

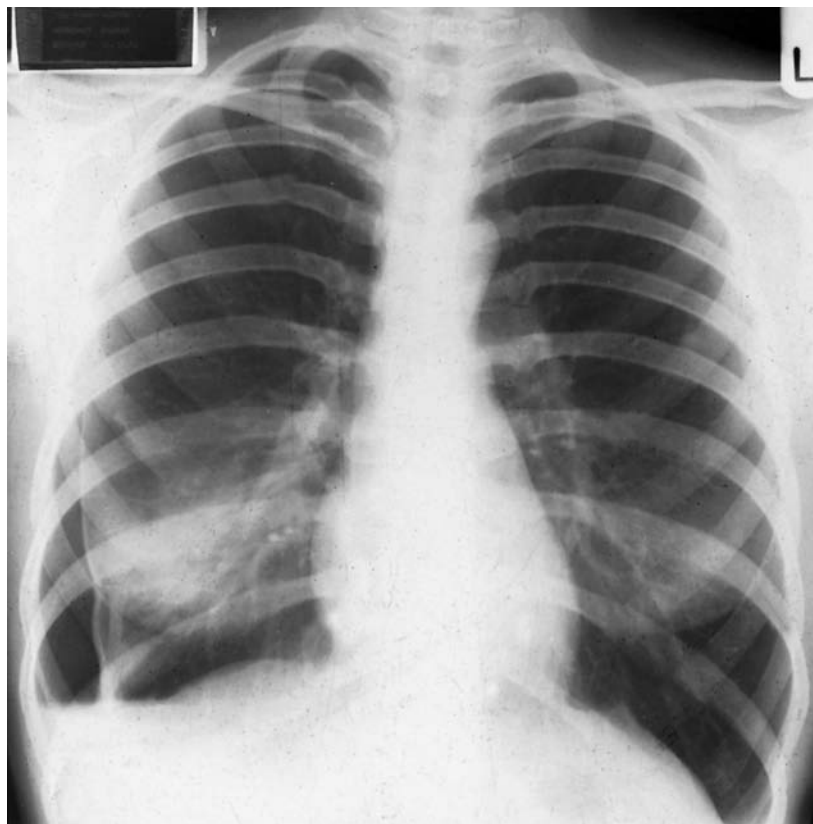
It has been suggested that CT may be useful in the unusual case where the distinction between a bulla and a pneumothorax cannot be easily made but in practice this is seldom necessary [102].

In patients under intensive care only supine films may be available for interpretation. In this situation a pneumothorax may be indicated by increased lucency on the ipsilateral side due to an anterior collection of gas, and by a deep lateral costophrenic angle also on the involved side. This last feature has been called the 'deep sulcus sign' and

when present should lead to a request for a lateral decubitus or 'cross table lateral' view to confirm [174].

### Differential diagnosis

Although the differential diagnosis includes many conditions associated with chest pain and dyspnoea, in practice few difficulties are encountered. Pain due to myocardial infarction, pleuritis associated with pulmonary infarction or pleural infection, and the pain of intra-abdominal inflammatory disease, such as a perforated peptic ulcer, may occasionally suggest pneumothorax to the clinician but any doubts should be resolved by physical examination and the chest radiograph. It should be noted that changes in the ECG typical of a transmural myocardial infarction may be produced by a left-sided pneumothorax, although these changes resolve once re-expansion has occurred [175]. A breathless patient with generalized emphysema may have physical signs that give rise to confusion with pneumothorax but again the chest film is generally diagnostic. Where a massive emphysematous bulla or congenital lung cyst occupies a large part of one hemithorax, the physical signs may be indistinguishable from pneumothorax and even the chest radiographic



**Fig. 44.8** Right hydropneumothorax showing basal fluid level.

appearances may not be dissimilar (Fig. 44.9). It is on such occasions that time taken to enquire about or to obtain previous chest radiographs is time well spent (Fig. 44.10). A lateral decubitus view is often helpful in differentiating an upper lobe bulla or cyst from a typical pneumothorax; in the first case, the gas is constrained by the anatomical boundaries of the upper lobe, whereas in pneumothorax it usually moves to lie along the lateral chest wall. The herniation of a large volume of gut through a diaphragmatic defect may also mimic the physical signs of a basal pneumothorax. Such defects may be congenital or acquired, in which case a history of recent or remote trauma to the lower chest or abdomen (e.g. road traffic accident) might be obtained. When radiographic uncertainty exists, barium contrast studies of the upper or lower bowel are diagnostic.

It is emphasized that pneumothorax should always be considered when patients with previously diagnosed lung disease, such as asthma or chronic obstructive pulmonary disease, present with an apparent deterioration.

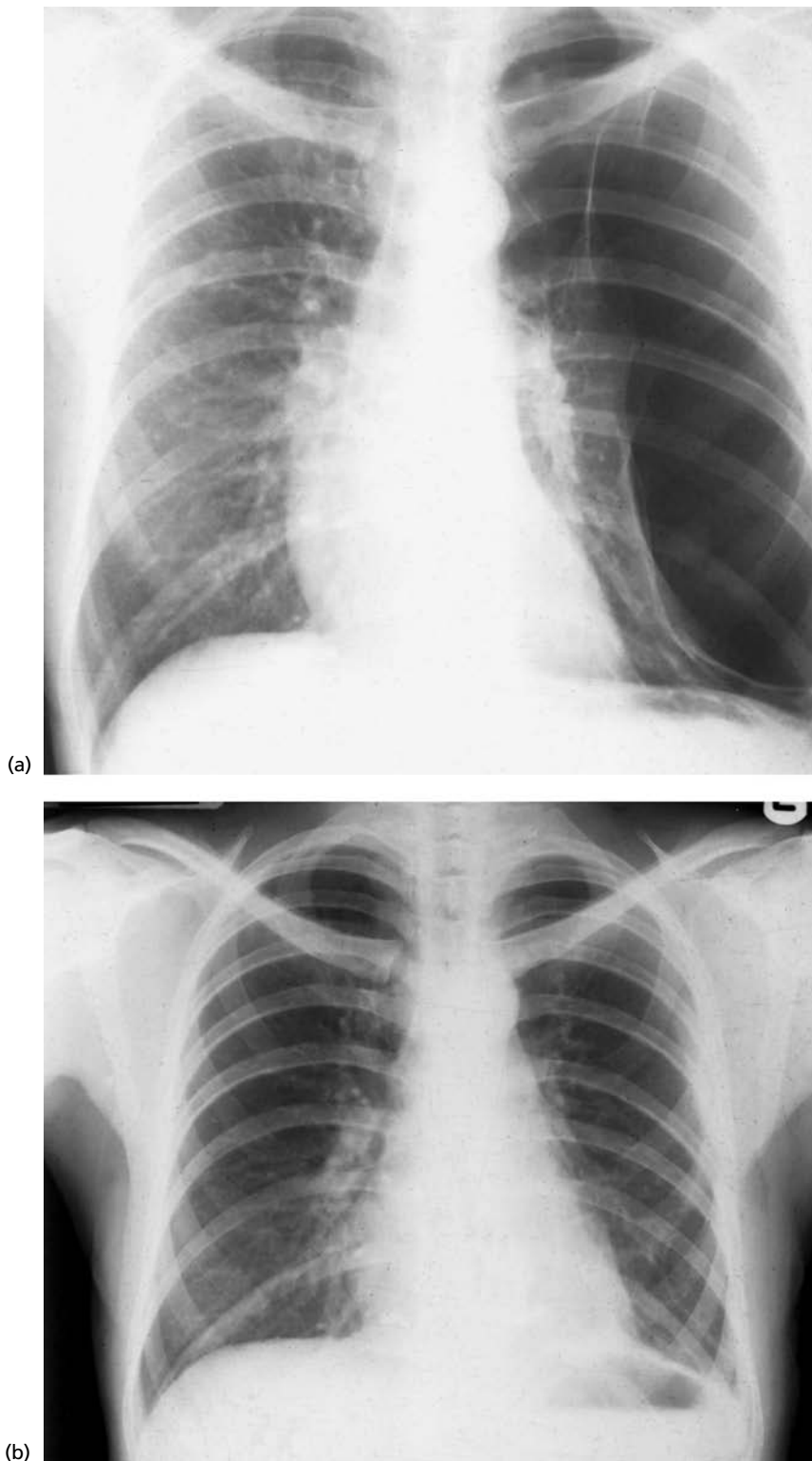
### **Management of spontaneous pneumothorax**

There is evidence of considerable variation in individual management of spontaneous pneumothorax, thoracic sur-

geons on the whole tending to resort to more active measures than physicians [176].

### **Conservative management**

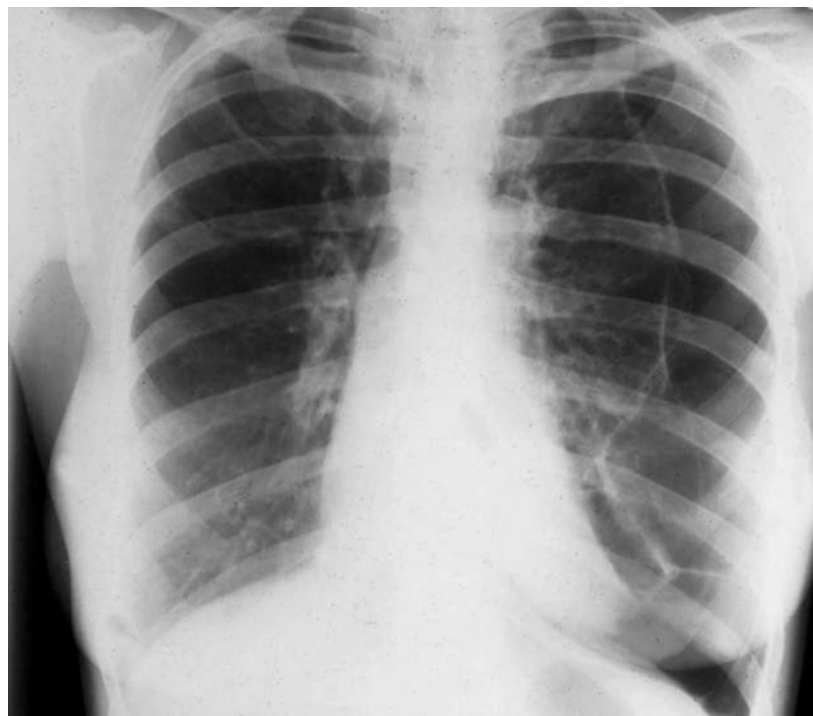
Conservative management relies upon the natural tendency of the gases in a pneumothorax space to be reabsorbed and has the attraction of avoiding any form of invasive procedure [177,178]. This approach is indicated in an otherwise healthy adult who is not breathless and in whom the volume of the pneumothorax is judged to be small. 'Small' is widely taken to mean that the pneumothorax occupies less than 20% of the hemithoracic volume. Various methods for calculating the volume of a pneumothorax have been published [179,180] but these are rarely used in practice. Thus most clinicians leave a primary spontaneous pneumothorax that they gauge as shallow, treating those that are moderate or large [181]. As a rule of thumb, if the lateral edge of the lung is separated from the ipsilateral chest wall in the horizontal plane and at the widest point of the pneumothorax by more than one-third of the transverse diameter of the hemithorax, then the pneumothorax can be regarded as moderate to large and active treatment is reasonable. Previously healthy patients with small spontaneous pneumothoraces need not be admitted to hospital and rest in bed is not manda-



**Fig. 44.9** (a) Large, presumably congenital, bulla in asymptomatic young woman mimicking pneumothorax. (b) Same patient after excision of bulla showing expansion of normal lung.

tory. Non-manual work may be continued but heavy physical exertion should be disallowed. The chest radiograph should be repeated at weekly intervals until full expansion has occurred; meanwhile the way should have been prepared for prompt admission should dyspnoea develop. If any doubt exists the safest course is to admit

and observe for 24 h in order to ensure that the pneumothorax is not enlarging. Patients with significant underlying lung disease such as emphysema should be admitted for observation even if the pneumothorax is shallow, since these patients are at risk of developing severe respiratory failure if the pneumothorax enlarges.



**Fig. 44.10** Somewhat similar appearance to that in Fig. 44.9a but due to a tethered pneumothorax. A previous film showed no abnormality.

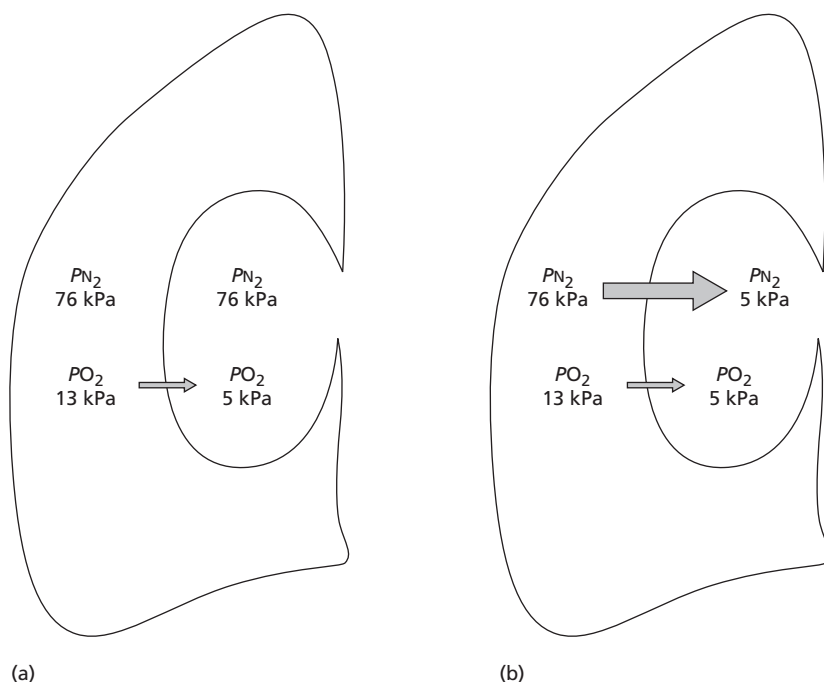
Provided the pneumothorax remains 'closed', the lung will re-expand slowly. This is because the rate of transfer of gases across a semi-permeable membrane is directly proportional to the difference in partial pressure of the gases on either side of the membrane. The total gas pressure of alveolar air is approximately 101 kPa (760 mmHg) at sea level, this being the same as the arterial total gas pressure; however, the venous total gas pressure is about 93.8 kPa (705 mmHg) due to the fall in  $P_{O_2}$  from approximately 13.3 kPa (100 mmHg) in the arterial system to 5.3 kPa (40 mmHg) in the venous system, the balance being due to the smaller rise in  $P_{CO_2}$  between the arterial and venous phases. Kircher and Swartzel [179] described a radiographic method to express the volume of pneumothorax as a percentage of hemithoracic volume and found an average rate of re-expansion of 1.25% hemithoracic volume per day. Thus, provided that there is no further air leak, a '10% pneumothorax' re-expands in approximately 8 days, a '20% pneumothorax' in 16 days, and so on.

Absorption of gas from a pneumothorax space may be hastened by breathing a high concentration of oxygen [180]. By breathing 100% oxygen instead of ambient air, which contains about 79% nitrogen, alveolar  $P_{N_2}$  falls and nitrogen is gradually washed out of the tissues and vascular system as oxygen is taken up, so that the end-capillary total gas tension eventually falls from approximately 93.8 kPa (705 mmHg) to around 22.6 kPa (170 mmHg). This produces a substantial gradient between the tissue capillary (low  $P_{N_2}$ ) and the pneumothorax space, which is nearer atmospheric pressure (about 101 kPa, relatively high  $P_{N_2}$ ), with the result that the rate of absorption of gas

from the pleural space increases several fold (Fig. 44.11). Clearly, high concentrations of oxygen are contraindicated in those patients with chronic obstructive pulmonary disease whose respiratory centres may be dependent upon 'hypoxic drive'; furthermore, the potential toxicity of high concentrations of oxygen for prolonged periods in otherwise healthy individuals has to be considered [182]. However, oxygen therapy may be a useful adjunct to the conservative treatment of pneumothorax in patients who also have a bleeding diathesis in order to avoid an invasive procedure such as tube drainage with its attendant risk of haemorrhage.

### Active management

Most reported hospital series show that in the majority of patients the volume of the pneumothorax exceeds 20%, fitting into the moderate or large categories mentioned above. Brooks [163], while acknowledging the difficulties in estimating size, reported 23% of patients presenting with 25% collapse, 31% with 25–50% collapse, 13% with 50–75% collapse and 33% with over 75% collapse in his series of 376 spontaneous pneumothoraces. In view of this, active treatment in hospital is employed in the vast majority of cases in order to achieve full expansion within a reasonable length of time. Hospital treatment is indicated not only for moderate or large primary spontaneous pneumothoraces but also for secondary spontaneous pneumothoraces, in which underlying lung disease is associated with a pre-existing impairment of lung function so that even a shallow pneumothorax may be serious.



**Fig. 44.11** Potential partial pressure differences for oxygen and nitrogen between a closed pneumothorax space and venous end capillaries that contribute to reabsorption of gas when the patient breaths (a) ambient air and (b) a high concentration of oxygen so that nitrogen is 'washed out'. The differences in  $P_{CO_2}$  are relatively small and are not illustrated. (a) No difference in  $P_{N_2}$ , small differences in  $P_{O_2}$ . (b) Large difference in  $P_{N_2}$ , small differences in  $P_{O_2}$ .

### Aspiration

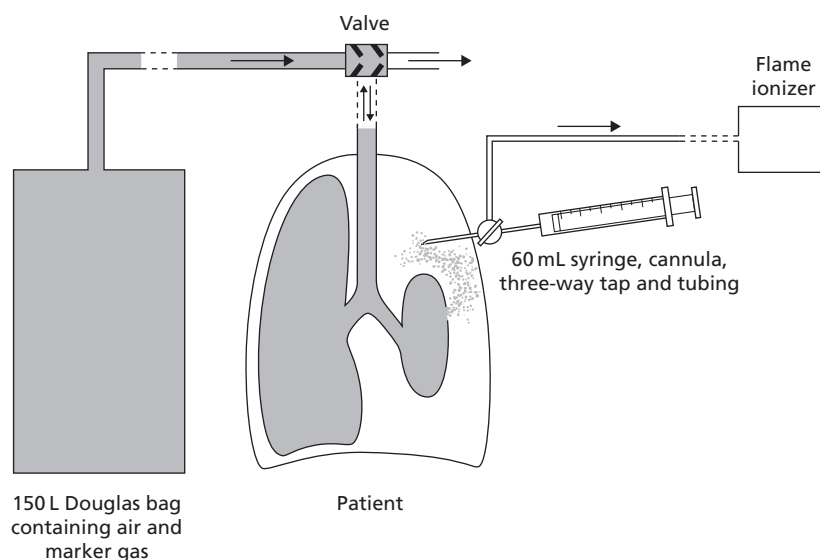
The insertion and removal of a standard intercostal drain is unpleasant for the patient and while the drain remains *in situ* regular analgesia is required. In view of this, simple manual aspiration has been re-evaluated [183,184]. The technique originally employed a needle and attracted condemnation because of the risk of lacerating the lung as it expanded [162,185]; however, this complication may be avoided if a modern plastic intravenous cannula is used and various clinicians have claimed success for their techniques [186–189]. The author prefers a small (8 cm long, 10 French gauge) neonatal pneumothorax cannula with trocar and side-holes as well as an end-hole. The second intercostal space in the mid-clavicular line is conventional, although an axillary approach in the fourth, fifth or sixth space between the mid and anterior axillary lines may be used as an alternative. The cannula is inserted aseptically with local anaesthetic and air withdrawn and expelled using a large Luer-Lok syringe with a three-way tap. Placement of the exit tube underwater reduces the chance of an embarrassing mistake. Provided that the patient's condition remains stable, the procedure may be continued until no more air can be withdrawn or until 3 L has been removed, which implies that a leak is still present. Aspiration is abandoned and an intercostal drain inserted if the patient's condition deteriorates.

Simple aspiration is contraindicated if the patient is distressed as a result of a tension pneumothorax or when there is more than a little pleural fluid present. It is unnecessary if the pneumothorax is shallow. For the remainder, while aspiration may avoid the need for an intercostal

drain in a significant number of patients [188], those in whom the technique fails due to reaccumulation of air require treatment by conventional means and their hospital stay is likely to be longer than would otherwise have been the case. A marker gas technique may be used in order to determine whether the pleural leak has sealed off at the time of aspiration, chest radiographs taken immediately after aspiration being unreliable in this respect. The hydrocarbon propellant gas found in metered-dose inhalers has been used in this way, being detected by a portable flame ionizer [190], the patients' breathing from a Douglas bag containing air or oxygen labelled with the tracer gas (Fig. 44.12). Those pneumothoraces that were negative for tracer gas were successfully treated by aspiration, whereas those that were positive for tracer gas frequently recollapsed over the following 12 h despite initial radiographic improvement, requiring tube placement in 60–80% of cases [191,192]. Patients negative for tracer gas may be discharged early if their general condition allows, provided that arrangements for prompt readmission have been put in place should the need arise [192].

There is evidence to suggest that patients who are treated by aspiration not only experience less pain but are also likely to spend a shorter time in hospital than those treated by intercostal tube drainage [192,193]. Manual aspiration is less likely to be successful in pneumothoraces in which the lung is completely collapsed at presentation [194]. When taking the requirement for a chest drain as the end-point, the marker gas technique has subsequently been found to have a negative predictive value of 95% and a positive predictive value of 67% when applied to 136 events.





**Fig. 44.12** Apparatus for detecting hydrocarbon marker gas in pleural leaks during manual aspiration of pneumothorax. (After Seaton *et al.* [191].)

**Table 44.2** Indications for intercostal tube drainage in spontaneous pneumothorax.

Tension pneumothorax
Presence of dyspnoea
Intermittent positive-pressure ventilation
Previous contralateral pneumothorax
Bilateral pneumothoraces
Presence of pleural fluid
Large/complete pneumothorax
Failed manual aspiration

### Intercostal tube drainage

When simple manual aspiration is contraindicated, the preferred method of treatment is intercostal tube drainage or 'tube thoracostomy', in which an intercostal drain is inserted into the pleural space and connected to an underwater seal bottle (Table 44.2).

It has been suggested that premedication with atropine 0.6 mg i.m. might reduce the chances of a vasovagal reaction. A common site for insertion is in the second intercostal space in the mid-clavicular line, thereby avoiding the internal mammary arteries (which run vertically 3–4 cm to the left and right of the sternum, posterior to the costal cartilages). The first intercostal space is immediately below the clavicle and is avoided because of the risk of major neurovascular damage; the second intercostal space is identified below the second rib, which articulates with the sternal angle of Louis.

An alternative site now commonly used and which may be preferred in women for cosmetic reasons is the fourth or fifth intercostal space between the anterior and posterior axillary lines. This site is also suitable when the pleural cavity contains fluid, because drainage is facilitated, and is also preferred in traumatic pneumothorax.

The choice of site may also be influenced by the presence of adhesions as seen on the chest radiograph. In order to avoid the upper limit of the diaphragm, it is a good rule for the physician not to insert a tube below nipple level in the male or below the sixth space in the female.

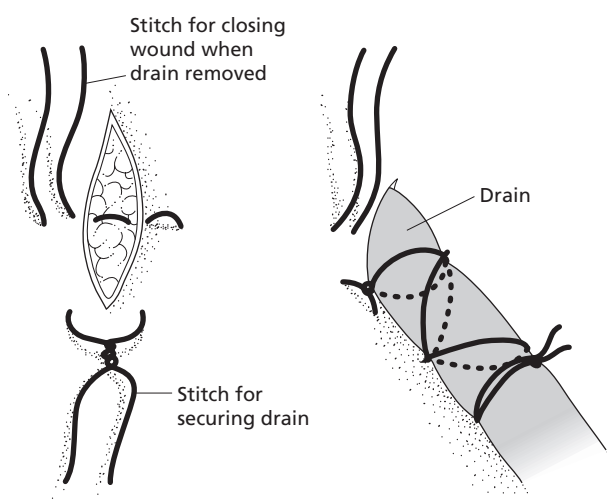
Once the entry point has been selected and the site marked with a pen, 10–15 mL of 1% lidocaine (lignocaine) is infiltrated from the skin to the parietal pleura, taking in the periosteum of the upper border of the rib at the chosen interspace and localizing the pneumothorax space by withdrawing air. This is done *before* skin preparation in order to give time for the local anaesthetic to have its effect. The needle can be left in place to mark the site of anaesthetic infiltration while aseptic skin procedures are then followed. A small (1–1.5 cm) incision is made through skin to subcutaneous fat over the body of the rib that lies below the chosen intercostal space. Two interrupted sutures, or better still a single central mattress suture, are inserted across the incision so that they can be tied later when the tube is removed. Purse-string sutures should be avoided as they may result in skin necrosis. A further silk or propylene securing suture (at least 0 gauge) is placed alongside the incision so that the drain can be tied in once inserted (Fig. 44.13). The track for the tube is made by blunt dissection with a haemostat (artery forceps). This is done by advancing the haemostat a short distance with the jaws closed, opening the jaws, withdrawing the instrument, closing the jaws and advancing it further [195]. The track is aimed obliquely upwards towards the upper border of the same rib, the objective being for the tube to follow this direction so that its tip lies at the apex of the hemithorax. The lower border of the rib above, with the neurovascular bundle lying behind its lower margin, is avoided.

The pleural cavity used to be routinely entered with a relatively short guarded steel trocar and cannula

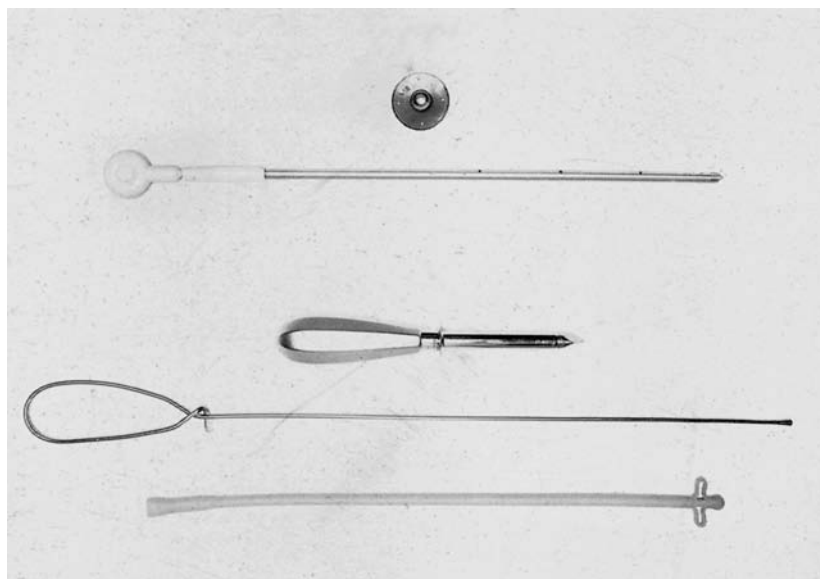
(Fig. 44.14). Following withdrawal of the trocar, a rubber self-retaining Malecot catheter stretched on a steel introducer was passed through the cannula and the introducer and cannula then withdrawn. Nowadays Malecot catheters are virtually museum pieces and a prepacked disposable plastic tube with a long central metal trocar is usually provided instead; 18–24 French gauge is suitable for air, whereas if blood as well as air needs draining a larger tube (e.g. 28–32 French gauge) may be more successful. The central trocar on such modern tubes may have a conical point that does not cut tissues but spreads them, so that in less experienced hands and if undue pressure is applied this assembly carries the risk of causing injury to the lung or other tissues by sudden deep penetration of the

chest. This may be particularly relevant in cases of traumatic pneumothorax dealt with by accident and emergency personnel; in these patients diaphragmatic rupture may have occurred, allowing abdominal viscera such as the liver, spleen or stomach to lie within the thoracic cavity, so that various advanced life support guidelines recommend that intercostal drains should be inserted without a trocar in trauma cases (see p. 1204). A protective guard has been devised to prevent such sudden deep entry [196] (Fig. 44.14) but in truth heavy pressure should never be applied. Once the forceps have entered the pleural cavity by blunt dissection, the track may be widened with the forefinger if necessary so that the tube can then be easily introduced while being gripped firmly about 5 cm from its tip to allow for any loss of resistance when the pleural cavity is reached and to avoid sudden overpenetration. The trocar may be withdrawn a few centimetres and used to help angle the tube, which is advanced about 8 cm towards the apex. As an alternative, curved blunt plastic-coated metal introducers are also available that can be placed through a side-hole of the plastic drain in place of a trocar to enable it to be directed towards the apex of the lung. The trocar or introducer is then removed completely in order to allow the intercostal drain to be attached with a suitable untaped connection to further tubing, which joins it with an underwater seal drainage bottle. The catheter connected to the bottle passes through a double-lumen stopper or similar arrangement to rest 2.5 cm below the surface of about 0.5 L sterile water, thereby acting as a one-way low-resistance valve. Correct placement of the tube is greeted by a satisfying stream of bubbles during expiration or coughing and a rise in the level of the fluid in the underwater seal tube during inspiration.

All connections and tubing require regular inspection to avoid either leakage or blockage by kinking. So-called



**Fig. 44.13** Sutures inserted to secure the drain and for closing the wound when the drain is removed. The drain is secured to the skin by tying knots on either side of it. (After Parmar [195].)



**Fig. 44.14** Disposable plastic cannula, metal trocar and plastic guard (above) and early rubber Malecot catheter with steel introducer, trocar and cannula (below)

'sleek' should be avoided, and simple adhesive tape is used to cover the gauze skin dressings and may also be used to fashion a supportive mesentery for the tubing but should not conceal any junctions in the drainage system. The tube itself should be attached to the skin by knotting the securing suture three or four times on each side of the drain (Fig. 44.13), which should also be looped and taped to the skin to further reduce the chance of it being accidentally pulled out.

Should the patient be in a state of cardiovascular collapse as a result of a tension pneumothorax, release of the positive pressure in the pleural cavity is a matter of urgent necessity. Provided that there is no doubt about the diagnosis, this may be quickly achieved with rapid clinical improvement by the insertion of a wide-bore hypodermic needle or preferably a plastic intravenous cannula into the pleural cavity. This allows the pressure in the pneumothorax to become atmospheric and if the diagnosis was correct results in immediate improvement in the patient's condition so that an intercostal tube can then be inserted in a more orderly manner [197].

The application of suction to the second opening of the underwater seal drain bottle has been recommended by some in order to assist expansion of the collapsed lung. This has been applied either at constant high flow using an appropriate pump (e.g. Thompson or Tubbs-Barrett rather than Roberts) or at constant pressure (e.g. 1.5–5.0 kPa, 15–50 cmH<sub>2</sub>O) using wall suction with a pressure reducing valve. However, if the pneumothorax is closed this should be unnecessary as expansion will occur within 2–3 days anyway. If the pneumothorax is open then the application of suction at practicable flow rates might in theory prevent it from sealing off by drawing air through the point of leakage. This is in agreement with observations that mechanical suction does not influence the rate of re-expansion [198].

The tube is left *in situ* until the lung is fully re-expanded on the chest radiograph and the tube has not been seen to bubble for 24 h. Once this has been achieved, the tube may be removed. It is safer to remove tubes with the help of an assistant. One throw of the knot in the mattress suture is made. The patient inspires fully and is then asked to perform a Valsalva manoeuvre, thereby reducing the risk of air entering the pleura again as the drain is withdrawn. The drain is removed with one smooth quick movement while the track is compressed and the knot in the mattress suture is then completed [195]. Some practitioners prefer to clamp the tube for about 12 h once the tube has apparently stopped blowing and when no bubbles are seen on coughing, after which the intercostal tube is removed if the lung remains fully expanded. However, if the pneumothorax has reaccumulated, the clamp is removed and the air once again fully drained before the cycle is repeated. The obvious drawback of clamping is that the patient may become distressed if a substantial leak does

occur and the clamp is not removed promptly because of lack of understanding by staff either at the bedside or while the patient is being transported between departments; the British Thoracic Society guidelines thus advise against this practice [181].

It is usually possible to re-expand the lung and remove the tube within 3–4 days. Intercostal tubes may occasionally kink or become blocked by blood or fibrous material before full re-expansion has taken place. The column of water in the underwater seal drainage bottle is seen to stop swinging in this situation and the intercostal tube needs to be unkinked or replaced through a second clean incision in order to achieve a satisfactory result. Sometimes several such tube changes are required and re-expansion is slow. This is particularly common in patients with diffuse emphysema, although almost always in such cases if drainage is continued the leak eventually seals. A retrospective study of 214 patients with spontaneous pneumothorax found that 51% still had a persistent leak after 2 days of tube drainage. Of those who continued to be treated medically, the median time to resolution was 7 days for those with primary spontaneous pneumothorax and 11 days for those with underlying lung disease [199]. It has been claimed that patients with uncomplicated pneumothoraces treated by intercostal catheter are usually fit to return to work within 1 week [162]. Other authors have reported an average hospital stay of 13 days for cases of pneumothorax treated with underwater seal drainage [200].

### Flutter valves

Commercially available (Heimlich-type) flutter valves may be connected to the chest tube in order to avoid the encumbrance of an underwater seal drain [201,202]. This method has been used satisfactorily in battle casualties [201] and also in the civilian outpatient management of pneumothorax, sometimes by using narrow 8–14 French gauge intercostal catheters [203–207]. These valves may be more prone to blockage than standard underwater seal drainage [208] and their use in general management has not gained full acceptance. Prepacked water-free ambulatory chest drainage kits incorporating a conventional intercostal drain that connects to a plastic bag with an integral flutter valve are also available for use in trauma cases.

### Chemical pleurodesis

The tendency for a pneumothorax to recur (see p. 1202) has led to the development of certain procedures intended to cause the visceral pleura to adhere to the inner surface of the chest wall. Various foreign substances may be introduced into the pleural cavity in order to produce a sterile pleurisy, with the subsequent formation of adhesions between the visceral and parietal pleural layers [209].

This method, known as chemical pleurodesis, was first described by Spengler over 80 years ago [210]. The wide variety of different substances that have been used to achieve pleural symphysis, ranging from irritants such as tetracycline, 50% glucose solution, autologous blood and iodized oil to more caustic chemicals such as silver nitrate solution to physical irritants such as iodized talc slurry or kaolin and more recently to fibrin glue sealant, implies that the search for an ideal agent continues. These substances may be injected or insufflated through an intercostal drain or in some cases may be applied to the surface of the visceral pleura under general anaesthesia using a thoracoscope.

As a rule these procedures produce pleural effusions that require drainage. Cerebral embolism has rarely been reported following the use of talc [211] and there have been fears about the possibility of subsequent mesothelioma due to potential contamination with asbestos, although this has not been borne out by experience [212,213]. Patients treated by chemical pleurodesis remain in hospital longer than those treated by intercostal tube drainage alone and the efficacy of the procedure in preventing recurrence has been questioned [214], although the balance of evidence is that it is more effective than tube thoracostomy alone but less so than surgical treatment [215,216].

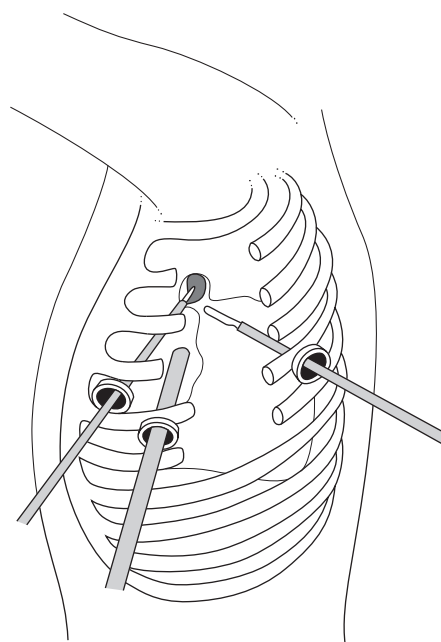
Despite these disadvantages, chemical pleurodesis finds occasional application in the prevention of recurrent spontaneous pneumothorax, particularly in patients with serious respiratory impairment due to chronic lung disease, in whom more invasive surgery for pleurectomy or pleural abrasion might carry an unacceptable risk. Of the many substances that have been used, a solution of tetracycline hydrochloride (1–1.5 g in 50 mL of normal saline with 10 mL 1% lidocaine added) is currently favoured. Lidocaine is added to the solution to diminish the considerable pain that the procedure often produces. Once the lung has almost inflated and the pleural leak sealed or become minimal, the tetracycline is injected into the chest tube and flushed through with a further 50 mL saline. The tube is then clamped for the next 60–120 min while the patient is frequently repositioned (e.g. 5 min supine, prone, left and right lateral decubitus) so that the tetracycline comes into contact with all pleural surfaces, before the tube is unclamped for drainage (with or without suction) of any effusion that might have accumulated. Talc may be more effective than tetracycline, producing a vigorous granulomatous reaction but seemingly also producing greater pain and more prolonged fever [217]. Tetracycline has been claimed to be no less effective than silver nitrate, to cause less pain, diminished exudation and a shorter hospital stay [218]. Tetracycline pleurodesis has been shown to reduce ipsilateral recurrence rate significantly in a prospective controlled trial of patients with primary and secondary spontaneous pneu-

mothorax [215]. As a standard procedure for primary spontaneous pneumothorax, chemical pleurodesis does not currently find wide acceptance but continues to be used in some centres [216,218].

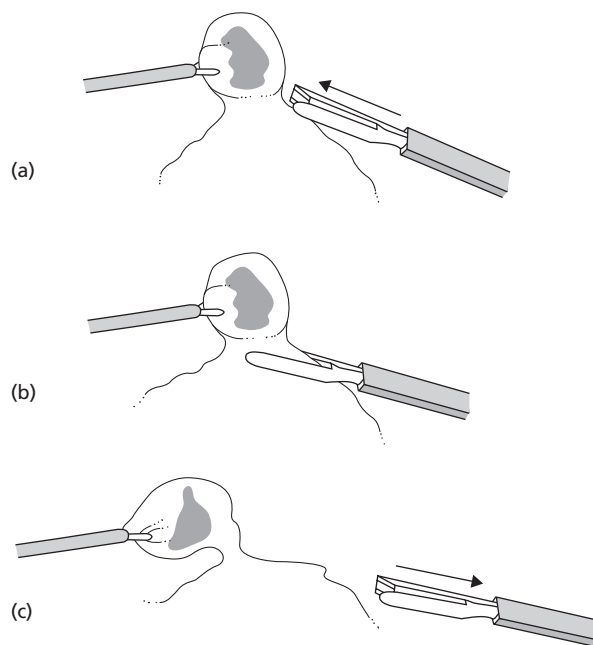
### **Parietal pleurectomy, pleural abrasion at thoracotomy and video-assisted thoracoscopic procedures**

A more major operative procedure is indicated if the lung fails to expand fully with tube drainage. Most leaks close within 2–3 days of insertion of a well-placed intercostal tube [219,220], failing which it is reasonable to consider a surgical opinion provided that the patient's general condition permits thoracotomy or thoracoscopy. A further delay of a few days is not important, so that an operation can proceed if still needed after about a week has elapsed from the insertion of the drain [199]. Patients with underlying lung disease are often left longer because of the increased risks that surgical intervention carries for this group. Prior to the advent of video-assisted thoracoscopic surgery (VATS), the standard procedure was parietal pleurectomy carried out through a posterolateral thoracotomy, in which the parietal pleura is stripped off the chest wall and upper mediastinum leaving a raw area that becomes adherent to the remaining visceral pleura [211]. Some surgeons prefer to produce a similar effect less radically by either limiting the procedure to the apex of the lung (apical pleurectomy) or alternatively by scarifying the parietal pleura with a dry gauze sponge or nylon pan scourer, a procedure known as pleural abrasion [221,222]. Both types of operation may include the excision, oversewing or stapling of any visible pleural blebs or bullae and, after either of these procedures, tube drainage is maintained for a few days to allow the visceral pleura to come into close apposition with the chest wall while adhesions form. Parietal pleurectomy is almost guaranteed to prevent recurrence (0.4%) and recurrence after pleural abrasion is also unlikely (2%) [38,223,224].

Although these 'open' procedures are still carried out in many centres, increasing use is being made of VATS. The indications for this intervention are broadly similar to those for the open procedures mentioned above and the temptation to refer patients routinely after a first episode of primary spontaneous pneumothorax should be resisted as the recurrence rate is only 20% or so. VATS usually entails the surgeon making three 1–2 cm incisions to establish a port for the thoracoscopic camera and one each for the grasping forceps and stapler. This compares with a thoracotomy wound, which although sometimes limited may extend anything up to 30 cm in length and is associated with greater morbidity and a longer hospital stay. VATS lends itself to the identification of leaking apical blebs in patients with recurrent or persistent primary spontaneous pneumothorax. These blebs can often be resected after placing a row of staples across their necks



**Fig. 44.15** Approximate sites of routine trocar positioning for video-assisted thoracoscopic surgery in pneumothorax, also demonstrating the stapled resection of an apical bleb. (a) The bleb is grasped; (b) the stapler is applied above a rim of normal lung tissue; (c) each staple application cuts between six rows of staples. (After Hazelrigg *et al.* [225].)



**Table 44.3** Indications for parietal pleurectomy or abrasion in spontaneous pneumothorax.

Failed tube drainage (persistent pneumothorax)
Ipsilateral recurrence (First or second)
Contralateral occurrence (First)
Bilateral simultaneous pneumothorax
Persistent pleural effusion
Initial episode life-threatening
Special risk groups e.g. aircrew, divers, etc.

[225] (Fig. 44.15). The bullae in patients with emphysema tend to merge with adjacent lung and are more difficult to deal with using VATS so that leaks are more frequent and other surgical techniques may need to be used, including formal thoracotomy. In addition to dealing with the leak, VATS may be used to establish a pleural symphysis by parietal pleurectomy, pleural abrasion or chemical pleurodesis. The recurrence rate is known to be higher if no leak can be identified and dealt with at thoracoscopy, in which case VATS pleurectomy may be a surer way to proceed [226]. There are reports of thoracoscopic ablation of pulmonary blebs and bullae by laser but in the setting of pneumothorax, the recurrence rate may be too high [226].

Parietal pleurectomy or abrasion may also be recommended after the first or second ipsilateral recurrence or following the first contralateral recurrence in order to avoid the future possibility of simultaneous bilateral spontaneous pneumothoraces [227]. Pleurectomy is indicated after the initial event for categories of patient in whom a recurrence would carry a special risk, such as aircrew, divers who refuse to stop diving, seafarers or other travellers to remote parts and those in whom the first pneumothorax was a life-threatening 'near miss' (Table 44.3). Surgical treatment is also indicated when pneumothorax is complicated by a large haemothorax, pleural effusion or

empyema that cannot be satisfactorily managed by aspiration or tube drainage alone. One potential problem with pleurectomy in a patient with pneumothorax is that the symphysis is so good that were a thoracotomy to be required in the future for some other reason, it would be made technically very difficult.

Patients with spontaneous pneumothorax secondary to cystic fibrosis may be managed with aspiration or tube thoracostomy. Cases of recurrence may be treated with chemical pleurodesis or thoracoscopically with ligation of bullae and limited pleural abrasion rather than with pleurectomy, unless it is quite certain that they are not candidates for future transplantation. It is sensible to discuss the management options for those patients with cystic fibrosis who are transplant candidates with the transplant centre concerned [59].

Spontaneous pneumothorax in pregnancy has rarely been reported. It can be treated with aspiration or tube drainage. Surgical treatment during pregnancy is sometimes necessary and there is no good evidence of teratogenesis, increased risk of abortion or premature labour following general anaesthesia. However, the risks from pneumothorax in pregnancy are also small [228] and

prolonged drainage with a flutter valve until after term has been reported as an alternative to surgical intervention [203,229].

Cases of catamenial pneumothorax thought to be associated with endometriosis may be treated medically by inducing a hypo-oestrogenic state with drugs such as danazol and analogues of gonadotrophin-releasing hormone, but are likely to produce improvement only while treatment is continued [230,231]. Endometriosis resolves at the menopause; however, apart from these pharmacological interventions, an earlier permanent cure requires bilateral oophorectomy, which may be appropriate (with hysterectomy) for women in their fifth decade. This may be followed with hormone replacement therapy without any recrudescence of pneumothorax since the problems in endometriosis seem to depend on cyclical variation in oestrogen level [232].

Sometimes patients with barotrauma due to diving accidents, in addition to possible pneumothorax and pneumomediastinum, may develop air embolism that should be treated by transport to the nearest centre with facilities for emergency hyperbaric oxygen therapy. This has the effect of reducing the volume of the air emboli physically according to Boyle's law, as well as accelerating absorption of gas by 'washing out' nitrogen from the body, thereby increasing the gradient for diffusion of nitrogen between the trapped gas and the tissues (see Fig. 44.11). The US Navy uses a protocol of rapid recompression with air to 600 kPa for 30 min, followed by 100% oxygen at 280 kPa [135].

## Complications

### Failure to re-expand

Failure to re-expand the lung by tube drainage may require the insertion of a second intercostal drain [9]. A persistent air leak requiring surgical intervention is reported in 4–14% of cases in whom tube drainage has been attempted [6,8,9,162]. These failures may be caused by multiple leaks in generalized emphysema or by adhesions preventing a bronchopleural fistula from closing. In such cases the treatment of choice is a surgical procedure to produce pleurodesis (see above), provided that the patient does not have severe respiratory impairment that would make the risk of thoracotomy or thoracoscopy unacceptable. Such high-risk patients usually have severe emphysema and with prolonged tube drainage the leak frequently seals off, although this may occasionally take weeks. However, an otherwise healthy subject should be offered a surgical procedure if tube drainage remains unsuccessful after 3–7 days [199,224,225]. Occasionally re-expansion of the lung is delayed by atelectasis resulting from retained secretions. This situation is treated by chest physiotherapy with an intercostal drain in place, although

rigid bronchoscopy may be required occasionally to suck out tenacious intrabronchial material and the passage of an endotracheal tube may be required in order to achieve full reflation.

Rarely a pneumothorax becomes chronic, with the result that the lung becomes surrounded and bound down by a thickened non-expansive layer of fibrin known as a pleural rind or peel. This is more likely to occur if there is an associated pleural effusion. A chronic pneumothorax is sometimes seen in cases of inactive tuberculosis that were treated with the now obsolete technique of artificial pneumothorax; in such cases the pleural rind is frequently heavily calcified [233] (Fig. 44.16). Surgical decortication of the pleura may be required to achieve re-expansion of the trapped lung, although this is seldom technically possible because of the dense nature of the adhesions.

### Recurrence

There is a tendency to overestimate the recurrence rate of spontaneous pneumothorax in the published series, many of which are retrospective and contain an unduly high proportion of patients referred to surgical units because of 'failed conservative treatment' or for the treatment of recurrence itself rather than for the primary event. In a study of 294 patients comprising all medically and surgically referred cases of spontaneous pneumothorax in a single institution, a recurrence rate of 16% was found in those treated for the first event either conservatively or with tube drainage [6]. Other series have reported a first recurrence rate of 16–50% [30,38,162,211,234,235]. At least half of those patients who experience a recurrence do so within 4 months of the initial episode [7,9,162]. Some series have recorded slightly lower recurrence rates following an intercostal tube as opposed to conservative treatment [162,236,237], although this experience is not universal [7]. After each recurrent spontaneous pneumothorax treated conservatively or by intercostal tube, the likelihood of a further episode increases; thus the chance of a third pneumothorax following the second has been found to be 40–64% [6,7,38] and the chance of a fourth pneumothorax following the third is reported to be 80% [238]. There is a risk of a subsequent contralateral spontaneous pneumothorax of 10–15% [9], although simultaneous bilateral pneumothoraces are unusual occurring in 1.3–2.5% of cases [38,162,163].

### Haemopneumothorax

Significant haemorrhage in association with spontaneous pneumothorax is uncommon but potentially fatal, early reports indicating a mortality rate approaching 20% [211,239]. It was reported in 2.3% of one recent surgical series with no mortality [240]. The source of blood loss is usually the chest wall side of a vascularized adhesion that



**Fig. 44.16** Chronic bilateral fibrothoraces, with heavily calcified visceral pleura, in a patient previously treated for tuberculosis with artificial pneumothorax.

is torn apart as the pneumothorax develops [163]; it is of historical interest that this was also a recognized complication following the induction of artificial pneumothoraces when these were used in the treatment of pulmonary tuberculosis [241]. Blood loss may produce shock with sweating, nausea and syncope. Treatment comprises prompt replacement of blood; if blood loss is excessive, early surgical intervention to achieve haemostasis is necessary [240]. Adequate aspiration or drainage is all that is required for smaller amounts of blood. Thoracoscopy or thoracotomy may be required if the organization of substantial clot prevents expansion of the lung, although smaller amounts may gradually reabsorb without intervention.

### **Pyopneumothorax**

Pyogenic infection of the pleural space was reported in less than 1% of cases of spontaneous pneumothorax in one early Scottish series and was also found to be surprisingly uncommon following penetrating trauma to the chest wall [104,162]. This does not apply to countries with less well-developed healthcare facilities and those with a high prevalence of tuberculosis. The infecting organisms may enter the pneumothorax space as a result of suppurative pneumonia or rupture of a lung abscess or may be introduced at pleural aspiration, during intercostal tube

drainage or at thoracotomy. Treatment comprises prompt and adequate drainage by aspiration or intercostal tube and appropriate antibiotic therapy. When these measures fail surgical intervention is indicated (see Chapter 14).

### **Respiratory failure**

This is unlikely to occur in the absence of pre-existing respiratory disease other than when a tension pneumothorax is present. It is characterized by hypoxia, hypercapnia and respiratory acidosis and treatment involves urgent re-expansion of the deflated lung and controlled oxygen therapy according to arterial blood gas analysis.

### **Re-expansion pulmonary oedema**

Unilateral pulmonary oedema is an unusual but well-documented complication that may follow the re-expansion of a completely collapsed lung, not only after the treatment of pneumothorax [242] but also sometimes following the aspiration of a large pleural effusion or after the relief of bronchial obstruction, as in the case of the withdrawal of a misplaced endotracheal tube. It is thought to be more likely to occur if the pneumothorax has been present for several days and if re-expansion is rapid, as may occur if suction has been applied [243,244], although



it can occur when collapse of the lung has been present for only a few hours. Radiographic evidence of unilateral pulmonary oedema on the side of the treated pneumothorax was found in 0.9% of a retrospective series of 320 episodes of spontaneous pneumothorax collected over an 8-year period and treated with intercostal tube drainage [245]. The mechanisms are open to conjecture but possibilities include increased pulmonary capillary permeability resulting from raised transpulmonary negative pressures acting on lung tissue, whose elastic recoil has been increased by loss of surfactant; alternatively, there may be pulmonary microvascular injury by oxygen free radicals or other substances produced as a result of hypoxic lung injury occurring during the period of collapse [246,247]. Curiously, contralateral or bilateral pulmonary oedema has also been described on rare occasions [248,249].

This complication may be asymptomatic, being detected on a routine film, or it may result in cough and dyspnoea [245]. Although unusual, marked respiratory distress with severe hypotension and death have occasionally been reported [245,248,250]. The radiographic findings are those of unilateral pulmonary oedema and are non-specific. Treatment is by correction of hypoxaemia and hypovolaemia if present and with inotropic support where appropriate. Mechanical ventilation may sometimes be necessary [251].

### Other complications of management

Some complications that may arise as a direct result of the placement of intercostal tube drains have already been mentioned. The most serious are haemorrhagic. Bleeding may occur as a result of injury to a vascular structure, usually one of the intercostal vessels, less commonly the internal mammary artery or another major vessel. Elderly patients may have more tortuous intercostal arteries than younger people and may therefore be more vulnerable [252]. Other serious structural injury is only likely to arise as a result of the misplacement or overpenetration of a trocar. Trauma cases who are dealt with as emergencies are particularly vulnerable since their thoracic cavities may contain abdominal viscera as a result of diaphragmatic rupture and the normal mediastinal structures may also be displaced. The liver, spleen, bowel, major vessels or even the heart may be inadvertently punctured during tube placement so that various advanced trauma life support guidelines recommend that intercostal drains should be inserted without a trocar in such cases [253,254]. Massive haemorrhage is best dealt with by clamping the tube in the hope that this tamponades the flow, by replacing lost volume as rapidly as possible and by requesting thoracic surgical help immediately. Smaller bleeds thought to come from intercostal vessels have been tamponaded by replacing the chest tube with a large Foley urinary catheter and applying traction to its overinflated

balloon, although experience with this technique is not widespread [255]. Misplaced tubes have been known to injure the brachial plexus and occasionally an apical drain may abut the sympathetic chain producing neuropraxia with Horner's syndrome [256]. Sometimes a track may develop between the outside of a drain and the chest wall so that the air is drawn into the pleural cavity on inspiration, thereby defeating the purpose of the exercise and necessitating removal and resiting or an alternative surgical approach, depending upon the circumstances.

Many of these problems can be prevented by scrupulous attention to detail as outlined in the section on intercostal tube drainage. It is notable that a retrospective North American study conducted to determine the complication rate of tube thoracostomy found a strikingly lower complication rate when tubes were placed by a surgeon rather than an emergency physician, implying that additional training might be important [257].

## Pneumomediastinum

Air in the mediastinal tissues is referred to as pneumomediastinum or mediastinal emphysema. Although the condition of pneumomediastinum has been recognized for over a century [258], the first detailed accounts are credited to Hamman [167,259]. A working classification based on cause, similar to that applied to pneumothorax, is recommended (Fig. 44.17). Thus any pneumomediastinum occurring in the absence of trauma may be described as spontaneous. The term 'primary spontaneous pneumomediastinum' is used in the absence of any demonstrable predisposing disease and 'secondary spontaneous pneumomediastinum' where the leakage of air has arisen as a result of a recognizable coexisting structural abnormality, usually in the lungs or mediastinum; thus any of the causes of secondary spontaneous pneumothorax may also result in secondary spontaneous pneumomediastinum.

### Aetiology

Pneumomediastinum may arise following alveolar rupture, in which case air tracks along interstitial and vascular supporting tissues (see Fig. 44.4) until it reaches the mediastinum [260]. Air may also be released directly into

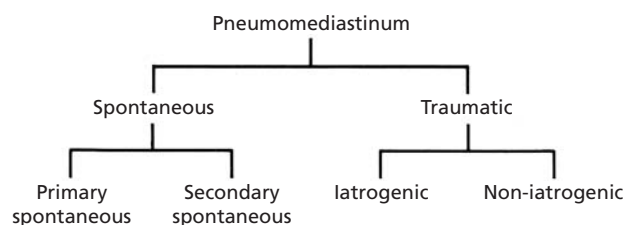


Fig. 44.17 Classification of pneumomediastinum.

the mediastinum following tracheal, bronchial or oesophageal rupture in association with chest trauma, local disease or endoscopic examination [261]. The initiating event may be a rise in intrathoracic pressure such as occurs with coughing, straining or during positive-pressure ventilation. In this regard the condition has been recorded in upper respiratory tract infection, asthma, bronchitis, whooping cough, obstructive laryngitis, choking on a foreign body and with various forms of physical exertion including childbirth [262–272]. Frequently, however, no precipitating cause is found as was emphasized in early reports [259].

Alveolar rupture may also follow the decompression of intrathoracic gas, as may occur in a surfacing diver or in aircrew subjected to sudden accidental cabin decompression at high altitude (p. 1187). The surgical dilatation of an oesophageal stricture is a frequent cause of rupture of this viscus, particularly if the lumen is blocked by carcinoma. Violent vomiting may sometimes give rise to a vertical tear in the lower 8 cm of the oesophagus posterolaterally [273]. Air is occasionally drawn into the fascial planes of the mediastinum from wounds in the neck, including tracheostomy and surgical procedures in the mouth, pharynx and upper gastrointestinal tract [274]. Gas in the mediastinum may also be introduced by high-speed air turbine dental drills [275,276] and even by attempting to uncup a carbonated beverage bottle with the teeth [277]. Strenuous physical exertion coupled with retching that may not be recalled could be the explanation for occasional reports of pneumomediastinum occurring in association with the recreational use of 3,4-methylenedioxymethamphetamine ('ecstasy'), typically taken at discothèques and 'raves' [278]. Rarely gas may enter the thorax from a ruptured viscus in the abdomen, ascending retroperitoneally alongside the oesophagus and aorta.

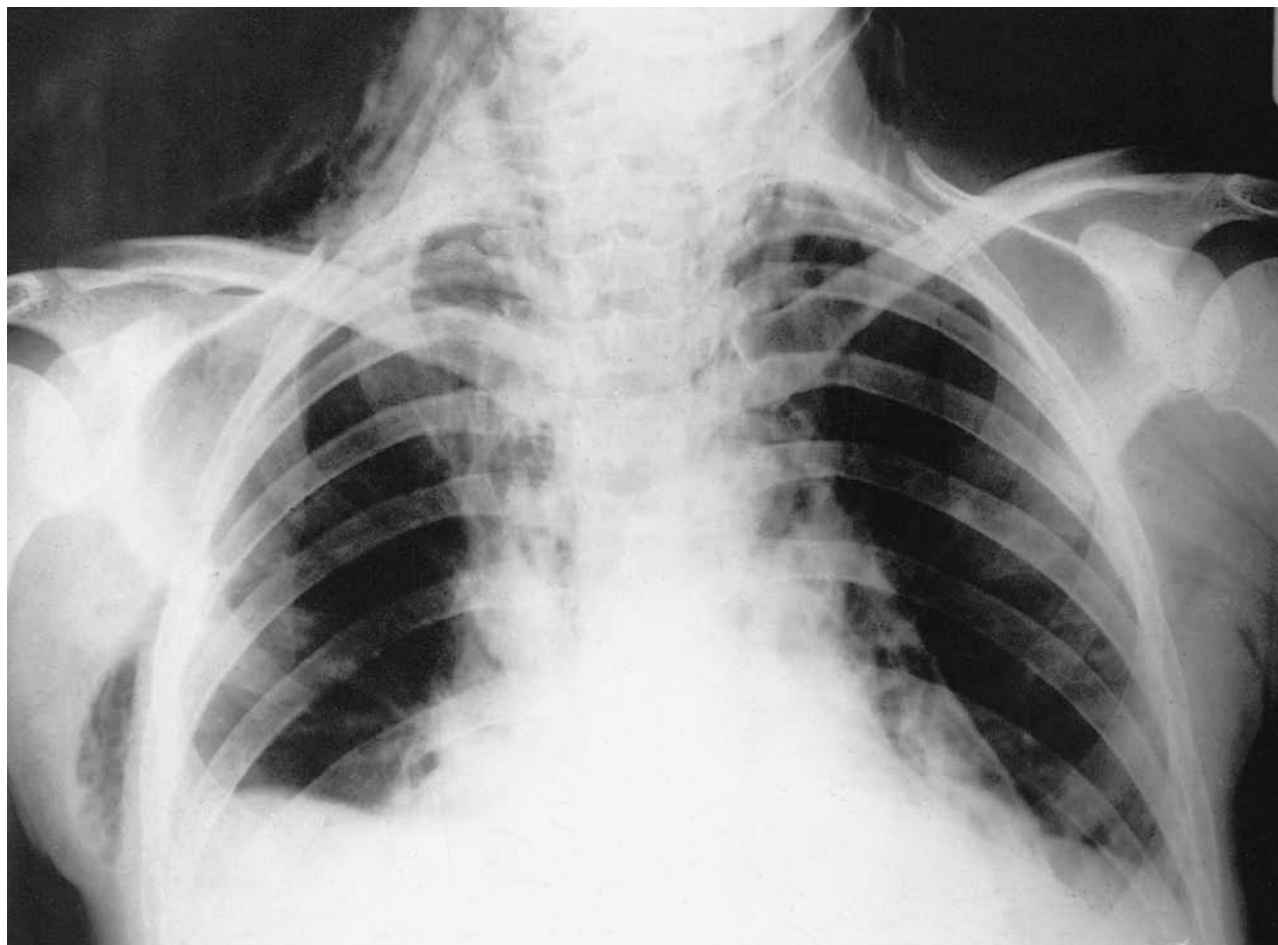
### Clinical features

Primary spontaneous pneumomediastinum occurs predominantly in young previously healthy males aged 15–30 years [264,279]. All grades of clinical severity exist and the condition is almost certainly underdiagnosed in milder cases. The most consistent symptom is central chest pain, produced as a result of air spreading about the mediastinal tissues [263]. It may be slight or severe, mimicking that of myocardial infarction or pericarditis and radiating to the shoulders, arms and neck. Any movement that disturbs the mediastinal structures, such as deep breathing, turning or swallowing, may aggravate the pain and the patient may obtain relief by leaning forwards in the sitting position and by breathing shallowly [280]. Pain in the neck may be accompanied by dysphagia, which may be the principal complaint [264]. There may be a change in the quality of the voice [265]. Surgical emphysema is frequently palpable in the neck and may be more

widespread, involving the face, chest or arms particularly if the channel through which air has entered the mediastinum remains patent or if the patient is being ventilated mechanically. Pulsus paradoxus has been described in the absence of asthma [264]. The normal area of cardiac dullness to percussion may be diminished and on auscultation the heart sounds may be indistinct. Hamman's sign is variously described as a crepitous, crackling or crunching sound that may be heard with the stethoscope to be synchronous with systole. It is usually maximal at the left sternal edge with the patient sitting forwards or lying in the left lateral decubitus position. This sign is present in about 50% of cases of pneumomediastinum and is occasionally noticed by the patient or even by a casual observer. It is not entirely specific for pneumomediastinum, having been described in left-sided pneumothorax [166], bullous emphysema of the lingula, distension of the lower oesophagus or stomach by air, and pneumoperitoneum with a high left hemidiaphragm [281]. On rare occasions sufficient air under tension surrounds the heart to cause cardiac tamponade, with breathlessness, cyanosis and hypotension. When secondary spontaneous or traumatic pneumomediastinum occurs, the symptoms and signs of associated disease such as pneumothorax or oesophageal rupture are frequently present. The latter condition is often indicated by the presence of fever and a pleural effusion or empyema, the source of which may be demonstrated by asking the patient to swallow dye such as methylene blue, which can then be shown to be present in an aspirate of pleural fluid. In lower oesophageal rupture the upper part of the abdomen may be rigid, suggesting a perforated gastric or duodenal ulcer. There may be the symptoms and signs of an associated pneumothorax.

### Radiographic features

It is usually the chest radiograph that provides indisputable diagnostic evidence of pneumomediastinum (Fig. 44.18). Free mediastinal air is usually seen as sharp lines of increased lucency that enhance the mediastinal viscera, run along and outline one or both of the cardiac borders and extend to the superior mediastinum, which may appear widened [172]. A continuous diaphragmatic 'shadow' has also been described [282]. If posteroanterior views only are taken, then about 50% of cases that would otherwise be detected with a routine lateral view may be missed [283]. This projection may show a collection of air lying between the sternum and heart. In the neck posteroanterior and lateral views may show air tracking along the fascial planes. In cases of doubt, mediastinal air may be evident using either echocardiography or CT [261,278]. A water-soluble, non-ionic (e.g. Iopamidol, Gastrografin) contrast examination may be helpful where oesophageal perforation is suspected.



**Fig. 44.18** Mediastinal and subcutaneous air due to instrumental perforation of pyriform fossa.

### Diagnosis

Failure to diagnose pneumomediastinum usually results from the omission of this possibility in the differential diagnosis when a subject presents with central chest pain. Difficulty may arise when the air leak has been small, with the result that the usual physical signs are absent; in this case, free air must be assiduously sought on the radiographs. Myocardial infarction is usually easily distinguishable by serial changes on the ECG and a rise in cardiac enzyme levels. However, caution should be exercised in interpreting the ECG since ST and T wave changes have been described in both pneumothorax and pneumomediastinum [175,263,284].

### Management

Primary spontaneous pneumomediastinum seldom requires any treatment other than reassurance, observation and simple analgesia should the pain require it. The

administration of high concentrations of oxygen may be beneficial in the rare situation in which trapped air in the mediastinum is limiting diastolic filling of the heart. This causes nitrogen to be washed out of the body, thereby increasing the gradient of  $P_{N_2}$  between the pneumomediastinum space and the tissues so that the trapped air is more rapidly absorbed (see Fig. 44.11) [285].

When a pneumomediastinum is secondary to another disease process or to trauma, therapeutic efforts are directed to the primary condition since it is usually of much greater clinical importance. Coexisting pneumothorax should be treated on its own merits (see above) and should be searched for, particularly when pneumomediastinum develops in patients who are being mechanically ventilated. When tracheobronchial or oesophageal ruptures are suspected, endoscopic examination or contrast swallow may be required. Major perforations, especially if they have resulted from trauma, usually require operative treatment. Minor oesophageal tears, which may have arisen from endoscopy itself, are frequently managed conservatively with antibiotics and drainage of any coexisting pleural effusion. Although air may have entered the mediastinum by purely physical means, the finding of gas in

these tissues should certainly alert the physician to the possibility of mediastinitis from anaerobic organisms that may have been introduced from adjacent areas.

The majority of cases of primary spontaneous pneumothorax are absorbed within 1 week. Recurrence is unusual but has been described [260,263].

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# CHEST WALL AND NEUROMUSCULAR DISORDERS

ANTHONY SEATON

## Congenital abnormalities of the chest wall

### Rib abnormalities

Bifid ribs are common, particularly in the upper six ribs, and if not appreciated on the chest radiograph may give rise to confusion in interpretation [1]. Fused and absent ribs may also occur but are only of radiological interest. An asymmetrical congenital deformity has been described in adolescent patients in whom the ribs and costal cartilages on the right side are deeply depressed and the sternum rotated to the right [2]. Reconstructive surgery is possible.

Cervical ribs occur in 0.5% of the population, usually arising from the seventh cervical vertebra; they may vary greatly in size and shape, and are bilateral in 80% of cases [3,4] (Fig. 45.1). They are usually asymptomatic but may give rise to the thoracic outlet syndrome due to compression of subclavian vessels or nerves in the root of the neck. Symptoms due to compression are more prevalent in females and more common on the left [3]. The production of symptoms bears no relation to the size of the rib; a small cervical rib with a fibrous attachment may cause severe symptoms whereas a large cervical rib may be asymptomatic. The thoracic outlet syndrome has been described following correction of scoliosis in a patient with cervical ribs [5].

Neurological symptoms of cervical ribs commonly consist of pain and weakness of the arm with paraesthesiae of the fingers. Atrophy of the intrinsic muscles of the hand may occur [6,7]. Vascular symptoms may mimic Raynaud's phenomenon, and emboli from a thrombosed subclavian artery may cause fingertip gangrene [6,7]. Neurological complications need not require resection of the offending rib since the majority respond to shoulder girdle strengthening exercises and the avoidance of heavy loads. However, vascular complications may require arteriographic investigation and treatment depends on the findings, ranging from simple rib resection to arterial

reconstructive surgery plus embolectomy or thrombectomy [3,4].

### Jointed xiphoid process

A jointed xiphoid process may masquerade as an upper abdominal mass but may be readily recognized on a lateral chest film or by ultrasound examination, thus preventing unnecessary operation [8].

### Pectus carinatum or pigeon chest

In this condition the sternum is prominent, forming an anterior ridge like the keel of a ship with the ribs falling away steeply on either side, sometimes with a vertical groove on each side of the sternum [9,10]. It may be associated with other congenital anomalies, especially cardiac lesions and coarctation of the aorta [11].

### Aetiology

Pectus carinatum may result from obliteration of all the sternal sutures at an early age, possibly due to inadequate segmentation during fetal life, with a resulting synostosis [9]. An alternative explanation, which has been confirmed at postmortem, is that the deformity results from malattachment of the anterior portion of the diaphragm to the posterior portion of the rectus sheath rather than to the xiphoid process, with consequent distorting mechanical effects [12].

### Management

There is no associated functional defect and correction is not normally indicated. However, corrective procedures for both types of pectus carinatum have been described and may be required for cosmetic reasons [10,13]. Such patients are almost invariably happier with the large scar than with the deformity, though this effect of the operation

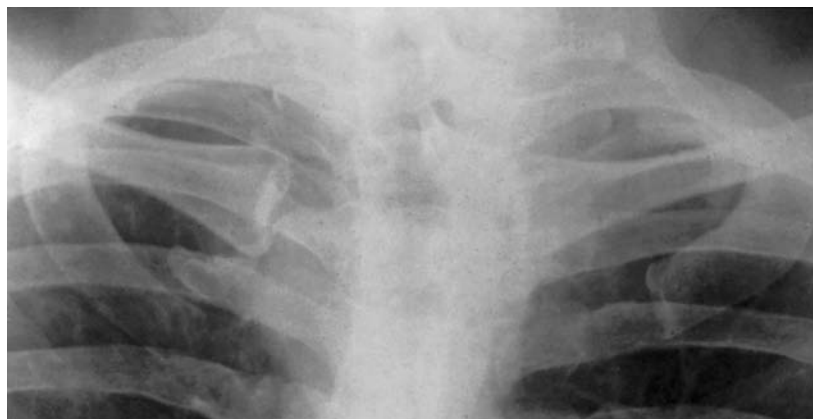


Fig. 45.1 Bilateral cervical ribs.

should be discussed with them before referral to a thoracic surgeon.

### **Pectus excavatum or funnel chest**

In this condition the manubrium is normal but the body of the sternum is angled backwards towards the spine from the manubriosternal joint downwards with maximum recession at the xiphoid, below which the costal margin bends forwards. The condition is usually symmetrical but occasionally the sternal recession may be greater on one side than the other. As with pectus carinatum, there may be associated congenital anomalies and Marfan's syndrome may be present.

### **Aetiology**

Pectus excavatum probably results from an imbalance of forces counteracting the inward pull of the diaphragm on the xiphisternum. Biopsies have shown that the anterior portion of the diaphragm is replaced by fibrous tissue. In the normal person the muscle in this region contracts on inspiration and its attachments to the lower chest wall on either side of the xiphisternum and lower sternum prevent these being dragged backwards as the diaphragm descends. When this muscle is lacking, the unopposed action of the posterior diaphragmatic muscle displaces the sternum and xiphisternum backwards as the diaphragm descends [12]. This movement occurs in affected newborn infants only on inspiration but after the age of 3 months the deformity progresses, with resulting secondary changes in the sternum and costal cartilages.

It has been suggested that an additional factor is a congenital laxity of the pericardium that allows the heart to fall to the left, removing its support from the sternum [14], and it has been recommended therefore that at operation the pericardial sac should be sutured into a central position. It has also been suggested that upper airway obstruction, whether due to enlarged tonsils and adenoids or segmental bronchomalacia, appears to predispose to

pectus excavatum, which may resolve if the obstruction is treated early enough [15–17]. An association between pulmonary sequestration and pectus excavatum has been described [18].

There is said to be a hereditary tendency to the development of pectus excavatum but no sex linkage. The condition was reported in 2.2% of boys and 2.5% of girls in a German series [19].

### **Pulmonary function**

Minor decreases in vital capacity (VC), total lung capacity (TLC) and maximal ventilation volume (MVV) have been reported in pectus excavatum with normal or increased residual volume (RV) and a normal forced expiratory volume in 1 s ( $FEV_1$ ) [20–22]. Even in the presence of normal pulmonary mechanics and lung volumes, it may be possible to demonstrate abnormal findings during exercise in symptomatic patients. Of eight such patients with exercise limitation, five demonstrated a diminished tidal volume expressed as percentage vital capacity at maximal exercise and had excessive oxygen uptake at higher loads consistent with an increased work of breathing [23].

### **Clinical features**

In most cases the main symptom due to the deformity is the embarrassment caused to the patient by the deep furrow in the chest. In surgical series, however, where selection by degree of severity has occurred, patients are recorded with severe symptoms of dyspnoea, precordial pain, syncope on moderate exertion, palpitations and recurrent lung infections [12]. Incapacitating supraventricular tachycardia provoked by exercise and cured by surgery has been reported [24].

In children with pectus excavatum the majority have auscultatory findings suggestive of cardiac disease, with murmurs mimicking those of pulmonary stenosis or a small atrial septal defect [25]. These murmurs are

presumed to be due to the resultant cardiac displacement. It has been reported that a cartilaginous horn from the inner surface of the xiphoid may impinge on the heart with resultant ECG changes and/or angina and that this may be cured by operation [26]. The ECG may show persistence of the juvenile pattern, with T inversion in the right precordial leads, incomplete right bundle branch block and right axis deviation. Because of cardiac rotation there may be P-wave inversion in  $V_1$  and a QR pattern [27].

### Radiology

On the posteroanterior chest film the heart is often displaced to the left and anterior ribs may show marked obliquity (Fig. 45.2). The depressed sternum is obvious on the lateral chest film and various indices for assessing the severity of disease and response to surgery using this film have been described [28]. Paradoxical cardiac enlargement during inspiration in children with pectus excavatum has been reported and is due to reduction of the anteroposterior diameter of the thorax caused by diaphragmatic descent [29].

### Treatment

Surgery is rarely required because of cardiorespiratory symptoms, although these may occur in a minority and be disabling as described above. More often, surgical repair is sought for cosmetic reasons. It is usual to resect the deformed costal cartilages and perform an osteotomy of the anterior table of the sternum, providing internal fixation by the use of a bar that passes anterior to the rib cage but behind the sternum. Early cosmetic and functional results are usually good, and most recent reports indicate a satisfactory long-term result [30,31]. Unsatisfactory results have been recorded in patients with severe and asymmetrical deformities and with Marfan's syndrome [31]. Lung function is likely to deteriorate rather than improve shortly after surgery, thereafter sometimes recovering to its original level [22,32,33]. Nevertheless, the majority of patients are happy with the cosmetic results.

### Straight back syndrome

The straight back syndrome is a presumed congenital abnormality in which there is absence of the physiological dorsal kyphosis of the spine as determined on a lateral chest radiograph.

### Clinical features

Presumably because of compression of the heart and great vessels between the spine and sternum, with resultant

compression of the pulmonary outflow tract, a pulmonary ejection systolic murmur is not infrequently found [34,35]. A palpable left parasternal systolic impulse may be present and exaggerated respiratory splitting of the second heart sound may be heard. An ECG may show an rSr pattern in  $V_1$ . These subjects are reported not to differ from controls in work capacity, FEV<sub>1</sub>, diffusing capacity or arterial blood gas tensions, although total lung capacity may be reduced [36].

### Radiology

The lateral chest radiograph suggests the diagnosis, showing loss of dorsal kyphosis and reduced anteroposterior diameter of the chest. On the posteroanterior film the pulmonary arteries may be prominent and the heart shadow is often displaced to the left, sometimes with a pancake configuration [36].

### Poland's syndrome

Poland's syndrome consists of syndactyly plus ipsilateral absence of the pectoralis major muscle [37]. This results in hypoplasia of the ribs on the affected side and hypertranslucency of the lung on the posteroanterior chest radiograph.

### Sternal abnormalities

An unusually wide sternum, with the suggested name eury sternum, and sternal foramina visible on chest radiography and bone scans have been described [38]. They are of no clinical significance.

### Congenital kyphoscoliosis

A minority of cases of kyphoscoliosis are congenital in origin and these are considered later in this chapter.

## Acquired abnormalities of the chest wall

### Fractures [39]

#### Traumatic fractures

Trauma to the chest wall may be inadvertent and unnoticed by the patient, particularly when under the influence of alcohol, anaesthetics or in a coma, and may sometimes give rise to problems in differential diagnosis. A rib fracture should be suspected if there is acute local rib tenderness at the site of pain of recent onset or if pain occurs on springing the ribs. Palpable or audible crepitus may be found at the site. If penetration of the parietal and visceral pleura occurs, there may be signs of pneumothorax and



(a)



(b)

**Fig. 45.2** Posteroanterior (a) and lateral (b) chest films of patient with pectus excavatum. Slight apparent enlargement at the left hilum is due to compression by the depressed sternum.

subcutaneous emphysema. The presence of multiple healed rib fractures on a chest film should call attention to the possibility of alcohol abuse.

### Fatigue fractures

These may occur in the first or second ribs, most commonly in young soldiers carrying heavy rucksacks or rifles. Often there is little pain but the fracture may result in fibrous union or a residual cyst [40].

### Cough fractures

Cough fractures are common and most frequently seen in patients with severe chronic airways obstruction, usually due to chronic bronchitis and emphysema, and in whooping cough. Predisposing factors include corticosteroid therapy or senile osteoporosis and osteomalacia. Cough fractures are associated with sudden onset of pain while coughing, the subsequent pain usually being worse on coughing than breathing. The local signs are as for a traumatic fracture, although pneumothorax is not usually seen. They are located most frequently in the mid-axillary line.

### Pathological fractures

Pathological fractures may occur with rib metastasis or osteolytic primary tumour of rib such as myeloma.

### Radiology

Unless there is displacement of a fracture it may not be visible on the radiograph even in the acute stage, and radiologically visible callus formation does not occur for several weeks. The diagnosis is therefore frequently clinical. Pneumothorax and/or subcutaneous emphysema may be seen with traumatic lesions, while the primary lesion may be visible in the case of pathological fractures. Sometimes the film may show linear shadows 2–3 cm long underlying a traumatically fractured rib, possibly due to bruising of the lung [40].

### Treatment

Treatment with adequate analgesia is usually all that is required, although occasionally it may be necessary to infiltrate with local anaesthesia. Lower respiratory tract infection, particularly on the affected side, may develop in patients with chronic airways obstruction and require intervention with antibiotics. Chest wall strapping is contraindicated since it predisposes to the same complication.

## Scoliosis

Scoliosis is defined as a lateral curvature of the spine and is associated with rotation of the spine and viscera adjacent to it. It may be (but is usually not) accompanied by kyphosis [41].

### Aetiology

An abbreviated aetiological classification is shown in Table 45.1 [41]. Non-structural causes include the well-known sciatic scoliosis, a temporary scoliosis occasioned by irritation of sciatic nerve roots. Structural causes are identified by the persistence of fixed rotation of the spine on forward bending. The majority of cases of scoliosis nowadays are idiopathic in origin. Idiopathic scoliosis may be seen at all ages during growth and at all spinal

**Table 45.1** Aetiological classification of scoliosis.

<b>Non-structural</b>
<i>Postural compensatory</i>
Sciatic
Inflammatory
Hysterical
<b>Structural</b>
<i>Idiopathic</i>
Adolescent kyphosis
<i>Osteopathic</i>
Congenital scoliosis
Klippel–Feil syndrome
Spondylolisthesis
<i>Myopathic</i>
Duchenne muscular dystrophy
Faciohumeroscapular dystrophy
<i>Neuropathic</i>
Poliomyelitis
Cerebral palsy
Syringomyelia
Neurofibromatosis
Friedreich’s ataxia
<i>Hereditary syndromes</i>
Dominant
Marfan’s syndrome
Ehlers–Danlos syndrome
Recessive
Homocystinuria
Morquio’s syndrome
Sex-linked
Turner’s syndrome
<i>Miscellaneous</i>
Long-standing unilateral lung fibrosis
Burns
Irradiation
Thecoperitoneal shunts
Empyema
Thoracoplasty
Hiatus hernia

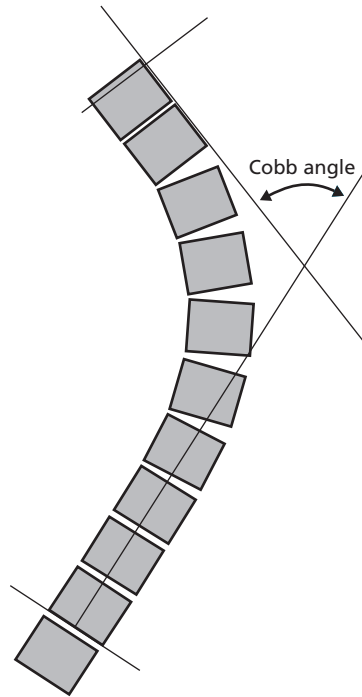


Fig. 45.3 Measurement of a thoracic scoliosis by Cobb's angle .

sites, although thoracic scoliosis to the right is the most common presentation [42,43]. The condition is more prevalent in girls. The higher in the spine the structural curve, the worse the prognosis. Prognosis is also a function of the angle of curvature, which is measured as shown in Fig. 45.3; lines are drawn parallel to the upper border of the upper vertebral body and to the lower border of the lowest vertebra of the structural curve. Perpendiculars are then erected from these lines to cross each other, the angle between the perpendiculars being the angle of curvature or Cobb's angle [44].

Neuropathic and myopathic conditions, of which poliomyelitis is the most common example, are usually associated with a worse prognosis for a given degree of curvature as a result of the associated muscle weakness and consequent ventilatory problems. Scoliosis due to poliomyelitis usually appears within 2 years of infection.

### Pathology

In scoliosis the total lung volume is reduced and the lungs differ in size, with distortion of lobar shapes due to the deformity [45]. Alveolar size may vary; if scoliosis has been present from an early age, alveolar numbers per acinus may correspond to that developmental stage [46]. In severe scoliosis progressing to cor pulmonale, the pulmonary changes of marked vascular medial hypertrophy are indistinguishable from the changes seen in other causes of cor pulmonale [47].

### Physiology

Because of the reduction in height occasioned by the spinal deformity, it is conventional to calculate predicted values for lung function in scoliosis on the basis of arm span measurements, arm span correlating closely with height in normal subjects [48]. Lung volumes are reduced, with a restrictive pattern even in asymptomatic adolescents with scoliosis. VC, TLC, MVV, functional residual capacity (FRC) and peak expiratory flow (PEF) and are all reduced and there is a direct relationship between the angle of curvature and the degree of reduction of these indices [49–54]. The higher the curve in the dorsal spine, the more severe its effect on function. RV may be maintained, resulting in an increased RV/TLC ratio [50]. The FEV<sub>1</sub>/forced vital capacity (FVC) ratio is normal unless obstructive disease such as asthma supervenes [49]. Diffusing capacity for carbon monoxide (DLCO) is reduced in proportion to the reduction in lung volumes, giving normal values for Kco [49,52,53,55]. In paralytic scoliosis, similar changes are seen in lung volumes; however, for a given angle of curvature diminution of lung volumes is more severe [56] and the correlation of lung volume changes with Cobb's angle less clearly seen, reflecting the contribution of affected muscle to the disorder of lung function.

Lung compliance in scoliosis is commonly low, perhaps reflecting occurrence of small airway collapse due to inability to take a deep breath or a sigh [51,57,58]. This decreased compliance is also most pronounced in those with muscle weakness and can be increased by positive-pressure ventilation [59,60]. In scoliotic patients with impaired cardiorespiratory response to exercise, maximal oxygen uptake is reduced compared with age- and sex-matched normals, and ventilation at a given oxygen uptake is 20% higher than in normal subjects [61]. Exercise tolerance is thus limited in these patients by ventilatory factors.

Regional perfusion and ventilation are often normal in patients with scoliosis studied with xenon-133 techniques, although reduction in ventilation and perfusion at the lung bases does occur to a greater extent with increasing angle of curvature and age [55,62–64]. Pao<sub>2</sub> is diminished even in asymptomatic adolescents with scoliosis, and with severe disease carbon dioxide retention occurs [64]. As a consequence of increasing hypoxia, pulmonary artery hypertension occurs, the pressure being inversely proportional to Pao<sub>2</sub> [65,66]. In patients with severe scoliosis (with an angle  $\geq 100^\circ$ ), severe desaturation may occur during sleep with episodes of central or obstructive apnoea and hypopnoea, particularly during REM sleep [67,68]. The occurrence of carbon dioxide retention raises the possibility of defective chemical control of ventilation. Diminished ventilatory responses to carbon dioxide have been demonstrated in patients with both the idiopathic



and paralytic types of scoliosis, where the mechanical deformity has been the presumed explanation [51,55].

Finally, in patients with scoliosis of whatever degree, diminution in the maximum inspiratory and maximum transdiaphragmatic pressures has been recorded, suggesting that inspiratory muscle function is impaired, as a consequence of either a primary muscular problem or defective mechanical coupling between the inspiratory muscles and the rib cage [57,69].

### Clinical features

It is unusual for patients with mild scoliosis to have respiratory symptoms. However, physiological studies of such patients have shown reduced muscularity and work capacity and an excessive cardiovascular response to exercise, suggesting cardiovascular unfitness [70]. Daytime somnolence may indicate the presence of nocturnal desaturation, a common occurrence as the patient's condition deteriorates. In more severe cases exertional dyspnoea may occur and is due to the restriction of lung volumes that these patients have. Airways obstruction, which is often reversible, may also develop. In patients with a mid or high thoracic curve greater than about 100°, progression to pulmonary hypertension and right ventricular failure often occurs in the fourth decade, usually presenting with increasing dyspnoea; syncope, angina or sudden death may occur. Death most commonly occurs as a result of respiratory failure or cardiac disease, and the risks are highest in juvenile scoliosis and scoliosis after polio [71]. In severe scoliosis, acute respiratory failure may be precipitated by respiratory tract infection, and deterioration in these patients may be more rapid and severe than in patients with end-stage chronic bronchitis and emphysema for example. This necessitates careful attention to antibiotics, oxygen and physiotherapy with recourse to assisted ventilation, which is employed if the future prognosis warrants such intervention.

### Treatment

#### *Surgery*

Although surgical intervention, for example by spinal fusion, may ameliorate the angle of curvature and halt the progression of scoliosis, remarkably little benefit has been documented in terms of pulmonary function tests apart from an improvement in submaximal exercise ventilation [72].

#### *Medical treatment*

Following the initial episode of acute respiratory failure in severe scoliosis, the rate of deterioration of FEV<sub>1</sub> has been shown to be much slower than in patients with chronic

bronchitis and emphysema, and prolonged survival is possible after such an initial event [73]. Long-term domiciliary oxygen therapy may be useful as initial management of respiratory failure [74], although most patients ultimately need some form of assisted ventilation (see Chapter 58). In patients with late-onset respiratory failure in paralytic poliomyelitis, it has been shown that improvised long-term intermittent positive-pressure ventilation not only improves the patient's sense of well-being but also arterial blood gas tensions [75]. It is now apparent that home ventilation is of substantial benefit to patients with severe scoliosis. The most usual starting regimen is nasal intermittent positive-pressure ventilation, which has been shown to reduce admissions to hospital and to result in improvements in blood gases [76,77]. Alternative means of support for patients with life-threatening hypoventilation include tank respirators or cuirass shells. The latter can be individually moulded and tailored for each patient's deformity, and nocturnal ventilator support with such a system produces dramatic improvement in daytime blood gas tensions and also reduces the need for hospitalization [78–81]. Less satisfactory for the patient, but equally effective, is nocturnal ventilation via a permanent tracheostomy [82]. The effectiveness of nocturnal assisted ventilation is probably due to abolition of the more severely reduced blood gas tensions found at night [67,68]. Respiratory muscles that are rested at night and prevented from becoming fatigued are more capable of sustaining satisfactory ventilation and blood gas tensions by day.

Needless to say, appropriate diuretic therapy is indicated where right heart failure is present, and individual patients may also have superadded obstructive ventilatory defects that respond to bronchodilator therapy. Infective episodes are treated along routine lines.

### Ankylosing spondylitis

#### *Aetiology*

The aetiology of ankylosing spondylitis is unknown but the strong association with HLA-B27 is now well recognized, and individuals homozygous for HLA-B27 may have more severe disease [83–88]. Blood donor studies have suggested a disease prevalence of 1–2% depending on the frequency of B27 in the population [89]. The disease is much commoner in young adult males than in females.

#### *Pathophysiology*

Fixation of the thoracic cage occurs in ankylosing spondylitis as a result of ankylosis of costotransverse and costovertebral joints. Sternomanubrial and sternoclavicular joints may also be affected [90]. In one study, 70% of patients had chest expansion of less than 5 cm when first

seen [90]. In severe disease a restrictive pattern of abnormality is seen, with a reduction in VC due to reduced inspiratory capacity and a reduction in TLC [90,91]. RV and FRC are normal or slightly increased [90,92]. Gas exchange is normal [92]. As might be expected, thoracic and total respiratory compliance are decreased but lung compliance is normal [93]. Xenon-133 studies have shown normal perfusion but reduced apical ventilation in patients, although later studies suggested that apical underventilation is only seen in the presence of fibrosis [94,95].

### Clinical features

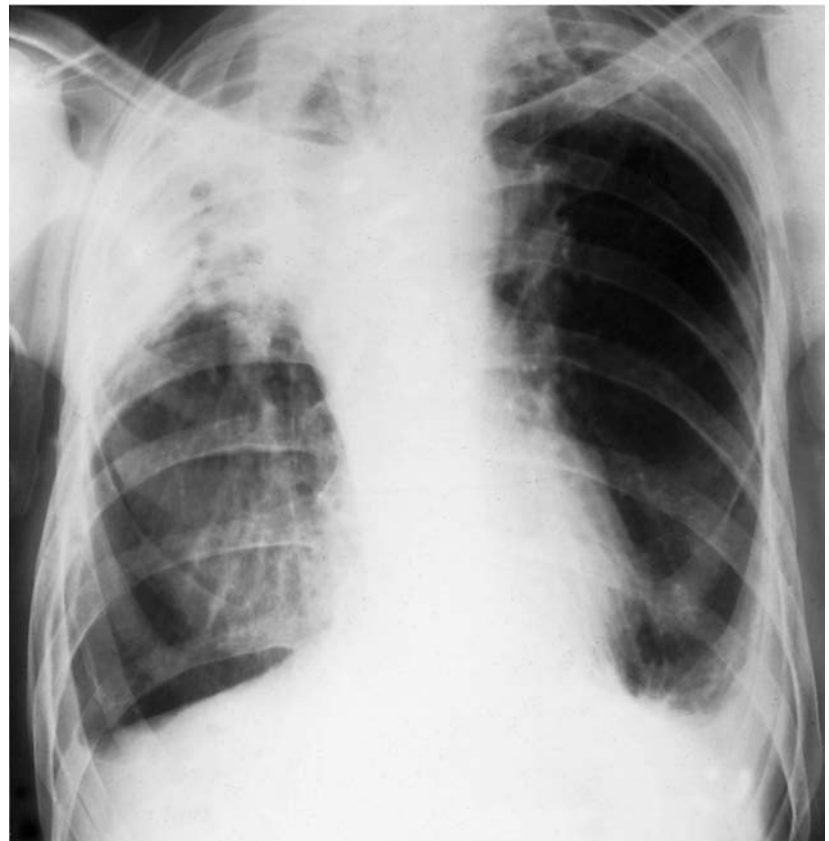
Despite the functional abnormalities described, respiratory disability is uncommon in ankylosing spondylitis, although dyspnoea on exertion may occur. In most cases the diaphragm appears to compensate more than adequately for the restriction of thoracic wall movement. However, an occasional patient may develop respiratory failure due to very extensive chest wall disease. Chest pain is not uncommon and may be diffuse and prolonged or short and stabbing in character. It is usually located in the lower anterior chest and there may be an associated island of pain higher up posteriorly, suggesting that the phenomenon is one of radiating intercostal pain from posterior spinal joints [96].

In 1972, Davies [97] described seven patients with ankylosing spondylitis and apical lung fibrosis. Found late in the history of the disease, the fibrosis begins as consolidation that may extend to upper and mid zones bilaterally (Fig. 45.4) and may subsequently cavitate with bulla formation. Aspergillomas may form in the cavities or bullae with attendant symptoms of cough and/or haemoptysis (see Chapter 21). Transient pleural effusions have also been reported in ankylosing spondylitis but such pleuropulmonary manifestations are rare, occurring in only 1.3% of 2080 patients in one study [98].

Adenocarcinoma has been reported in association with the apical fibrosis of ankylosing spondylitis [99]. There has also been a further report of pathology suggestive of bronchocentric granulomatosis associated with *Aspergillus* colonization [100]. Other rare complications of ankylosing spondylitis that have been reported include acute respiratory failure from extrathoracic airway obstruction due to ankylosis of the cricoarytenoid joints [101] and amyloidosis of the lungs [102].

### Treatment

Chest pain usually responds to minor analgesics. No other treatment is usually required or indicated apart from the management of mycetoma complications. In occa-



**Fig. 45.4** Bilateral upper lobe fibrosis with disappearance of the main pulmonary arteries into the fibrotic lesions. There is also cavitation due to secondary bronchiectasis in the right upper lobe and bilateral basal pleural thickening. The patient had severe ankylosing spondylitis.

sional patients with severe disease, surgical attempts have been made to mobilize the chest by resection of the posterior parts of several ribs or by other procedures, some of which appear to have improved respiratory function [103].

### **Slipping rib syndrome**

#### **Clinical features**

The slipping rib (syn. rib tip or clicking rib) syndrome [39,104,105] consists of intercostal radicular pain that may be episodic or continuous, mild or severe, and which is exacerbated by movement, as on rising from a chair. The pain is due to irritation of the intercostal nerve anteriorly by an adjacent rib or costal cartilage, and most commonly involves the eighth, ninth and tenth ribs, more frequently on the right than the left. The condition is more common in women than men, with an average age at onset of 29. The symptom may be reproduced by moving the affected rib, when a clicking or grating sound may be heard.

#### **Treatment**

The condition may respond to local injection of anaesthetics or steroids but if severe may require subperiosteal excision of the affected rib and costal cartilage. At operation the affected rib is found to be unduly mobile and to slip under the superior adjacent rib. The results of operation are good, with 82% of patients being pain-free at 7 days [106].

### **Sternocostoclavicular hyperostosis**

#### **Clinical features**

Kohler and colleagues [107] described five patients presenting between the ages of 44 and 46 years with an 11–34 year history of a persistent pulling pain in the sternum, clavicles and upper ribs that was exacerbated by cold and dampness. Others have reported episodes of painful hot swelling at the same sites [108–110]. Club-like symmetrical enlargement of the clavicles was present, and in two patients venous congestion of the upper half of the body was seen. In these patients, atrophy of the shoulder girdle and occlusion of the subclavian vein, which was sometimes bilateral, appeared to occur for mechanical reasons [107,110]. The erythrocyte sedimentation rate (ESR) was markedly elevated.

Chest radiographs show symmetrical hyperostosis of the sternum and middle thirds of the clavicles, with synostosis of the sternoclavicular joints. The upper ribs are variably involved, with early ossification of the costochondral

junctions. The disease appears to begin with an ossifying periosteitis. Biopsy of affected bones shows hyperostotic sclerosis of the spongiosa.

The aetiology is unknown, although there appears to be an association with ankylosing spondylitis and with vulgar or pustular psoriasis [108,110]. The disease is rare in the West, where it appears to be linked with HLA-B27, and is commoner in Japan where no such linkage occurs [110].

#### **Treatment**

No definitive treatment exists but symptomatic relief may be obtained with non-steroidal anti-inflammatory agents or with corticosteroids.

### **Tietze's syndrome or costochondritis**

This condition of obscure origin results in pain, swelling and tenderness of one or more of the upper six costal cartilage, although the sternoclavicular joint was thought to be involved in one of Tietze's original four cases [111]. It has been suggested that the condition is the mechanical consequence of differences in leg length [112]. Alternatively, on the basis of an 'epidemic' of six cases occurring within 6 weeks in Zambia, a viral aetiology has been proposed [113].

#### **Clinical features**

It may occur at any age although it is commoner in young adults. There is no sex predisposition. The most common presentation is with painful swelling of one or more of the upper six costal cartilages, most commonly the second. The pain is localized and may be described as aching, gripping, sharp or dull. The intensity varies from mild to severe and may be exacerbated by coughing or deep breathing [114,115]. The onset may be sudden or gradual and the condition may persist for weeks, months or, rarely, years [116]. Biopsy shows normal cartilage [117]. The blood picture, including ESR, is normal and there are no radiological changes.

#### **Treatment**

The majority of cases respond to reassurance and the passage of time with or without the administration of a minor analgesic. Exceptionally, local injection of hydrocortisone may be required for relief of symptoms [118].

### **Relapsing polychondritis**

This serious condition results in painful inflammation,

most commonly of the ear, nose and eyes, in association with systemic upset including fever, elevated ESR, anaemia and hyperglobulinaemia [119,120]. It is a disease of the middle decades with an equal sex distribution and is thought to be autoimmune in aetiology; antibodies to types IX and XI collagen and associations with systemic lupus and HLA-DR4 have been demonstrated [121–123]. Costochondral junction involvement is seen in about 50% of cases and laryngotracheal involvement in 70%. The disease may be rapidly fulminant, with death from pneumonia refractory to antibiotics or tracheal narrowing due to oedema, scarring and collapse of tracheal rings. Of the 49 cases reported in one series, the average lifespan of 11 who succumbed was 7 years, with a range from 10 months to 24 years [124]. The usual treatment is with systemic corticosteroids in a high initial dose (30–60mg) followed by a maintenance dose (5–10mg) [124]. Corticosteroids appear to suppress the fatal tracheo-bronchial complications of the disease. The use of stents may be necessary when tracheal or bronchial collapse is a problem [125].

## Rib defects

### Rib notching

Erosion of the inferior border of ribs or rib notching is most commonly seen in patients with coarctation of the aorta, when it is due to the enlarged intercostal arteries acting as collateral vessels (Fig. 45.5). It is present in 75% of adult patients but, since it is acquired, is less common in children although it has been seen in an infant [126,127]. The first two and last three ribs are never involved [126]. All other causes of this radiographic abnormality are rare, including subclavian artery obstruction after the Blalock–Taussig operation, ‘pulseless disease’, pulmonary arteriovenous fistula and intercostal neuroma. An idiopathic group is also recognized [126].

## Superior marginal rib defects

Loss of superior marginal cortical bone in the third to sixth ribs has been reported in patients with poliomyelitis and in patients with restrictive lung disease due to connective tissue disorders, such as rheumatoid arthritis, systemic lupus erythematosus and scleroderma [128–130]. The aetiology is unknown.

## Tumours of the chest wall

Tumours of the chest wall may originate in soft tissues or the bony thorax and the most common primary tumours found in these sites are shown in Table 45.2. Metastatic tumours of the chest wall are much more common than primary tumours.

### Soft tissue tumours

#### Benign tumours

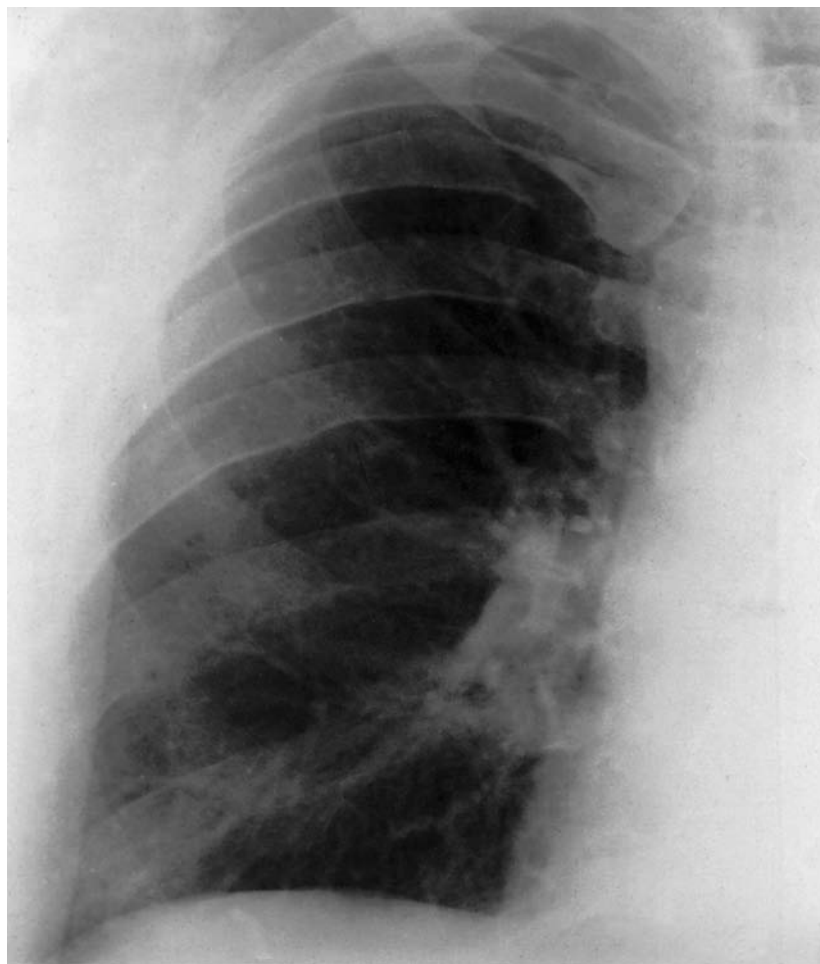
Lipoma is the most common benign soft tissue tumour of the chest wall. It is characteristically spongy, transilluminates well and is readily identified by CT. Rarely it may extend into the pleural cavity giving rise to an hourglass-shaped mass that indents the lung [131].

Chest wall haemangiomas are slow-growing tumours that arise in striated muscle. As they enlarge they may produce radiographic evidence of rib hypertrophy and notching. Phleboliths are uncommon but pathognomonic. Eventually a pulsatile mass that may have an audible bruit may form and this may be mistaken for a metastasis from thyroid or renal carcinoma.

Cystic hygroma or cavernous lymphangioma is an uncommon thin-walled multilocular tumour, usually found in the region of the neck in small children, that may extend into the mediastinum and chest wall rendering

**Table 45.2** Benign and malignant tumours of the thoracic soft tissues and the bony thoracic cage.

	Benign	Malignant
Soft tissue	Lipoma Haemangioma Cystic hygroma Neurofibroma	Fibrosarcoma Liposarcoma Leiomyosarcoma Synovioma Neuroectodermal tumours
Bony cage	Osteochondroma Chondroma Simple cyst Osteoid osteoma Fibrous dysplasia	Chondrosarcoma Ewing's tumour Fibrosarcoma Osteogenic sarcoma Myeloma



**Fig. 45.5** Notching of the lower borders of upper thoracic ribs in a patient with aortic coarctation.

removal difficult. The author has seen haemorrhage into one such tumour cause acute tracheal obstruction (Fig. 45.6).

Multiple neurofibromas, varying in size from a pea to a ping-pong ball, may be found in the intercostal spaces of the chest wall (Fig. 45.7). They are associated with neurofibromas elsewhere in the body and with the characteristic *café-au-lait* spots. Rarely malignant change may occur, with sudden acceleration in the rate of growth of a nodule.

The fibrous benign desmoid tumour, which usually arises from the fascia of the anterior abdominal wall, has also been described arising in the intercostal space [132–134].

### **Malignant tumours**

Fibrosarcoma is the most common malignant soft tissue tumour of the chest wall and usually presents in young adults as a tumour in the region of the shoulder [133]. Haematogenous dissemination does happen but cure is possible if wide surgical excision is performed before this occurs.

Liposarcoma arises *de novo* and not from a pre-existing lipoma. It rarely metastasizes, although 50% recur after surgical resection.

Chest wall sarcomas including leiomyosarcoma have been reported in children and have proved amenable to surgical resection [135,136]. Malignant synovioma of the chest wall has also been reported [137]. A malignant chest wall tumour with features of adenocarcinoma and squamous carcinoma has been described 2 years after iodized talc pleurodesis [138]. Neuroectodermal tumours (Askin tumours) may occur in the chest wall. They are most frequent in children and may present as a large mass or with lung metastases [139].

### **Tumours of the bony thoracic cage**

Tumours of the bony thoracic cage are most commonly found in the ribs and least commonly in the sternum, with intermediate frequencies in scapula, thoracic vertebrae and clavicle. The most common tumours are metastases from other primary tumours, most often breast, bronchial and prostatic carcinoma. Prostatic and breast metastases in particular may be osteosclerotic (Fig. 45.8). Of primary



**Fig. 45.6** Barium swallow in a patient who presented with stridor showing tracheal displacement to left. At surgery the lesion proved to be a cystic hygroma into which an acute bleed had occurred.

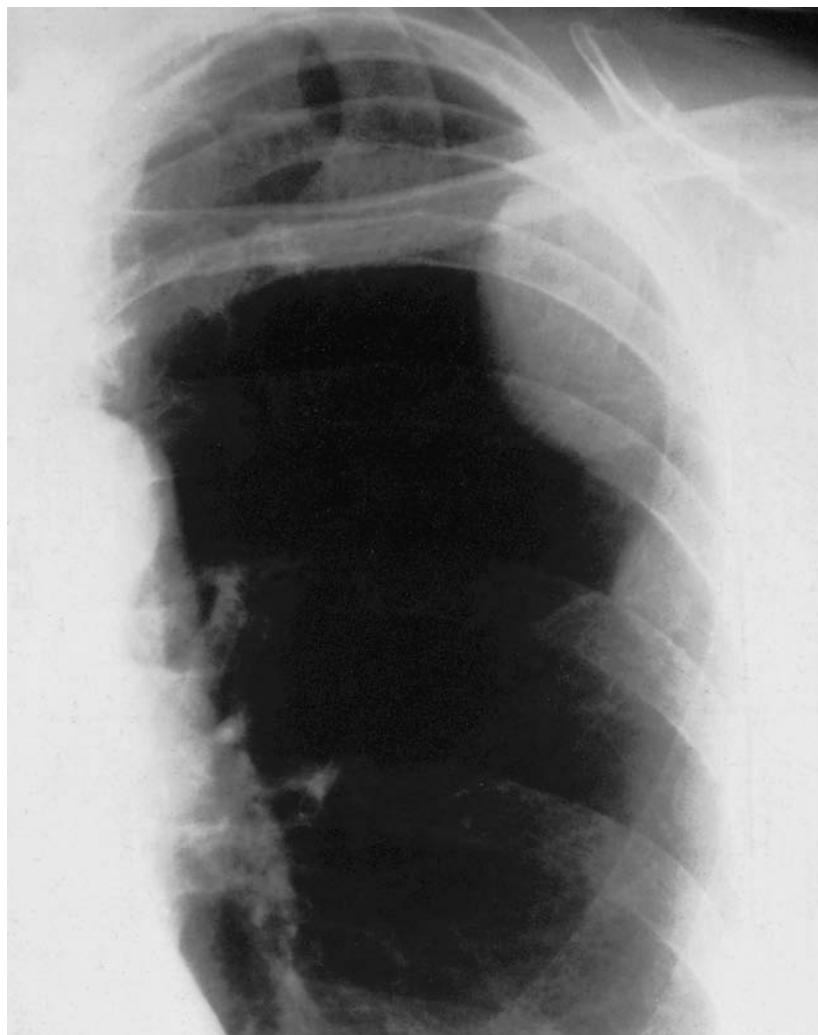
tumours of the thoracic cage, approximately 50% are benign [140–144]. Secondary tumours tend to have a short duration of symptoms, averaging 3 months in one series, whereas the mean duration of symptoms averaged 4.1 years for primary benign and 1.7 years for primary malignant tumours in the same series [141]. Patients with benign tumours are half as old on average as those with malignant tumours and about 30% of all thoracic cage tumours are discovered on routine chest radiography [141].

Patients may be asymptomatic, although the most common presentation is with local pain, which may vary from a dull ache to pain of great severity, and a mass on the chest wall. The pain of benign lesions tends not to change, whereas that of malignant lesions tends to progress and may be more readily affected by movement and coughing [140]. Where local structures are infiltrated or compressed,

pleuritic pain and referred pain, for example from intercostal nerves, may occur. It is generally agreed that it is unwise to assume that a tumour of the thoracic cage is benign, and all tumours should be treated with wide excision so that a pathological diagnosis can be obtained on the entire surgical specimen.

#### *Benign tumours*

Osteochondroma or exostosis is the most common benign tumour, often presenting as a mass arising from the scapula or a rib, most frequently near the costochondral junction, in patients in the second decade. Growth begins in childhood and is believed to stop when adult stature is achieved. There is often a bony base to the tumour with a cartilaginous cap over which a bursa may be present. These tumours may cause local pain and



**Fig. 45.7** Three neurofibromas on left lateral chest wall in patient with multiple neurofibromatosis.

should be excised since the diagnosis is never certain and chondrosarcomatous transformation of the cartilage can occur.

Chondromas appear radiologically as well-demarcated expansions of a rib near a costochondral junction. A well-defined lucent area in the rib may contain flakes of calcium. Tumours of mature cartilage, they may give rise to chondrosarcomas and the treatment of choice is wide surgical excision.

Simple (or unicameral) bone cysts are found in the anterior portion of ribs, in the clavicle or sometimes in the head of the humerus. They produce a radiolucent defect on chest radiographs that may expand and thin the cortex resulting in a pathological fracture.

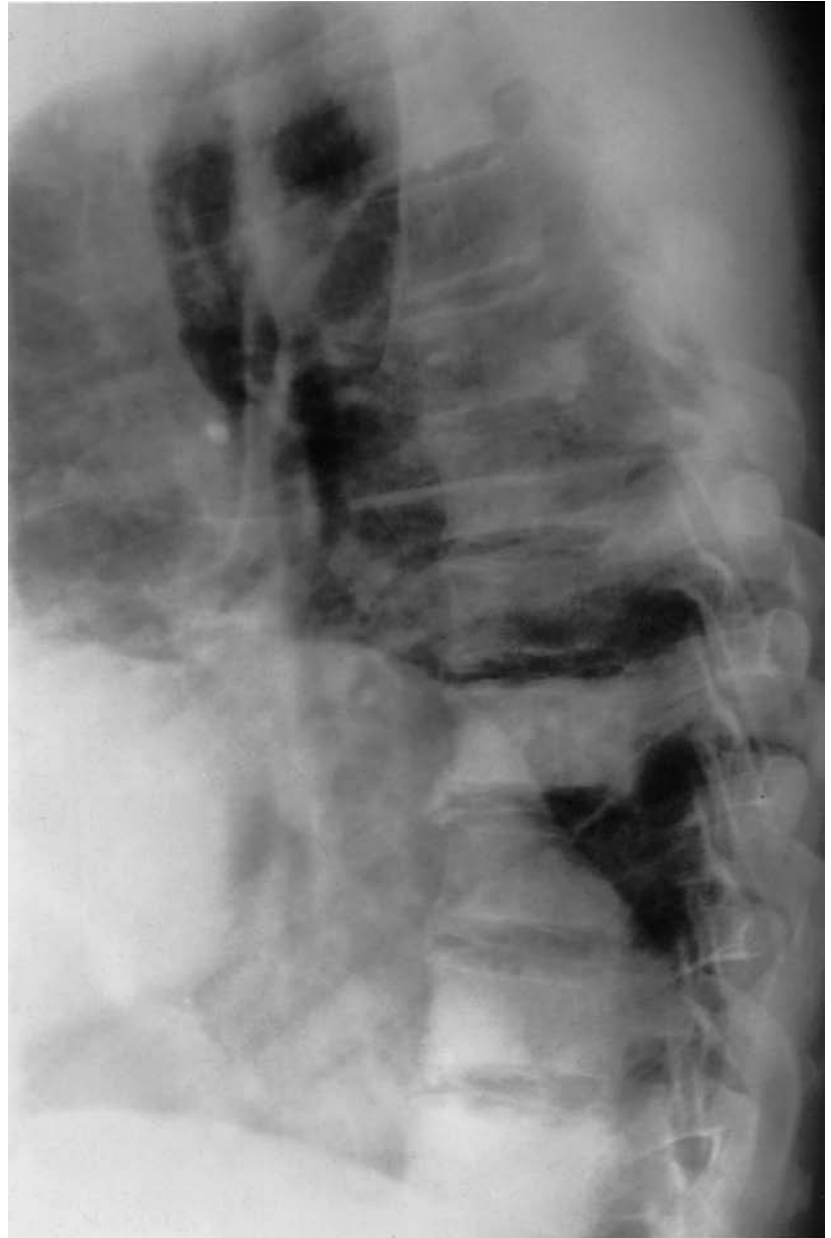
Osteoid osteoma is uncommon in the thoracic skeleton but may be confused with osteomyelitis or malignancy since it causes severe progressive pain that is worse at night. The radiographic picture of a round or oval lucent

area about 1 cm in diameter surrounded by sclerotic bone often assists diagnosis.

Fibrous dysplasia is the most commonly encountered rib abnormality in young adults aged 20–30 years [145, 146]. The condition is one in which primitive fibrous tissue proliferates in the medullary cavity and erodes the cortex from within, often producing expansion or distortion of the bone. The lesion is usually single and located in the posterior aspect of the ribs, although multiple lesions are found in Albright's syndrome where *café-au-lait* spots, precocious puberty or hyperthyroidism may be found [145]. Radiologically, the cortex may be thinned by a transradiant swelling that may be traversed by irregular bony trabeculae [140]. Clinically, pain is unusual but pathological fractures do occur. Excision is the treatment of choice [147].

Osteoclastoma is a rare tumour in the thorax, where it may be found in the head or tubercle of a rib; 10% are malignant and treatment is by excision.





**Fig. 45.8** Chest film of thoracic and upper lumbar spine showing radiodense osteosclerotic metastases from prostatic carcinoma.

### ***Malignant tumours***

Chondrosarcoma is the most common primary malignant tumour of the bony thoracic skeleton and presents usually with chest pain and swelling [140,141,148]. It has been described after radiation therapy, in Paget's disease and on one occasion following repetitive trauma from the arm of a wheelchair [149]. Most common in the upper anterior ribs, it is seen radiologically as a mass arising from the periosteum in such a way that the underlying bone shows minimal destruction (Fig. 45.9). Flakes of calcium may be seen in the tumour. It is locally invasive and may also spread via the bloodstream to the lungs in the first

instance. Treatment is by wide surgical excision and chemotherapy.

Ewing's tumour, an aggressively malignant tumour, is most common in those under 30 years of age and usually involves the ribs and less commonly the scapula or sternum [140,150]. Systemic features of fever, weight loss and malaise may occur with progressive local changes of pain, swelling and tenderness [150]. Radiographs may show progressive rib destruction with little reactive change and a soft tissue mass develops in most cases (Fig. 45.10). Multiple areas of periosteal new bone formation may produce an onion-peel appearance. The tumour metastasizes to lungs and other bones in most patients.

Treatment involves chemotherapy usually with combined radiotherapy and surgery; survival rates at 4 years of 56% have been reported after combined treatment, with no later recurrences [151].

Fibrosarcoma and osteogenic sarcoma behave like chondrosarcoma both clinically and radiologically [140].

Myeloma may present as a solitary lesion or as multiple lesions most commonly of the ribs [152,153]. The most common presenting feature is rib pain, often due to pathological fractures. Lytic lesions are seen on chest radiographs. Treatment consists of radiotherapy for local lesions and chemotherapy for multiple lesions.

## Infections of the chest wall

### Osteomyelitis

Osteomyelitis of ribs is relatively uncommon and is more frequent in children than adults. It often occurs after trauma and affects one of the upper three ribs, most commonly the first. The suppuration may strip the periosteum from the rib, forming a subperiosteal extrapleural abscess that may be large. Radiologically, the rib appearance may not change for 10–12 days. Initially, there is non-specific local destruction and osteolysis with reactionary sclerosis as the lesion becomes established [153].

Local osteomyelitis of a rib may be secondary to the drainage of an empyema, with infection spreading from the drainage site into the bone. Sequestra may be formed and discharge into the empyema, which persists until they are removed [154]. The most common offending microorganism is *Staphylococcus aureus*, management with appropriate antibiotics leading to resolution in most cases.

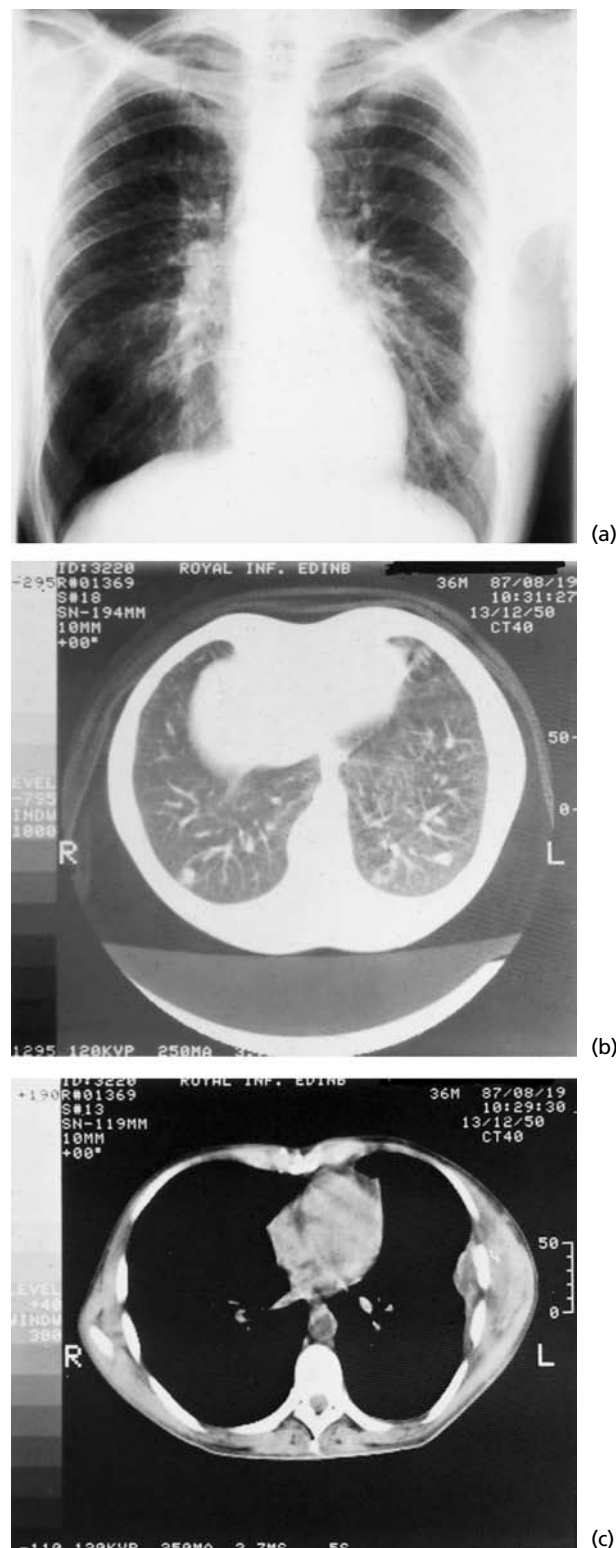
Osteomyelitis of the sternum is very uncommon [155,156]. It presents with fever and a tender swelling with radiographic evidence of bony erosion and sclerosis. *Staph. aureus* and *Pseudomonas aeruginosa* have been reported as causative organisms. Surgical drainage and curettage may be required in addition to antibiotic therapy [156].

### Septic arthritis

Sternoclavicular joint infection is an unusual cause of chest pain [157]. The joint is usually swollen and tender, with fever and systemic evidence of infection. The condition is commoner in heroin users in whom infection with both *Ps. aeruginosa* and *Staph. aureus* has been reported [158]. Treatment is with antibiotics and aspiration as required.

### Tuberculosis of the thoracic cage

Costal tuberculosis is rare but may give rise to local pain,



**Fig. 45.9** (a) Left lateral chest wall mass that on biopsy proved to be chondrosarcoma. CT shows (b) small metastatic deposits within the lungs and (c) soft tissue expansion round enlarged rib, containing dense areas of new cartilage. (Courtesy of Dr J.R. Walsh.)



**Fig. 45.10** Posterior mediastinal tumour. Destruction of the eighth rib provided the clue that this was a primary Ewing's sarcoma.

swelling and sinus formation. Radiologically there is an initial small area of bone destruction that may progress to periosteal elevation and soft tissue swelling. There is usually no evidence of pulmonary tuberculosis. Similar disease may arise in sternoclavicular or acromioclavicular joints.

Multiple lesions of the costovertebral portion of the ribs may accompany Pott's disease of the spine with paravertebral abscess formation.

#### **Cold abscess of the chest wall**

Cold abscess of the chest wall, which originates in tuberculosis of the intercostal lymph glands, can be divided into two main groups: the first lies at the angle of the ribs, from which the pus may track either backwards with the posterior primary division of the intercostal nerve, presenting near the erector spinae muscles, or forwards with the anterior division to present in the lateral chest wall; the second may arise from nodes in the region of the internal mammary artery and present near the costal cartilages. Cold abscess usually presents as a painless fluctuant swelling that may be mistaken for a lipoma. Diagnosis is made by aspiration of pus or during surgical exploration. It responds well to conventional antituberculous chemotherapy.

#### **Syphilitic gumma of chest wall**

This is now very rare and is described as arising in the

anterior mediastinum and giving rise to a hard, fixed lump in the intercostal space that may later soften and form a punched-out ulcer. Radiologically, the lesion may resemble a tumour of the anterior mediastinum. The true nature may be suspected if a punched-out ulcer has developed or as a result of positive serology.

#### **Actinomycosis**

Actinomycosis may spread from the lungs into the chest wall and give rise to destructive lesions with irregularity of the rib margins caused by periosteitis. It is described in Chapter 21.

#### **Echinococcosis**

Costal echinococcosis is very rare and usually presents as a multiloculated osteolytic lesion in rib [159]. The lesions are usually posterior and may expand to transgress the bony cortex. In the costovertebral region soft tissue masses may form and neurological presentations are common in this situation. The condition is described in Chapter 22.

#### **Fungal infections**

Blastomycosis, coccidioidomycosis and cryptococcosis can cause osteolytic lesions of ribs similar to those described above for tuberculosis. These organisms are discussed in Chapter 21.

### Thoracoplasty

This operation, in which a varying number of ribs was removed from one or both sides of the upper thoracic cage (Fig. 45.11), was widely practised from the 1930s until the mid-1950s as a treatment for tuberculosis [160]. In many cases it appears to have arrested previously progressive cavitating disease, one study carried out during the 1980s having shown survival of 93% at 10 years and 79% at 20 years [161]. However, the combination of the effects of the tuberculosis, the loss of the chest wall and, often, smoking has in many cases resulted ultimately in the development of respiratory failure.

### Neuromuscular conditions affecting respiration

It is uncommon but not unknown for patients with neurological disease to present primarily to the chest physician. However, respiratory problems in the course of neurological disease occur frequently, and the advice of someone interested in respiratory management is often sought. These conditions may be separated into those causing acute ventilatory problems and those causing chronic failure (Table 45.3).

### Acute respiratory failure

Acute problems occur most commonly as a consequence of overdose of drugs with a central nervous depressant effect, such as barbiturates and opiates, producing hypoventilation and carbon dioxide retention [162]. Management of these episodes includes a requirement for ventilatory support and, if necessary, cardiac support. Alcohol may not only cause central respiratory depression but has also been described as causing an acute rhabdomyolysis after a prolonged drinking bout [163]. A unique drug-induced cause of respiratory failure is the myasthenia syndrome that occurs as a rare side-effect of treatment with D-penicillamine, which usually resolves when the drug is discontinued [164]. Organophosphate and carbamate poisoning as a result of the widespread and careless use of insecticides is a not uncommon cause of acute respiratory failure in underdeveloped countries [165]. Similar problems occur as a result of neurological disease in acute ascending polyneuritis (Guillain-Barré syndrome), poliomyelitis, status epilepticus, tetanus and myasthenia gravis; as a result of accidents, following high spinal cord trauma and air embolism in diving; and as a consequence of lesions causing acute rises in intracranial pressure. Hypothyroidism may cause respiratory failure by a combination of central respiratory depression, upper airway



**Fig. 45.11** Right-sided eight-rib thoracoplasty carried out for cavitating tuberculosis in the late 1940s. Calcified lesions of healed tuberculosis are visible in both lungs.

**Table 45.3** Neuromuscular causes of ventilatory failure.

	Acute	Chronic
Neurological disease	Acute polyneuritis Poliomyelitis Myasthenia gravis Cerebral haemorrhage Cervical cord injury High intracranial pressure Epilepsy Critical illness neuropathy Tetanus Air embolism Hypothyroidism Bilateral phrenic palsy	Motoneurone disease Poliomyelitis Cervical cord injury Idiopathic Ondine's curse Brainstem tumours Myasthenia gravis Eaton–Lambert syndrome Multiple sclerosis Bilateral phrenic palsy Hypothyroidism Parkinson's disease
Muscular disease	Acute polymyositis Dermatomyositis Steroid myopathy Hypokalaemia	Muscular dystrophies Acid maltase deficiency Dystrophia myotonica Rigid spine syndromes Nemaline myopathy
Drugs' poisons	Opiates Barbiturates Hypnotics Anaesthetics Muscle relaxants D-Penicillamine Alcohol Botulinus toxin Organophosphates Carbamates	

obstruction and perhaps respiratory myopathy [166,167]. Acute respiratory muscle paralysis may occur in hypokalaemia [168], most commonly of the familial type but whatever the cause, and as a result of muscular or peripheral nerve dysfunction occurring in patients acutely ill on respirators [169–171], where it may cause problems in weaning from the machine. A steroid myopathy has also been described as causing similar problems [172], and this is something to be considered especially in severe asthma attacks when a patient has required ventilation and is proving difficult to wean. Primary muscle disorders may cause acute respiratory failure, particularly those having an inflammatory basis such as polymyositis and dermatomyositis [173].

### Chronic respiratory failure

Chronic ventilatory failure may be due to lesions involving the respiratory centre in the floor of the fourth ventricle, the nerves of the respiratory reflex arc or the muscles of respiration. The sleep apnoea syndromes are discussed in Chapter 47, although it should be noted that sleep hypoventilation is a usual accompaniment of all neuromuscular syndromes affecting respiration. The most common neurological causes of chronic ventilatory failure are motoneurone disease [174], poliomyelitis [175], multiple sclerosis [176] and spinal cord transection.

Chronic hypoventilation may also occur in myasthenia gravis [177], Eaton–Lambert syndrome [178] associated with bronchial carcinoma, hypothyroidism [179] and Parkinson's disease [180,181]. The drug L-dopa, used in the treatment of Parkinson's disease, may also cause respiratory muscle and respiratory centre dysfunction leading to ventilatory insufficiency [180]. Ondine's curse, a condition in which there is failure of brainstem autonomic control leading to suppression of respiratory drive when the subject is asleep, occurs as a congenital defect or may be a consequence of stroke or other pathological processes in the respiratory centre [182]. Bilateral phrenic nerve palsy has been discussed above. Muscle diseases causing chronic respiratory failure [173] include muscular dystrophies, of which the limb girdle and Duchenne types are the most common, adult acid maltase deficiency [183], dystrophia myotonica, rigid spine disorders including Emery–Dreifuss syndrome, and the autosomal dominant nemaline myopathy that sometimes presents in adult life.

### Assessment of respiratory function

In neuromuscular ventilatory failure the patient may remain asymptomatic from a respiratory point of view because of the inactivity imposed by the primary disease [184]. As the condition progresses, the patient may be seen

to be breathing rapidly and shallowly, except when the cause is drug overdose or brainstem disease, when the rate may be much reduced. Daytime somnolence is often present. The cause is usually obvious from the symptoms and signs of the primary disease, and treatment should be directed at its alleviation where possible. Thus it is important not to miss the less obvious causes such as hypokalaemia in, say, periodic paralysis, myxoedema or poisoning with organophosphorus insecticides. Physical signs may include the paradoxical chest wall and abdominal movements described in the section on diaphragmatic paralysis, poor cough, and difficulty with speech and swallowing. Vital capacity may be reduced but is often normal until the condition is quite advanced; nevertheless, at an earlier stage it should be possible to demonstrate reduced MVV and maximal inspiratory pressures using an oesophageal balloon. Sleep studies are essential, as the condition is usually worse during this time and in a number of conditions both central and upper airway dysfunction combine to cause the respiratory failure. In conditions with a fluctuating or progressive course, serial measurement of vital capacity is a useful means of monitoring progress and assessing the need for ventilatory assistance.

## Management

Wherever possible treatment should be directed at the primary cause. General management includes assistance with coughing and treatment of any respiratory infections, although the important decision relates to the need for ventilatory assistance. This clearly depends on the primary condition and its other effects on the patient, and there is little problem in deciding to use this in acute venti-

latory failure. Increasingly, however, patients with chronic neuromuscular conditions who would not have been considered suitable for long-term ventilation a decade ago are now benefiting from advances in management, which may provide fewer hospitalizations and respiratory infections and a better quality of life. Most such patients should be considered for such treatment [185]. In this chronic situation, there is time for detailed discussion of the implications of long-term support with patients and relatives, and for assessment of their suitability for domiciliary ventilation [186]. It is usually desirable to start with non-invasive measures and to delay tracheostomy until it becomes essential. Administration of low-flow oxygen to such patients without assisted ventilation is likely to give rise to carbon dioxide retention and is therefore undesirable [187]. A simple rocking bed may be suitable in some cases, where diaphragmatic weakness predominates or in relieving symptoms in terminal care [173]. The methods of ventilatory support available are described in Chapter 58. After full assessment, including polysomnography, the patient is often helped by nasal intermittent positive-pressure ventilation during the night. As the condition progresses it is often necessary to convert to intermittent positive-pressure ventilation via a permanent tracheostomy. In some cases a cuirass respirator is found to be more suitable (see Chapter 58).

All patients with chronic ventilatory failure reach a stage at which their quality of life seems not to justify initiation or continuation of ventilation, a matter that should be as fully discussed as practicable with patient and relatives. When the decision is made, some expertise in the use of drugs and ventilators is required to ensure that the gradual withdrawal of support does not cause undue distress.

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# ABNORMALITIES AND DISEASES OF THE DIAPHRAGM

ANTHONY SEATON

The diaphragm is the most important muscle of respiration. It is rarely affected by intrinsic disease but because of its complex embryological development is subject to a number of congenital anomalies. Primary disorders of the diaphragm may present with symptoms suggestive of intrathoracic disease. Conversely, radiographic abnormalities of the diaphragm may indicate disease in the chest or abdomen.

## Embryology

The arched musculotendinous division between the thorax and the abdomen has its origin in vertebral, costal and spinal attachments from which muscular fibres curve upwards and inwards from the periphery to be inserted into the fibrous sheet called the central tendon [1]. The diaphragm derives developmentally from four sources [2].

1 The *septum transversum* is first seen at the third week of development as a mass of mesoderm situated cranial to the pericardial cavity. This structure contributes to the more ventral portions, i.e. the sternal and costal parts.

2 The second source is derived from paired dorsolateral portions, the *pleuroperitoneal membranes*, which fuse with the dorsal mesentery of the oesophagus and the dorsal portion of the septum transversum to complete the partition between the thoracic and abdominal cavities and form the primitive diaphragm at about the seventh week of development.

3 The median portion of the diaphragm is derived from an irregular medial dorsal portion of primary oesophageal mesentery that fuses with the septum transversum and pleuroperitoneal membranes. The curves of the diaphragm develop from the growth of muscle fibres into the dorsal mesentery of the oesophagus.

4 During weeks 9–12 the fourth source is contributed by marginal ingrowths of the body wall. These contributions from the thoracic myotomes also contain nerve fibres of the lower six or seven intercostal nerves that distribute sensory fibres to the peripheral parts of the diaphragm.

During the development of the diaphragm, striking positional changes of its components are seen. At the third or fourth week the septum transversum lies opposite the upper cranial somites. During the fifth week nerve fibres from the third, fourth and fifth cervical segments of the spinal cord grow into the septum transversum via the pleuropericardial membranes and together constitute the phrenic nerves, which in adult life lie within the fibrous pericardium.

A more rapid growth of the dorsal embryo results in an apparent migration of the diaphragm, which by the sixth week is at the level of the thoracic somites. The phrenic nerves are also lengthened. By the beginning of the eighth week, the diaphragm is attached to the dorsal body wall at the level of the first lumbar vertebra, giving the diaphragm the domed contour characteristic of its adult form. In the adult a threefold variation in diaphragm muscle mass has been recorded, being related to an individual's overall muscularity [3].

## Radiological appearances

The right hemidiaphragm is usually higher than the left, the average level of the right dome being at the anterior end of the sixth rib [4]. The left hemidiaphragm lies half an interspace lower than the right but appreciable unilateral elevation is not uncommon [5]. In one study a raised diaphragm was seen on the left in 9% and on the right in 2% of 500 normal chest films [6]. In half the individuals with a raised diaphragm on the left the two domes were at the same level, while in the other half the left was actually higher than the right.

The normally higher position of the right hemidiaphragm is usually and illogically attributed to the bulk of the underlying liver, but the truth is that the left hemidiaphragm is depressed by the heart. In partial situs inversus with liver and heart on the same side, the diaphragm is lower on that side [7]. Inversion of the diaphragm may occur on both the right and left sides, most commonly as the result of a massive pleural effusion or a tension pneu-

mothorax. Difficult to demonstrate on a plain chest radiograph, it is readily detected by ultrasound examination [8].

Unequal excursion of the two hemidiaphragms is normal [5]. In one series the hemidiaphragms moved asynchronously in 77%, although the difference in excursion was usually less than 1 cm [9]. The excursion in this group of normal subjects ranged from 3 to 6 cm in 75%, with 23% showing excursion of less than 3 cm and 2% more than 6 cm. Unilateral paradox on sniffing has been seen in up to 6% of normal subjects and is more common on the right [10].

## Function

In normal quiet breathing the diaphragm is responsible for 75% of inspiration and the intercostal muscles for 25%. Contraction of the diaphragm leads to its descent, with a resultant rise in intra-abdominal pressure and movement of the abdominal wall outwards [11,12]. A secondary effect of diaphragmatic contraction is to elevate and push the lower ribs outwards [13]. This secondary action is a function of the costal parts of the diaphragm, for when the costal parts only are stimulated the diameter of the lower rib cage increases [14,15]. During severe hyperinflation, as seen in chronic bronchitis and emphysema, contraction of the diaphragm produces paradoxical inward movement of the lower rib cage or Hoover's sign [15].

Diaphragmatic function may be assessed clinically by checking for appropriate thoracic and abdominal wall movements during inspiration and by performing tidal percussion, although one study found poor correlation between chest radiographic and clinical measures of diaphragmatic movement and wide interobserver variation [16]. Fluoroscopy allows diaphragmatic movement to be examined and is the conventional method of screening for diaphragmatic paralysis in patients with bronchogenic carcinoma. With paralysis of the diaphragm, the affected side descends poorly on inspiration and should move paradoxically upwards during a sniff. However, contraction of abdominal muscles may confound the findings, allowing apparently normal movement of a paralysed diaphragm [13].

Phrenic nerve stimulation, with recording of the diaphragmatic action potential using either oesophageal electrodes or surface electrodes over the lateral chest wall, allows the measurement of phrenic nerve conduction time. Unfortunately, the amplitude of the action potential is not an absolute index of diaphragmatic function. The most sensitive index of function is the measurement of transdiaphragmatic pressure ( $P_{di}$ ) during a quiet and a maximal inspiration. Pressures are recorded from balloons in the oesophagus and the stomach; in normal subjects  $P_{di}$  increases by 5–8 cmH<sub>2</sub>O in a quiet inspiration and by more than 25 cmH<sub>2</sub>O during a maximal inspiration. In bilateral

diaphragmatic paralysis no change in pressure occurs [13]. Even this index of diaphragmatic function has been criticized because of the wide range of normal values for maximum  $P_{di}$  (18–137 cmH<sub>2</sub>O) occasioned by interindividual variation in utilization of accessory muscles [17]. It has been suggested that measurement of  $P_{di}$  during a maximum sniff is of more value in detecting diaphragmatic weakness or paralysis (normal value 112–204 cmH<sub>2</sub>O) [18].

## Disorders of function

### Diaphragmatic fatigue

The diaphragm shares with the myocardium continuing regular activity of varying degree throughout life. Not surprisingly the muscle fibres comprising the diaphragm show a predominance of fibre types relatively resistant to fatigue; 50% are type I or slow-twitch fibres, with a high oxidative and low glycolytic capacity, and 20% type IIA or fast-twitch fibres, with both high oxidative and glycolytic capacities. The remaining 30% are type IIB or fast-twitch fibres, with low oxidative capacity and high glycolytic activity, and are relatively susceptible to fatigue [19–22].

At its customary resting length the human diaphragm only becomes fatigued when the force of contraction during inspiration exceeds 40% of the force that it can develop in a maximal static effort. During tidal breathing it operates at only about 10% of maximal [23]. The more the respiratory force exceeds 40%, the sooner the onset of fatigue [19]. Development of fatigue can be demonstrated by stimulating the phrenic nerve and constructing  $P_{di}$ -phrenic nerve stimulation frequency curves [24,25]. Fatigue produced in normal humans, for example by breathing through an inspiratory resistance for as long as possible, results in a reduction of force developed at all frequencies with a preferential reduction at low frequencies [26]. This 'low-frequency fatigue' is believed to represent a failure of excitation-contraction coupling in the muscle [13]. It has been shown to occur in normal individuals as a consequence of exhausting exercise and the exertions of the later stages of labour [27,28].

An alternative technique for detecting diaphragmatic fatigue is to record the power spectrum of the diaphragmatic electromyogram (EMG) using oesophageal or surface electrodes [13,26]. A decrease in the ratio of high-frequency to low-frequency power in the EMG indicates fatigue. Using this technique, fatigue has been detected in the normal newborn diaphragm when rib cage distortion is present [29]. The technique has also been used to detect fatigue early in neonates being weaned from a ventilator before the onset of clinical signs or carbon dioxide retention [30]. The predisposition of the neonate to diaphragmatic fatigue is presumably a reflection of the relative

absence of type I muscle fibres in the infant diaphragm; premature infants have only 10% type I fibres and the full-term newborn only 25%. The adult proportion of 50% type I fibres is only achieved at 8 months [31]. In adults with chronic obstructive pulmonary disease, the force reserve of the diaphragm has been shown to be greatly reduced so that slight modifications of the pattern of breathing can bring the diaphragm above the fatigue threshold [32].

### *Clinical features*

Two physical signs of diaphragmatic dysfunction are recognized. Prominent rib cage movement in the supine position indicates recruitment of other respiratory muscles and is a feature of any disease or condition that leads to increase in the work of breathing. More importantly, indrawing of the anterior abdominal wall during inspiration (when not due to abdominal muscle contraction) is a significant indication of diaphragmatic fatigue or paralysis [33,34]. In patients being unsuccessfully weaned from ventilators, the sequence of events that culminates in respiratory acidosis has been described [20]. Initial EMG evidence of fatigue either precedes or accompanies an increase in respiratory rate. This is followed by alternation between abdominal and rib cage breathing (respiratory alternans) and then by a paradoxical inward motion of the abdomen during inspiration (abdominal paradox). Finally, minute ventilation and respiratory rate fall with a resultant increase in  $P_{aCO_2}$ .

### *Management*

The immediate management of diaphragmatic fatigue, which is probably present in all cases of life-threatening respiratory failure, involves ventilatory support with positive-pressure ventilation to allow recovery of the fatigued muscle while the precipitating factor is treated. In the longer term, in subjects predisposed to fatigue by virtue of associated disease such as chronic obstructive airways disease, quadriplegia and cystic fibrosis, ventilatory muscle training, which involves breathing against an inspiratory resistance for 30 min daily, increases both the strength and endurance of the diaphragm as well as protecting against fatigue [35–39]. Pharmacological intervention also seems possible since both aminophylline [40] and caffeine [41] have been shown to increase the contractility of the diaphragm and to increase the pressure the diaphragm develops at a constant frequency of phrenic nerve stimulation after fatigue [40].

Finally, in selected subjects, particularly quadriplegics with ventilatory failure, implanted receivers with electrodes stimulating the phrenic nerves have been used successfully in treatment. This procedure, which is restricted to a few specialist centres, involves placing a radio

receiver subcutaneously with electrodes leading to the phrenic nerve usually in the neck. An external battery-powered transmitter controls the receiver and can be used to modify respiratory rate and the depth of inspiration. Each phrenic nerve is paced alternately for 8 h in order to avoid diaphragmatic fatigue [42].

## **Diaphragmatic paralysis**

### **Unilateral paralysis**

#### *Aetiology*

The phrenic nerve is derived from the C3–C5 nerve roots and may be affected by compression, inflammation or injury anywhere in its course from cervical spine to diaphragm. The most common cause of unilateral diaphragmatic paralysis is involvement of the phrenic nerve by bronchogenic carcinoma. Such involvement by tumour above the pulmonary hilum excludes surgical treatment, although when the lesion is below the hilum resection of the tumour, nerve and pericardium may be attempted. The causes of unilateral diaphragmatic paralysis are shown in Table 46.1 [43].

Sometimes phrenic paralysis occurs without satisfactory explanation. In the days of mass miniature radiography, it was not uncommon to recall patients in whom the film had shown an elevated hemidiaphragm and who were shown to have paralysis on screening. Such patients often gave a history of a transient febrile illness, often associated with chest or shoulder pain; no other cause was found and led to the problem being attributed to a 'viral infection'. The recent evidence that idiopathic facial nerve palsy is often caused by herpes simplex virus 1 [44] suggests that this may not have been wide of the mark. Indeed, cervical herpes zoster is a known cause of diaphragmatic paralysis [45]. This appears to be analogous to the so-called neuralgic amyotrophy that affects the deltoid muscle and is attributed to inflammation of the C5–C7 nerve roots; diaphragmatic paralysis, both unilateral and bilateral, has been found in this condition [46].

The 'paralysis' seen in association with supraphrenic or subphrenic infection may be more apparent than real. In such subjects the diaphragm is often elevated and immobile but recovery occurs as the infection clears. The same is true of the elevation of the diaphragm associated with pulmonary embolism.

#### *Clinical features*

Paralysis of a hemidiaphragm alone does not usually give rise to symptoms, and where symptoms are present they usually reflect the causative disease. Altered diaphragmatic movement may be detected by careful

**Table 46.1** Causes of unilateral diaphragmatic paralysis.

---

<i>Surgical</i>
Thoracic and cervical operations
Cardiac cooling during open heart surgery [47]
<i>Tumour</i>
Bronchogenic
Metastatic
<i>Neurological</i>
Cervical myelitis, neuropathy
Encephalitis
Herpes zoster [46]
Poliomyelitis
Tetanus antitoxin [48]
Diphtheria
<i>Trauma</i>
Thoracic cage
Cervical spine
Brachial plexus block
Birth injury
Subclavian vein puncture [49]
<i>Mechanical</i>
Retrosternal goitre
Aortic aneurysm
Progressive massive fibrosis (silicosis, coalworkers' pneumoconiosis)
<i>Infection</i>
Tuberculosis [50]
Pneumonia
? Empyema
? Subphrenic or hepatic abscess
<i>Miscellaneous</i>
Syphilis
Pulmonary infarction
Congenital anomalies of lung and thorax
Pott's disease
<i>Idiopathic</i>

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percussion, although this sign requires practice to elicit and is associated with substantial interobserver variation [16].

### Radiology

The affected diaphragm may or may not be elevated and shows paradoxical movement on respiration. This is confirmed by fluoroscopy and may be accentuated by asking the patient to sniff, when the affected hemidiaphragm rises while the unaffected hemidiaphragm moves downwards. As discussed above, the diagnosis may not always be clear-cut even on screening, and ultrasonography has proved a useful means of confirming the radiological suspicions [51].

### Functional effects

Unilateral paralysis of the diaphragm reduces vital capacity by 20–25% in the upright posture, with a further 10–20% reduction in the supine position [52–54].  $P_{aO_2}$  may fall in the supine position due to an increase in closing volume, and compression of basal lung segments on the affected side has been demonstrated bronchographically [52,53]. A 20% reduction in ventilation and perfusion to the lung on the affected side has also been shown [52,55].

### Management

In the large majority of cases, no treatment is necessary as the condition is symptomless. Occasionally, however, the development of unilateral paralysis in someone with severe pulmonary impairment precipitates ventilatory failure. This has been described particularly after lung or cardiac surgery [56–58]. In such circumstances recovery may take place with time, such as when the paralysis occurred as a consequence of phrenic stretching or hypothermia, and ventilatory support may be all that is necessary. If recovery does not occur, diaphragmatic plication has proved to be an effective method of improving lung mechanics and the patient's condition [59,60].

### Bilateral paralysis

#### Aetiology

Paralysis or weakness of both hemidiaphragms is uncommon and may be idiopathic in origin [61], follow viral infections [62] or blunt trauma to the chest [63], or occur in association with rare neuromuscular diseases as well as the more common quadriplegia following trauma [46,64–70] (Table 46.2). A similar condition may occur in systemic lupus erythematosus [71].

**Table 46.2** Causes of bilateral diaphragmatic paralysis.

---

<i>Anterior horn cell disease</i>
Poliomyelitis
Kugelberg–Wielander disease
Motoneurone disease
Multiple sclerosis
<i>Peripheral nerve disease</i>
Guillain–Barré syndrome
Charcot–Marie–Tooth disease
Idiopathic
<i>Muscle disease</i>
Acid maltase deficiency
Limb girdle dystrophy
Type II atrophy
Dystrophia myotonica
Neuralgic amyotrophy

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### Clinical features

Dyspnoea is a usual feature of bilateral diaphragmatic paralysis as is paradoxical inward movement of the abdominal wall during inspiration, both particularly marked when the subject is in the supine position [13]. Respiratory rate is usually increased with a reduction in tidal volume. Alveolar hypoventilation may occur during sleep [63,72] with resultant carbon dioxide retention leading to disturbed sleep, morning headaches and daytime fatigue with hypersomnolence [66]. There may be associated sleep apnoea [61].

### Radiology

Both diaphragms may be elevated on the chest film, move sluggishly or paradoxically with inspiration, and paradoxical movement should be (but is not always) seen during sniffing [65]. That fluoroscopy can be misleading is due to contraction of abdominal muscles during expiration, which pushes the diaphragm up passively and allows it to descend passively and apparently normally during inspiration [13].

### Functional changes

In complete bilateral diaphragmatic paralysis, *P<sub>di</sub>* does not change during tidal breathing or a maximum inspiration, while reduced changes in pressure are seen in patients with bilateral weakness [13,67,68,72]. Vital capacity is reduced in the upright position and further decreased in the supine position [63,73]. Similarly, *P<sub>aO<sub>2</sub></sub>* is reduced and falls further on lying down. Studies have shown that the ventilation–perfusion ratio is the same in both lungs in a normal subject occupying the lateral decubitus position, whereas it is substantially reduced in the dependent lung of patients with bilateral diaphragmatic paralysis, a phenomenon that must contribute to the postural hypoxia via shunting of blood [74]. Measurement of pressure–volume relationships in diaphragmatic paralysis has disclosed decreases in both maximal transpulmonary pressure and static compliance [75]. The reduced compliance, tentatively ascribed to microatelectasis, may explain the rapid respiratory rate in these patients.

### Management

Although spontaneous improvement in diaphragm function has been seen [68], permanent paralysis is the rule. Some patients have benefited from the use of a cuirass respirator at night to manage the associated respiratory failure [65], and it would seem reasonable to apply the principles of management, including the use of nasal continuous positive airway pressure, described in Chapter 58.

The use of diaphragmatic pacing has already been mentioned [42].

## Involuntary movements of the diaphragm

### Hiccup

Sudden inspiratory spasm of the diaphragm with associated closure of the glottis (hiccup, or singultus for the obscurantist) is a familiar and harmless symptom in the normal subject, usually caused by gastric distension. EMG recordings have demonstrated synchronous electrical discharge in both the diaphragm and external (inspiratory) intercostal muscles [76]. The usual cause is a reflex transmitted by vagal efferents, via vagal and respiratory nuclei in the medulla, and phrenic nerves to the diaphragm and by somatic nerves to other respiratory muscles. Occasionally the symptom becomes persistent and distressing to the patient, especially in uraemia and neurological disease [77]. The best-recognized causes of persistent hiccup are shown in Table 46.3 and reflect the reflex pathway. It has been suggested that some apparently idiopathic cases may be a vagal analogue of trigeminal neuralgia and hemifacial spasm, where the neural hyperactivity may be triggered by contact between nerve and blood vessel [78].

### Treatment

Treatment depends on the cause and severity. Everyone is familiar with the various empirical homely remedies recommended for transient hiccup that act via vagal stimula-

**Table 46.3** Causes of hiccup.

<i>Local causes, stimulating vagal afferents</i>
Gastric distension or inflammation
Oesophageal reflux, achalasia
Pericarditis
Pleural effusion
Mediastinal disease
Chest and upper abdominal surgery
Diaphragmatic irritation
Subphrenic abscess
<i>Metabolic causes</i>
Anaesthesia
Uraemia
Addison's disease
Hypocalcaemia
<i>Central causes, affecting brainstem</i>
Medullary infarction, tumour
Multiple sclerosis
Viral encephalitis, including HIV
Meningitis

HIV, human immunodeficiency virus.



tion. More persistent episodes may respond to stimulation of the pharynx with a catheter introduced through the nose [79]. This intervention is believed to initiate afferent vagal impulses that inhibit the hiccup reflex. Prolonged or distressing hiccup requires investigation and removal of the cause. If this is not possible, it may respond to intravenous injection of 50mg chlorpromazine [80]. Other drugs used have included haloperidol, metoclopramide, baclofen, antiepileptics and antidepressants [77,81]. In exceptional cases, phrenic nerve block by local anaesthetic or phrenic nerve crush has been used but is not recommended since it impairs lung function and is usually only partially successful. In one rather dramatic instance, neurosurgical separation of the vagus from contact with the posterior inferior cerebellar artery appears to have relieved the condition [78].

### **Tonic spasm of the diaphragm**

Tonic spasm may complicate rabies, tetanus and strychnine poisoning and less commonly pregnancy toxæmia, encephalitis and epilepsy. It results in upper abdominal pain and dyspnoea, and may necessitate assisted ventilation.

### **Diaphragmatic tic or flutter**

Diaphragmatic tic or respiratory myoclonus was first diagnosed and described by van Leeuwenhoek, the inventor of the microscope, who himself suffered from the condition [82]. It can occur at any age and in most cases the aetiology is unknown, although encephalitis and assorted causes of phrenic nerve irritation have been implicated in some [83]. The diaphragm or one hemidiaphragm contracts irregularly, with an average frequency of 150/min (range 35–480); the EMG shows bursts of electrical activity during inspiration and expiration [84,85].

#### *Clinical features*

Episodes may be precipitated by emotion, eating, exercise or assorted respiratory manoeuvres, and may last only a few seconds or persist for months. Attacks are usually associated with upper abdominal or lower chest pain that may mimic angina. Respiratory distress may occur and stridor and apneustic respiration (a prolonged breath-hold in inspiration) have been reported [86,87]. Other symptoms include belching, hiccups and retching. In some subjects epigastric pulsations may be seen, and if the stomach is full a rhythmic splashing sound may be heard [88]. Fluoroscopy demonstrates the abnormal movement of the diaphragm, which may also distort an ECG tracing [85]. The diagnosis may be confirmed if necessary by diaphragmatic EMG [89].

#### *Treatment*

Treatment with phenytoin 400mg daily or carbamazepine has been successful in some cases [85,89], but others have required phrenic paralysis by crush or injection of local anaesthetic [86,88].

## **Infection**

### **Subphrenic abscess**

#### *Clinical features*

Subphrenic abscess may occur spontaneously due to perforation of a viscus, amoebic liver abscess or pancreatitis, or may follow abdominal surgery [90–94]. Such abscesses may occur on either or both sides. Features include local costal or subcostal pain and tenderness, unexplained fever, tachycardia and leucocytosis. If antibiotics have been taken, the course may be more chronic with vague pains, chronic ill-health, unexplained fever and anaemia [95]. Its importance for the chest physician lies in the associated changes that may be seen on a chest film or on fluoroscopy.

#### *Radiology*

The most common finding is an elevated hemidiaphragm on the affected side with diminished movement of the diaphragm, although it should be noted that a reduction in diaphragmatic activity is a normal finding after upper abdominal surgery [96]. Other frequent findings include blunting of the costophrenic angle, pleural effusion and pulmonary infiltrates or atelectasis. Air–fluid levels may be seen in the abscess cavity. Fixation of the diaphragm and displacement of intra-abdominal viscera may be seen. Radiologically, it may be difficult to differentiate between a subphrenic abscess and a subpulmonary collection of fluid. Multiplanar ultrasonography, especially on the right side, and CT are useful means of making the diagnosis [94,97–99]. Outlining of a hemidiaphragm by contrast medium during pulmonary angiography has been reported in subdiaphragmatic inflammation [100], although it is not recommended that such an investigation be routinely employed! Scanning techniques using gallium–technetium subtraction or following injection of gallium-labelled leucocytes have also proved useful in the localization of subphrenic abscesses [101,102].

#### *Treatment*

The management of subphrenic abscess is by surgical drainage and appropriate antibiotic therapy [103]. Percutaneous drainage under ultrasonic or fluoroscopic guid-

ance using wide-bore catheters has been used with some success by those with special expertise [104].

**Trichiniasis**

One of the few primary diseases of the diaphragm is trichiniasis. When ingested in undercooked pork, or much less commonly bear meat, the larvae of the nematode *Trichinella spiralis* may be freed in the intestines where mating of male and female produces new larvae that can penetrate the intestinal wall and enter the bloodstream. Their subsequent fate is variable: some settle in organs where they die out; others reside in the muscles, including the diaphragm, where they may remain alive for years, subsequently becoming encysted.

*Clinical features*

The phases of intestinal invasion and encystment are usually symptomless but may be accompanied by diarrhoea and vomiting. The main symptoms usually occur 1 or 2 weeks after ingestion. These include fever, oedema that may affect the face only or be more widespread, muscle aches, skin rashes, chest pain (usually attributed to involvement of the intercostal muscles and diaphragm), hiccup, cough and haemoptysis (due probably to parasites in the lung). Respiratory failure secondary to weakness of the diaphragm and intercostal muscles has been described [105,106].

*Investigations*

Eosinophilia is a fairly constant and early feature and the parasite may be recovered from the blood in the early stages. Other diagnostic procedures in a suspected case are muscle biopsy (after the third week) and skin and precipitin tests with *Trichinella* antigen. In long-standing cases the calcified larvae are visible in muscles on the chest radiograph.

*Treatment*

The condition is usually self-limiting and no treatment is required. In severe cases treatment with corticosteroids and tiabendazole (thiabendazole) 25 mg/kg daily may be required. Prevention is the most important aspect of management of trichiniasis and the disease can be eradicated by making it known that the longer pork is cooked, the safer it is.

**Tumours**

Primary tumours of the diaphragm are exceedingly rare, and secondary tumours usually only occur as a direct extension from lung, liver or pleura.

**Metastatic tumours**

Metastatic tumours of the diaphragm are more common than primary tumours. Few are blood-borne, the majority occurring by seeding across serous membranes, infiltration from lung through pleura or direct spread, for example from the stomach [107]. The most common extrapleural primary sources are breast, ovary and stomach, while local involvement by bronchogenic carcinoma and mesothelioma is also seen. Mesothelioma is a tumour that is increasing in frequency in the UK, and it commonly involves the diaphragmatic pleura (see Chapter 43).

**Benign tumours**

Benign primary tumours occur more frequently than malignant ones [108]. The most common is the lipoma, which presents radiologically as a smooth rounded mass with a lower border continuous with the diaphragm [109]. The mass, which may appear less dense than would be expected on the basis of its size, usually arises from the posterolateral portion of the hemidiaphragm, more commonly on the left.

Other benign tumours include fibroma, angiofibroma, neurofibroma, neurilemmomas and haemangiopericytomas [110–113]. Angiofibromas may be calcified [111]. Mesothelial cysts may arise in relation to the pleuroperitoneal canal [112].

**Malignant tumours**

Most malignant tumours are of mesenchymal origin and the range of histological types is shown in Table 46.4 [111–113]; fibrosarcoma is the most common.

*Clinical presentation*

Malignant diaphragmatic tumours may present with severe lower chest or hypochondrial pain that radiates

**Table 46.4** Some malignant tumours of the diaphragm.

Fibrosarcoma
Fibromyosarcoma
Myosarcoma
Fibroangioendothelioma
Undifferentiated sarcoma
Neurofibrosarcoma
Rhabdomyosarcoma
Sarcoma
Mixed-cell sarcoma
Haemangioendothelioma
Haemangiopericytoma
Leiomyosarcoma
Malignant synovioma

along intercostal nerves or to the shoulder [112,113]. The pain is usually exacerbated by respiration and may be associated with cough, dyspnoea or upper gastrointestinal symptoms. A haemorrhagic pleural effusion may be present. A bulging of the hypochondrium that moves with respiration may occur. A palpable mass is found in 10%. Hypertrophic pulmonary osteoarthropathy has been described in 10% of cases [112]. The tumour may metastasize or invade lung locally.

### Diagnosis

On radiography a mass is seen in the lower thorax that is difficult to separate from surrounding structures. On fluoroscopy the mass is seen to move with the diaphragm. Pneumoperitoneum and pneumothorax may be needed to confirm that the mass arises from the diaphragm. CT may be helpful in diagnosis and in particular may identify lipomas by their decreased radiodensity.

### Management

If possible, surgical excision is indicated, with local repair using fascia lata or prosthetic material [114].

## Disorders of structure

### Eventration of the diaphragm

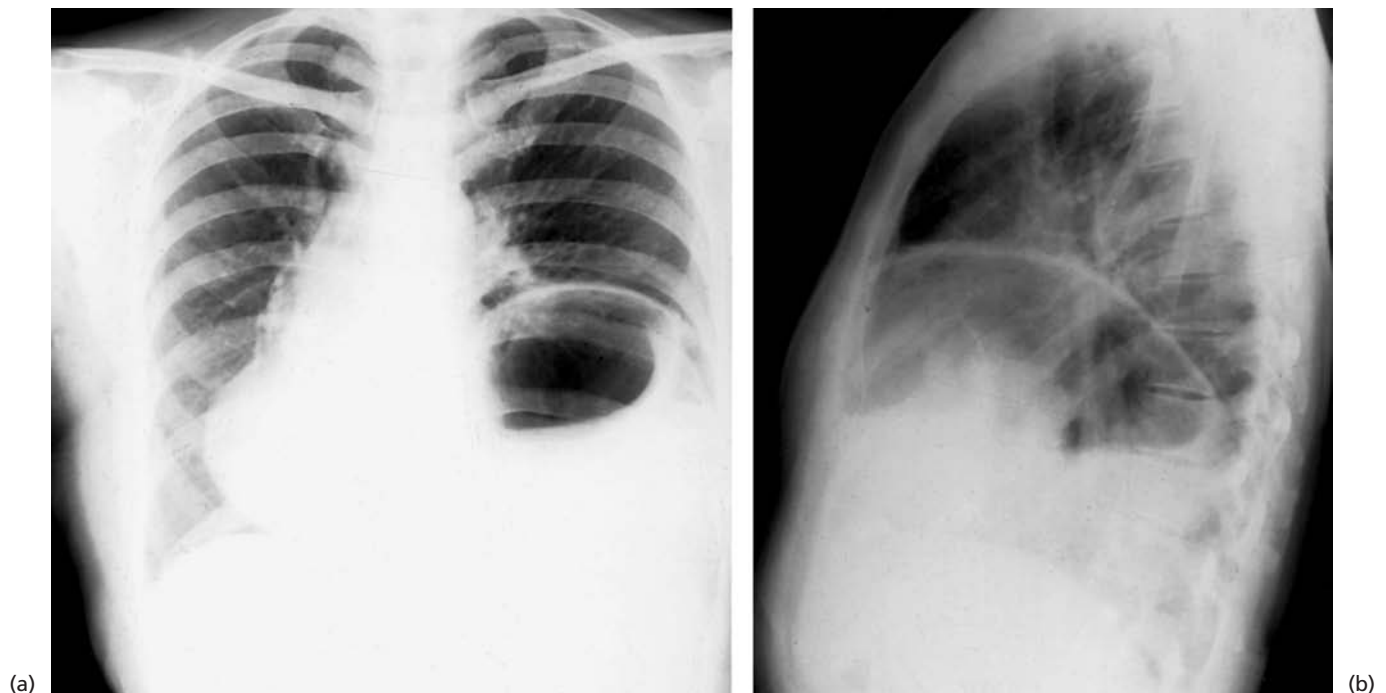
Eventration of the diaphragm is a condition in which all or part of the diaphragm is largely composed of fibrous tissue with only a few or no interspersed muscle fibres [115,116]. It is usually congenital but may be acquired.

#### Complete eventration

Complete eventration almost invariably occurs on the left side and is characterized by elevation of the left hemidiaphragm (Fig. 46.1), which on screening is virtually immobile and which moves paradoxically on sniffing. The condition is usually asymptomatic in adults but occasionally upper gastrointestinal symptoms such as undue flatulence may occur and operation, with plication of the diaphragm, has occasionally been undertaken because of the severity of dyspeptic symptoms [117]. In many patients barium examination shows the stomach to be inverted beneath the hemidiaphragm.

In infants, diaphragmatic eventration may occur on either side and may give rise to severe respiratory symptoms such as cough, dyspnoea and wheeze. Recurrent bronchopneumonia with associated dyspnoea and cyanosis may be seen. Anorexia and vomiting are less common. On examination there may be bulging of the affected hemithorax and a scaphoid abdomen. Fluoroscopy may show a 'dicrotic-like' pattern of diaphragmatic movement, with the lax portion of diaphragm

**Fig. 46.1** Posteroanterior (a) and lateral (b) chest films showing complete eventration of the left hemidiaphragm.



moving initially in a paradoxical manner followed by normal contraction of the periphery. Treatment by diaphragmatic plication usually gives excellent clinical and radiographic results [118,119]. However, a proportion of these patients have other congenital anomalies, including neurological and bowel disorders, that may influence their clinical outcome [120].

### Partial eventration

Partial eventration of the diaphragm occurs virtually exclusively on the right side. It is detected as an antero-medial bulge of the diaphragm that moves paradoxically on respiration [121] (Fig. 46.2). There is usually a corresponding deformity of the liver or 'superior accessory lobe' that can be demonstrated by pneumoperitoneum, liver scan or ultrasound examination [122,123]. Ultrasound is particularly useful in differentiating eventration from diaphragmatic hernias and pleuropericardial cysts, both of which it may closely resemble. Liver inversion with a suprahepatic gallbladder has been reported in association with partial eventration [124].

### Duplication of the diaphragm

An accessory diaphragm is a rare abnormality usually found in the oblique fissure on the right where it separates

all or part of the lower lobe from the rest of the lung [125–127]. It may be fibrous or muscular and contains a defect through which the normal bronchovascular supply passes to the lower lobe. Radiologically, thickening of the oblique fissure with elevation of the right hemidiaphragm may be apparent. It may be associated with neonatal respiratory distress; where the accessory diaphragm is muscular, bronchiectasis of the right lower lobe may result.

### Diaphragmatic hernias

The common sites for herniation of viscera through the diaphragm are shown in Fig. 46.3.

#### Hiatus hernia

Herniation through the oesophageal hiatus is the most common type of diaphragmatic hernia. It is not considered in detail here but is mentioned because it may present on a chest film as a retrocardiac opacity containing a fluid level (Fig. 46.4). The uninitiated may mistakenly diagnose a lung abscess or cyst.

#### Bochdalek hernia

Bochdalek [128] first described the embryology and the congenital absence of the posterolateral part of the diaphragm in 1848. This is the most common site for congenital diaphragmatic hernia and an incidence of 0.8 per 1000 live births has been reported [129]. The foramen of

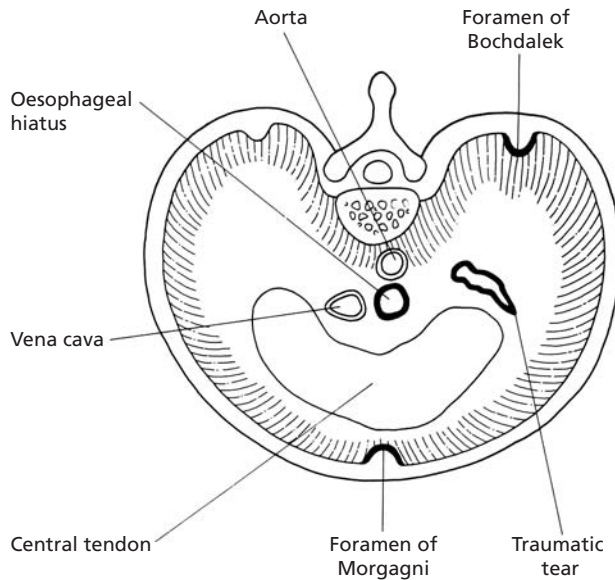
**Fig. 46.2** Posteroanterior (a) and lateral (b) chest films showing partial eventration of the right hemidiaphragm anteriorly.



(a)



(b)



**Fig. 46.3** Diaphragm viewed from above showing sites of possible herniation. Thick lines show most common sites.

Bochdalek is normally closed by the eighth week of fetal life. Failure of the pleuroperitoneal membrane to fuse with the septum transversum allows herniation of the abdominal contents into the hemithorax; 75% occur on the left and there may be other associated malformations, most commonly of the central nervous system [130]. A 13th pair of ribs is a reported association [131]. The lung on the side of hernia is usually hypoplastic with a reduction in the number of airway generations, although normal numbers of alveoli are found in the segments that are present [132,133]. The contralateral lung may also be hypoplastic and this heralds a poor prognosis [133,134]. In an extreme form, Bochdalek hernia merges with congenital diaphragmatic agenesis, a condition more readily diagnosed by antenatal ultrasound but which causes even more severe postnatal respiratory problems [135].

#### *Clinical presentation*

The majority present soon after birth with respiratory distress. A scaphoid abdomen is usually noted. Radiographically the diaphragm is not seen on the affected side and loops of intestine are found in the thorax, with displacement of the mediastinum. There is a relative absence of gas in the abdomen. Herniation on the right is less likely to be life-threatening, perhaps because the liver blocks the defect. While a right-sided hernia may occasionally present with respiratory distress, asymptomatic presentation with an intrathoracic mass of liver or bowel is more common [136,137].

Presentation in adulthood is uncommon. In a review of

50 cases in 1971, one-quarter were asymptomatic while the remainder presented with abdominal pain or vague remitting gastrointestinal symptoms with or without obstruction [138]. Delayed presentation following a previously normal chest film may occur [139].

#### *Management and prognosis*

Management of patients in respiratory distress is with ventilatory support and correction of acidosis, followed immediately by surgical repair, either by direct suture or with insertion of synthetic patches [140]. Contralateral pneumothorax may occur postoperatively due to the high inflation pressures required, and prophylactic pleural intubation has been employed by some [130,141].

Overall survival rates of 70–80% have been reported in neonates, with lower rates in those requiring operation within the first 24 h of life [142,143]. The majority of deaths are due to the presence of severely hypoplastic lungs that are incapable of sustaining life. In those with unilateral hypoplasia, compensatory emphysema may develop in the other lung [132].

#### *Morgagni hernia*

The foramen of Morgagni lies anteromedially and is bounded anteriorly by the sternum, medially by the sternal portion of the diaphragm and laterally by the costal portion of the diaphragm in the region of the attachment to the seventh costal cartilage. It is usually filled with loose connective tissue but omentum, colon, liver or other infradiaphragmatic structures, including gallbladder, may herniate through the foramen, more commonly on the right [144].

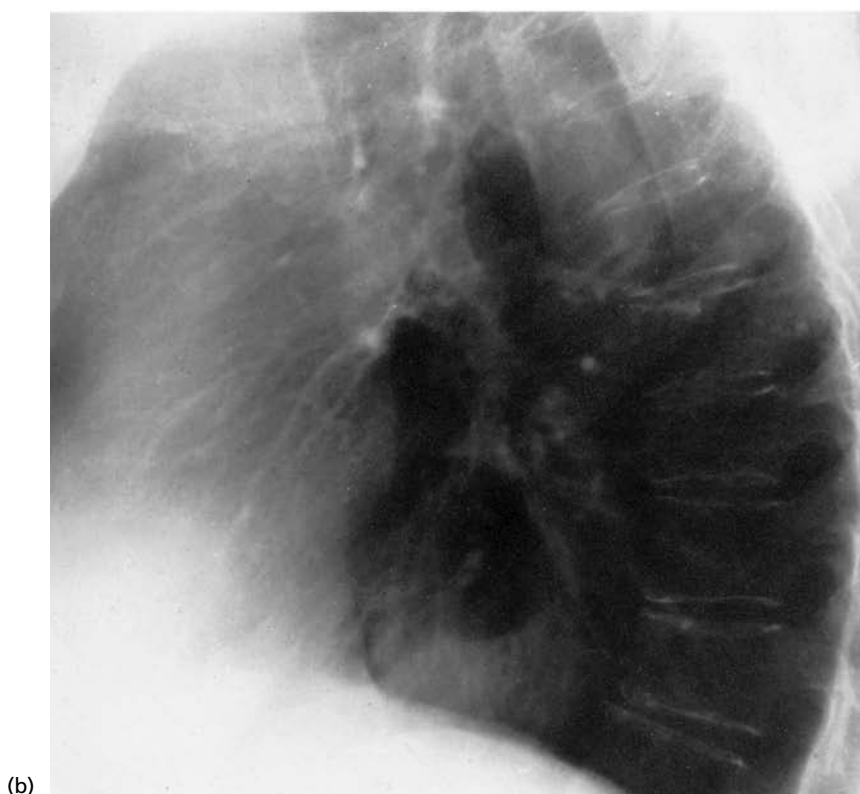
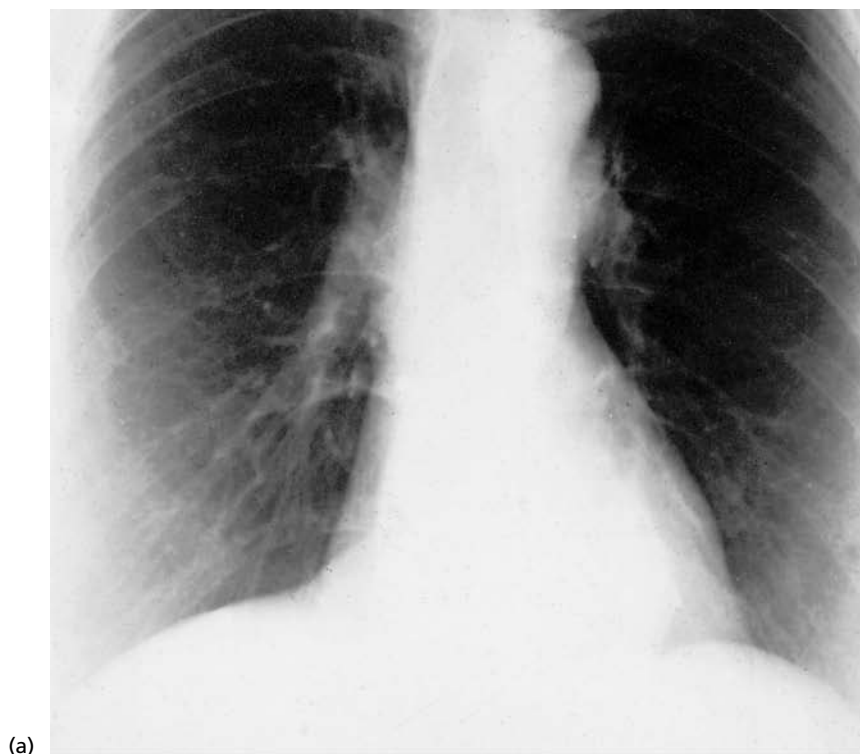
#### *Clinical presentation*

Presentation in childhood is rare, although Morgagni hernia has been reported as a cause of intermittent cyanotic attacks in an infant [145]. Where symptoms are present, feelings of pressure, tightness, fullness or pain in the right anterior chest occasionally with referral to the shoulder tip are admitted [146]. Strangulation of the bowel may occur.

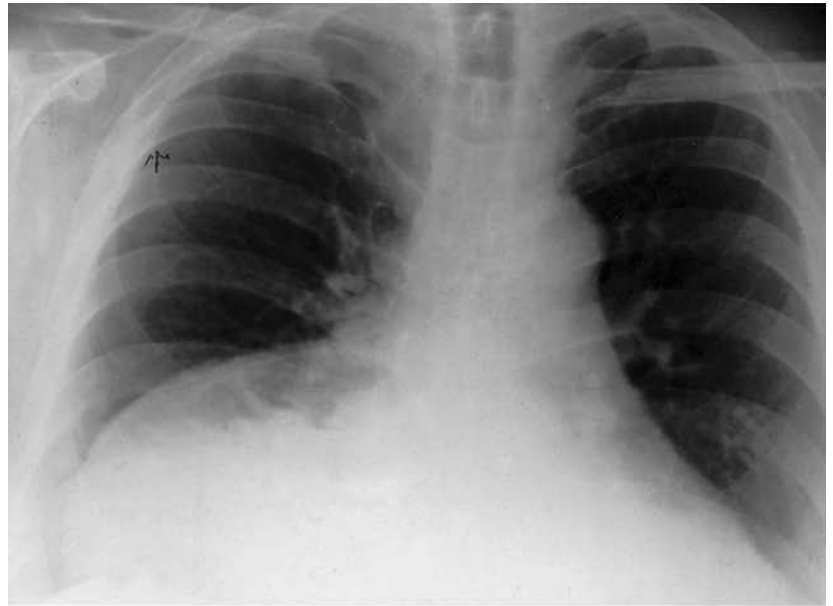
The chest film shows a rounded density in the cardiophrenic angle that may or may not contain gas (Fig. 46.5). Barium studies determine the presence of intestine, and in the case of an omental hernia the transverse colon is hitched up. Pneumoperitoneum may be needed to make a definitive diagnosis.

#### *Management*

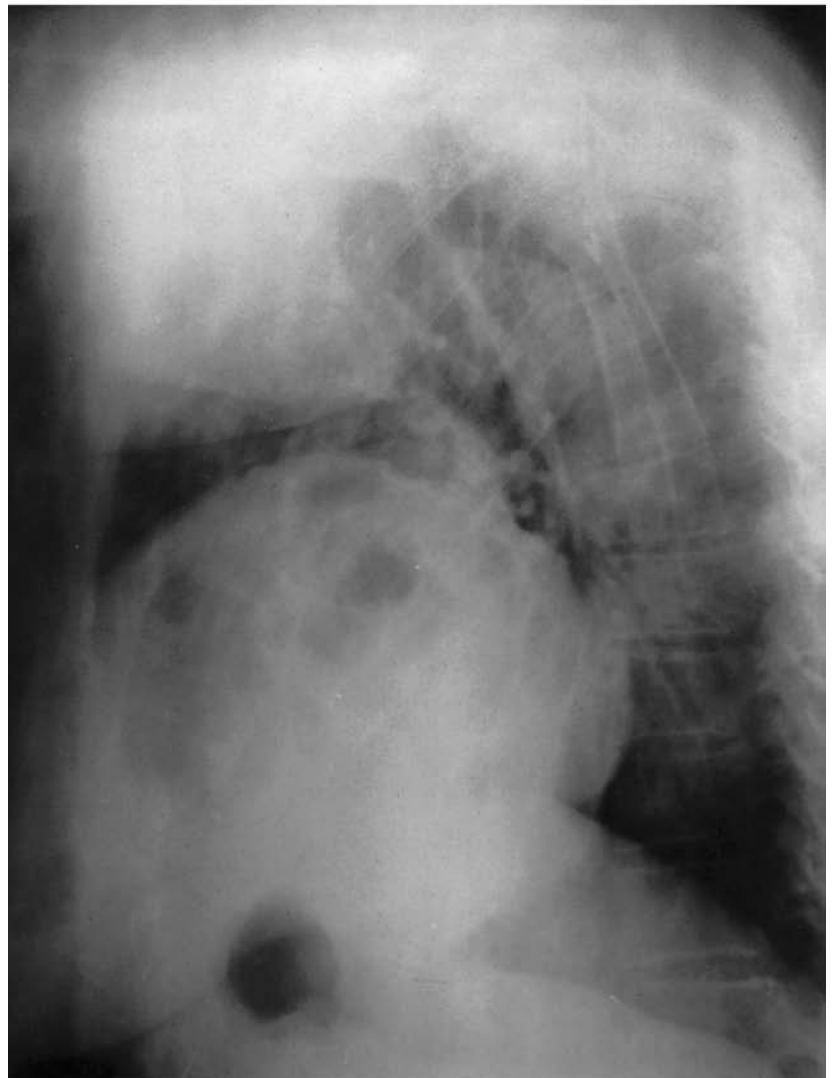
Surgical repair by suture after reduction of the hernia is normally sufficient.



**Fig. 46.4** (a) Solid lesion with indistinct air-fluid level behind heart. (b) Lateral view shows it to be a hiatus hernia.



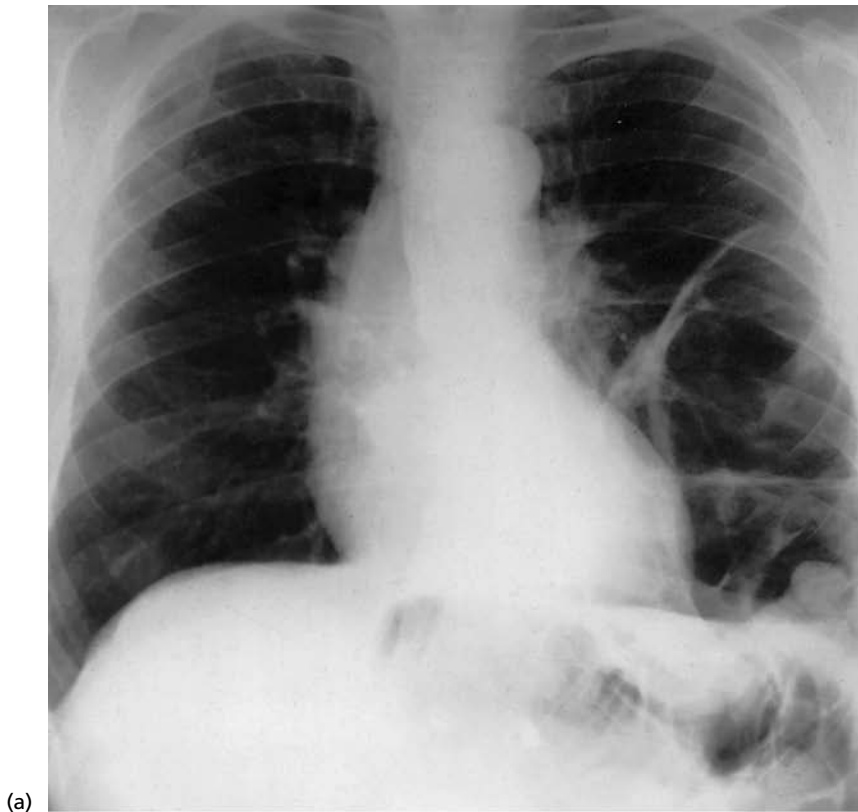
(a)



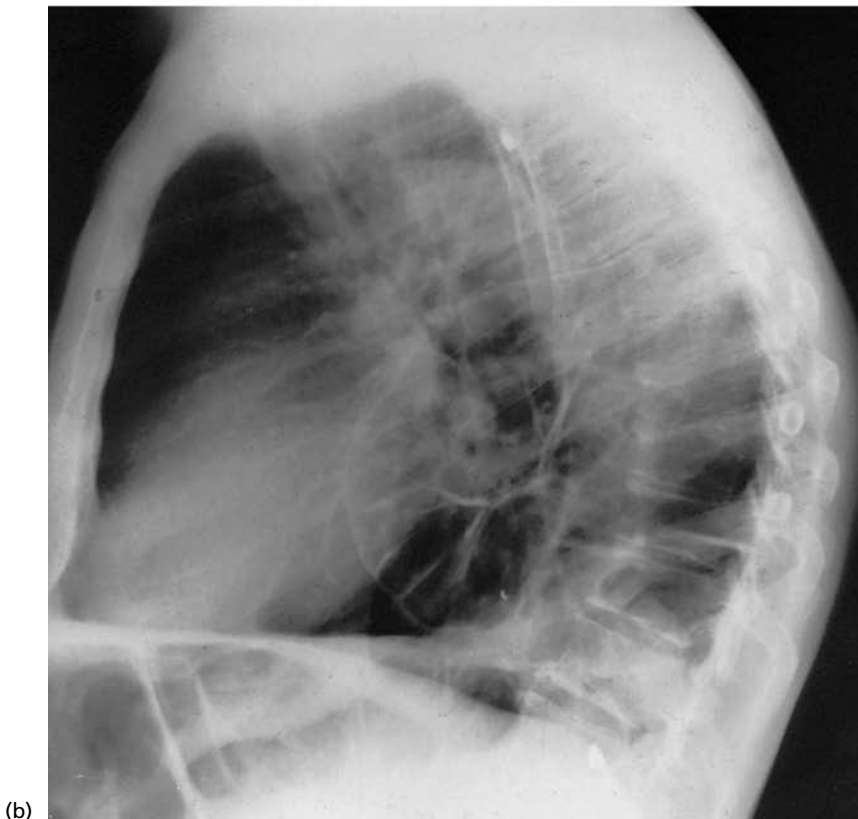
(b)

**Fig. 46.5** Posteroanterior (a) and lateral (b) chest films showing Morgagni hernia. This 68-year-old patient presented with increasing dyspnoea.





(a)



(b)

**Fig. 46.6** Traumatic hernia. Posteroanterior (a) and lateral (b) chest films taken in 1987 of a 67-year-old man who suffered a shrapnel wound in Normandy in 1942 that necessitated splenectomy. No diaphragmatic lesion was noted at that time and it was not until 1958 that colon was seen in the chest on a routine chest film. No action was taken and the patient remains asymptomatic. Presumably the diaphragm was lacerated or ruptured by shrapnel in 1942.

### Traumatic hernia

Traumatic diaphragmatic hernias are most commonly seen following blunt non-penetrating trauma to the chest in road traffic accidents or falls from a height. Many are detected at the time of the initial injury although a substantial number present later, even up to 15 years after the initial injury [147] (Fig. 46.6). It has been estimated that 90% of traumatic diaphragmatic hernias are overlooked at the time of injury [148].

Traumatic hernias represent only 5% of all diaphragmatic hernias, but 90% of all strangulated hernias result from trauma [149]; 90% of tears occur in the left leaf of the diaphragm, most commonly in the central and posterior portion. The most common hernial contents are omentum, stomach or colon, although any abdominal organ including kidney may be found. Rarely, herniation into the pericardium occurs [150–152].

### Clinical presentation

The most common complaints are of upper abdominal or lower chest pain with dyspnoea, which may be worse after eating [147,148]. Bowel sounds may be audible in the chest. If strangulation occurs, sudden and progressive severe lower chest or upper abdominal pain is experienced, with dyspnoea, vomiting or retching. Upper

abdominal guarding is found and progression to shock occurs [153,154]. On one occasion, the author has seen perforation of colon into the pleura following traumatic rupture of the diaphragm, causing pyopneumothorax. A rare complication of traumatic rupture is bronchopancratic fistula following acute pancreatitis; this can be diagnosed by finding high levels of amylase in the profuse frothy sputum [155].

### Radiology

Radiologically, the only evidence may be an elevated hemidiaphragm; at the other extreme multiple air–fluid levels may be present. Barium studies demonstrate obstruction or constriction of the stomach or colon as it passes through the tear [149]. With herniation of the liver on the right side, pneumoperitoneum (which results in pneumothorax) may be needed to confirm the diagnosis. CT may enable the discontinuity in the diaphragm to be seen [156].

### Management

Surgical repair may be achieved by the abdominal, thoracic or combined routes [148]. In view of the common concurrence of injury to abdominal viscera, the abdominal route is usually preferred [157].

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# SLEEP APNOEA/HYPOPNOEA SYNDROME

NEIL J. DOUGLAS

The sleep apnoea/hypopnoea syndrome is probably the most common medical disorder to be described in the second half of the twentieth century. It is not a new condition, merely a recently recognized one, as cases can be identified from manuscripts thousands of years old [1,2]. One of the earliest reports in the British medical literature was in 1829 when Wadd [3] reported a man who 'weighed 23 stone . . . and was withal so lethargic that he frequently fell asleep in company. He felt much inconvenienced and alarmed . . . and was sent to Edinburgh to consult Dr Gregory. He reduced himself to 15 stones . . . he is now well'. Joe, the fat boy in Dickens' *Posthumous Papers of the Pickwick Club* [4] made his appearance in 1837 and is testimony to Dickens' powers of observation, powers that exceeded those of most of his physician contemporaries or indeed those of physicians over the next century and a half. Joe was described as being obese, catastrophically sleepy, of ruddy complexion and having the dropsy (right heart failure).

The medical discovery of sleep apnoea occurred simultaneously in Germany and France in 1965 [5,6]. Both groups recorded physiological variables overnight and recognized the association between breathing pauses during sleep and daytime sleepiness, thus describing the condition that became known as the sleep apnoea syndrome [7]. Interest in the condition spread to North America and Australia and thereafter gradually to the rest of the world. With the identification of episodes of marked hypoventilation (hypopnoeas) during sleep not sufficiently severe to be true apnoeas but which have similar consequences [8], the condition has subsequently become known in many centres as the sleep apnoea/hypopnoea syndrome (SAHS).

## Epidemiology

Over the past few years, prevalence studies have been performed in different countries and continents using different techniques. However, their conclusions have been broadly similar, namely that SAHS occurs in 2–6% of

middle-aged men and 1–2% of middle-aged women [9–12].

Jennum and Sjol [12] randomly selected 2000 Danish citizens in the age group 30–60 years, of whom 1504 responded. Half the respondents were randomly selected for study of their breathing pattern overnight; 10.9% of the men and 6.3% of the women were found to have more than five apnoeas plus hypopnoeas per hour of sleep, while 1.9% of the men and 0.9% of the women had the same degree of abnormal breathing during sleep and also daytime sleepiness in socially unacceptable conditions.

Young and colleagues [9] studied a random sample of 602 employed men and women aged 30–60 years from Wisconsin using overnight polysomnography (the recording of sleep pattern from the EEG plus breathing and oxygenation patterns) in order to determine the frequency of irregular breathing during sleep; 9% of the women and 24% of the men had more than five apnoeas plus hypopnoeas per hour of sleep, whereas 2% of women and 4% of men had this degree of abnormal breathing during sleep plus daytime sleepiness. The methodology used in the study, including sampling techniques and the performance of overnight polysomnography, make this probably the most robust of the epidemiological studies, although the population studied may be more obese than is the norm in some countries.

Bearpark and colleagues [10] reported that 26% of 294 Australian men had more than five apnoeas plus hypopnoeas per hour in bed, with 3% having the same degree of breathing irregularity plus daytime sleepiness. Olson and colleagues [11], also from Australia, reported that at least 5.7% of middle-aged men and 1.2% of middle-aged women had more than 15 apnoeas plus hypopnoeas per hour of sleep but did not quote data for the coexistence of sleepiness.

With a prevalence of around 2–6% in the middle-aged, sleep apnoea thus has a similar frequency to symptomatic asthma or to diabetes in the same age group. This high prevalence, in conjunction with the significant associated morbidity, has led to the suggestion that it 'has an impact

on society that rivals that of smoking' [13]. Although the epidemiology is best documented in the middle-aged, sleep apnoea also occurs in children and the elderly but the precise prevalences are not yet clear.

### Mechanisms of upper airway narrowing

SAHS results from recurrent narrowing of the supraglottic airway during sleep. The patency of the pharynx depends upon a balance between transmural pressure and upper airway muscle activity (Fig. 47.1). During inspiration, the negative intraluminal pressure tends to narrow the upper airway and this is opposed by the action of upper airway dilating muscles. These muscles tense with each inspiration, thus resisting collapse of the upper airways and probably also stiffening the airway and so preventing vibration. The principal muscles involved are genioglossus, which tenses the tongue, and palatoglossus, which holds the soft palate in the downwards and forwards position thus resisting collapse of the nasopharynx (Fig. 47.2). Other palatal muscles, including palatopharyngeus, are also involved and there is some evidence to suggest that generalized tensing of palatal muscles, whatever their direction of action, results in palatal stiffening that resists upper airway collapse.

Muscle tone decreases throughout the body during sleep and the relaxation of the upper airway dilating muscles results in relative narrowing of the pharynx. In normal subjects, this narrowing results in increased airflow resistance that is of no major significance [14]. However, in about 50% of middle-aged men and 30% of middle-aged women, this upper airway narrowing is sufficient to cause marked turbulent flow with the associated vibration of snoring. In some, this tendency may progress to produce clinically significant upper airway narrowing or occlusion sufficient to cause sleep disruption and thus clinical sequelae.

The site of airway narrowing during sleep is usually at the retropalatal or retroglottal level [15,16]. In many patients, the occluded segment spans both the retropalatal and retroglottal segments and this probably explains why

surgical approaches designed to increase airway calibre in only one of these locations are frequently unsuccessful.

### Upper airway

Patients with SAHS tend to have narrower upper airways when awake than either normal subjects or simple snorers; however, there is substantial overlap between the groups [17–19]. There is considerable evidence indicating that anatomical factors contribute to this upper airway narrowing. Patients with SAHS have increased deposition of adipose tissue around their upper airway, particularly lateral to the pharynx [20,21]. This increased fat deposition is found in obese patients with SAHS compared with obese controls [20] and also in non-obese patients with SAHS compared with non-obese controls [21] (Fig. 47.3).

### Bony structure

Some patients with SAHS have abnormal facial bony structure [18,23,24]. The most common abnormalities are small maxillae and mandibles, with resulting retrognathia. The anteroposterior shortening of the face produces narrowing of the upper airway [18,24,25]. These abnormalities are more common in non-obese patients with SAHS [24]. The abnormalities may be familial, although it is not yet clear whether they are inherited or environmental [25].

### Physiological factors

It is difficult to test whether there are abnormalities of neuromuscular control in patients with sleep apnoea compared with normal subjects. Many studies have shown that the upper airway in patients with SAHS is more liable to collapse during both wakefulness and sleep [26–28], although this may be due to anatomical factors. Some studies [29], but not all [30], have indicated that there is

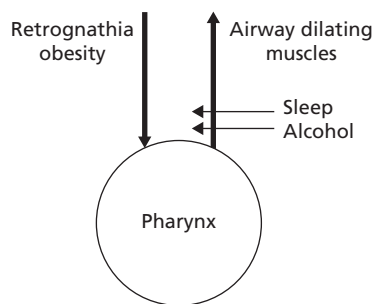


Fig. 47.1 Schematic diagram of upper airway physiology.

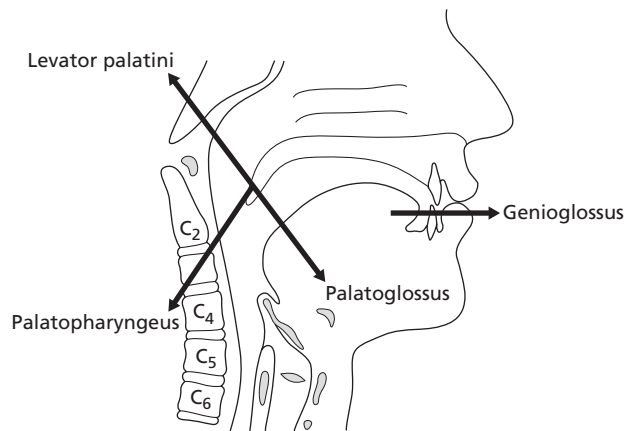
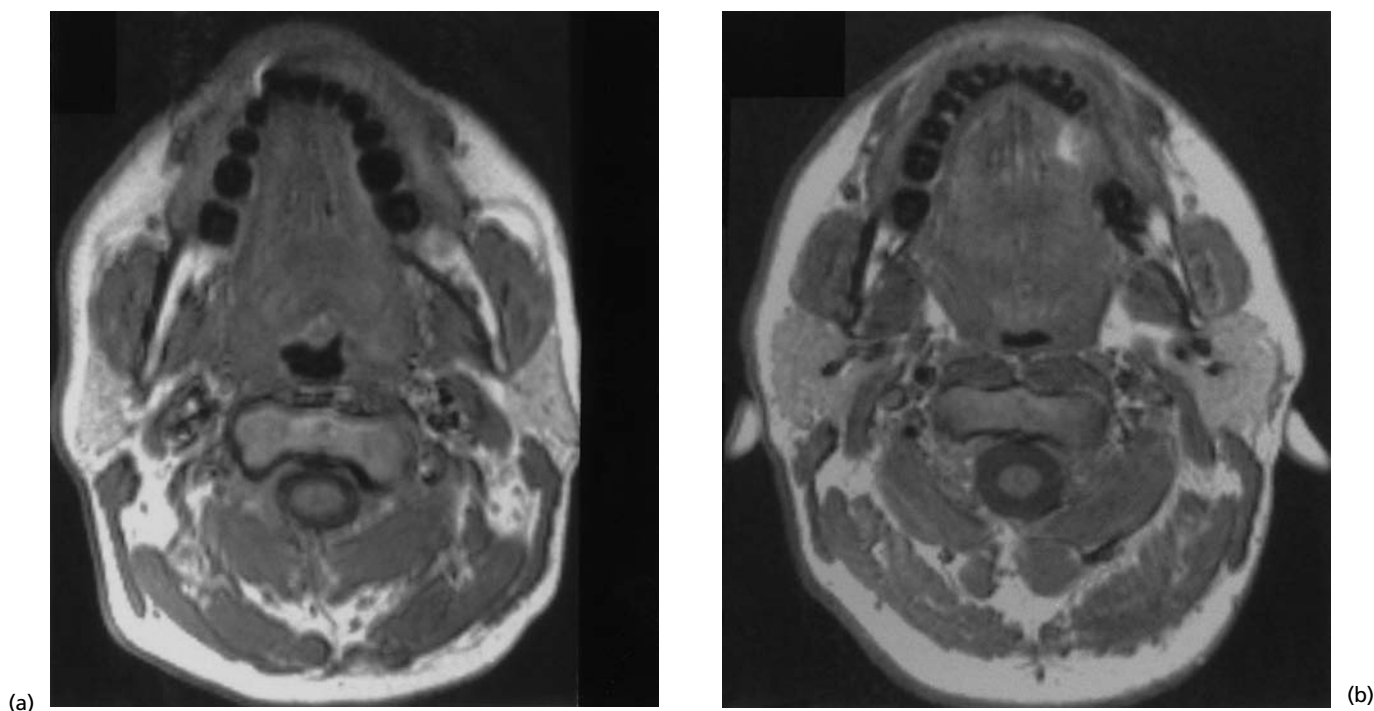


Fig. 47.2 Actions of upper airway dilator muscles.



**Fig. 47.3** Magnetic resonance images of a normal subject (a) and a patient of similar age and weight with the sleep apnoea/hypopnoea syndrome (b). The black area in the centre of each image is the upper airway, which is smaller in the patient

with sleep apnoea compared with the normal subject even during the awake scans. The white areas lateral to the upper airway in the patient with sleep apnoea/hypopnoea syndrome represent adipose tissue. (From Douglas [22] with permission.)

increased activity of the upper airway dilating muscles in awake patients with SAHS compared with controls, suggesting that patients need to defend their upper airways to keep them patent. This might therefore be a secondary response to anatomical narrowing. Upper airway muscles tense in a reflex response to negative upper airway pressure and Mortimore and Douglas [31] have recently compared this response in normal subjects and in patients with SAHS, finding that the latter have an impaired response to negative upper airway pressure. This suggests that there may be physiological as well as anatomical abnormalities in SAHS.

Sleep induces hypotonia of the upper airway dilating muscles. This is associated with both decreased and delayed responses to negative pressure [32]. These changes thus predispose to upper airway narrowing and occlusion. However, it is not yet clear whether the decrease in upper airway muscle activity and force generation differs between patients with SAHS and normal subjects.

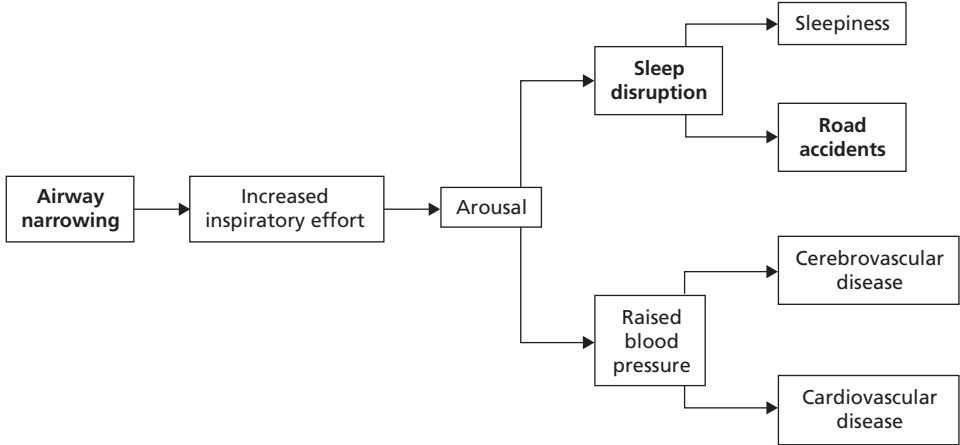
### Consequences of upper airway narrowing

Upper airway narrowing results in a compensatory increase in respiratory effort in an attempt to maintain ventilation. This increase in respiratory effort is the under-

lying trigger that stimulates arousal from sleep [33]. It was initially thought that total airway occlusion and cessation of ventilation were required for the pathophysiological sequelae to develop; it was later realized that continued, although diminished, ventilation in the form of hypopnoeas produced identical consequences [8]. There is now evidence that increased upper airways resistance in the absence of a diminution in ventilation may also produce identical sequelae [34,35]. These arousals restore upper airway dilating muscle activity, the patient gasps, takes a few deep breaths and then falls back to sleep, at which point the upper airway dilating muscles relax again and the cycle is initiated once more. These episodes of upper airway narrowing terminated by arousal may recur many hundreds of times per night and the recurrent arousals are thought to cause the major clinical features of the condition (Fig. 47.4).

The frequency of brief arousals from sleep correlates significantly with the impairment in daytime performance found in SAHS. Specifically, arousal frequency is correlated with reaction time and with the decrease in IQ observed [37]. Further evidence that it is sleep disruption which causes symptoms in SAHS come from modelling experiments in which normal subjects have been woken very briefly repeatedly through the night without any overall change in sleep duration. In these studies, recurrent arousals produce objective and subjective daytime





**Fig. 47.4** Mechanism and consequences of arousal following airway narrowing. (From Douglas & Polo [36] with permission.)

sleepiness and impaired daytime cognitive performance of the type found in SAHS [38].

Each arousal causes a transient rise in systemic blood pressure [39], the magnitude of which may vary from a small increase to a doubling of both systolic and diastolic pressures. These blood pressure rises may occur even when there are no visually discernible features of arousal on the EEG. Such repeated elevations of blood pressure hundreds of times per night over years or decades presumably account for the reported increase in morbidity and mortality from cardiovascular and cerebrovascular disease in patients with SAHS [40].

**Clinical features**

**Symptoms**

The patient’s major complaints are usually daytime sleepiness and unrefreshing nocturnal sleep (Table 47.1). Sleepiness must be differentiated from physical fatigue since both tend to be described as ‘tiredness’. Many patients admit to falling asleep at least once a day when not in bed [41] and many have been troubled by sleepiness for years prior to presentation. Sleep attacks can occur at any time of day but are usually worst in the early afternoon and evening, coincident with the circadian tendencies to sleepiness in the normal population. The urge to sleep usually comes on gradually but sometimes may be rapid and is often irresistible. Initially, sleepiness tends to present only during monotonous activities, classically watching television in the evening or during unstimulating driving such as on motorways or freeways. As sleepiness becomes more severe, it intrudes progressively into daily activities until sleep intervenes during all varieties of driving, when operating machinery or during conversations and meals. Some patients deny daytime sleepiness but report that they have impaired concentration that causes significant deterioration in their work performance.

**Table 47.1** Symptoms of the sleep apnoea/hypopnoea syndrome.

<i>Reported by patient</i>
Sleepiness
Poor concentration
Difficulty driving long distances
Unrefreshing sleep
Morning lethargy
Sleep-related choking/dyspnoea
Nocturia
Decreased sex drive
<i>Reported by partner</i>
Snoring: intermittent, loud
Apnoeas
Irritability

Most patients with SAHS find nocturnal sleep unsatisfying, usually waking up feeling as if they have not had a good night’s sleep. However, most do not report an increased frequency of nocturnal awakenings. Approximately one-third of patients have intermittent nocturnal choking attacks related to upper airways obstruction. Usually these are occasional but often terrifying events.

Nocturia is common and often troublesome. It is due to increased salt and water excretion at night [42] and ceases with adequate therapy. Young men with SAHS may complain of loss of libido and impotence. A few patients have reported automatic behaviour and disorientation after awakening, although many more report that they have difficulty getting started in the morning. Ankle oedema is reported by a minority, most of whom have coexisting respiratory disease [43,44], presumably because they have two causes for nocturnal hypoxaemia and thus have more severe hypoxaemia and therefore more marked sequelae.

Most spouses of patients with SAHS report that the patient is a loud snorer and often that their snoring is

intermittent, punctuated by multiple apnoeas. However, such a story cannot always be obtained, either because the patient does not have a bed partner or because these features have not been observed by a partner who is usually asleep. Normally, the patient has snored loudly for many years and snores in all body postures. Bed partners also report restless sleep as the patient fights for breath, the bedclothes often being rearranged. Partners may also report psychological changes, particularly irritability or depression.

### **Patient characteristics**

Around 80% of patients with SAHS are male [41]; the reason for this is not clear, although it relates to testosterone in some way since this can induce SAHS in hypogonadal men or in women [45–47]. Males have a central pattern of obesity and this produces greater deposition of fat in the neck of men than women. This may result in greater mass loading of the upper airway on lying down. Around 50% of patients with SAHS are obese. However, an increasing number of patients with SAHS are now found to have normal body weight, with more than 50% of our new patients having a body mass index of less than 30 kg/m<sup>2</sup> and some less than 20 kg/m<sup>2</sup>.

Most patients are middle-aged, although the reasons for this are unclear. Upper airway calibre has been found to narrow with age in awake men in some studies [48] but not all [49]. However, age has been found not to affect upper airway calibre in awake women [48].

All affected individuals should be examined for abnormalities of the nose or oropharynx. In some centres, all patients are seen by an otorhinolaryngological surgeon but in others this is reserved for selected patients with appropriate symptoms or abnormal findings on gross examination. Enlarged tonsils are a common cause of sleep apnoea in children and an occasional cause in adults and must be excluded by oropharyngeal examination. Other medical conditions that must be considered include hypothyroidism, acromegaly, Marfan's syndrome and upper airway tumours. Gross retrognathia is relatively uncommon but since it is a correctable cause it should always be sought.

## **Consequences of sleep apnoea**

### **Death**

Early data suggested that sleep apnoea was associated with increased mortality [40,50]. Later studies have not found any clear increase in mortality in patients with SAHS when allowance is made for coexisting risk factors such as obesity, smoking and age [51]. However, larger and better-designed studies are required before this issue can be satisfactorily resolved.

### **Road traffic accidents**

Many patients with SAHS report falling asleep at the wheel and some have road traffic accidents as a consequence. There is convincing evidence that members of the population with irregular breathing during sleep [52] and patients with SAHS have an increased frequency of road traffic accidents [53–55]. The overall increase in frequency is around two- to four-fold, although there may be a nine-fold increase in single-vehicle accidents, i.e. the type of accident typically caused by drivers falling asleep at the wheel [55]. Not only are these accidents common but they are also dangerous. Falling asleep at the wheel accounts for 15–20% of road traffic accidents and these sleep-related accidents are associated with an increased morbidity [56]. Indeed, a recent study in Bavaria has suggested that falling asleep at the wheel is the most common cause of fatal road accidents, and specifically caused more fatal accidents than alcohol [57]. Driving simulator studies show that untreated patients with sleep apnoea drive worse than normal subjects made legally drunk [58]. Obviously, sleep apnoea is only one of several causes of sleep-related road accidents and general fatigue may be more common. Patients with SAHS often report that they have no problems driving short distances in town or on minor roads where sensory input is fairly high but have great difficulties driving on motorways or freeways where the monotonous conditions predispose to sleep. Patients with sleep apnoea also underreport the severity of their driving impairment prior to receiving treatment [59].

### **Hypertension**

Many studies have attempted to assess whether there is an increased frequency of systemic hypertension in SAHS. Assessment of the significance of the differences observed is made difficult by the need to allow for potentially confounding factors, including obesity, age, smoking and alcohol consumption. Furthermore, some of the studies have used methods of diagnosing sleep apnoea that are not sufficiently precise by present-day criteria. Several studies have also used single measurements or even retrospective measurements of blood pressure rather than repeated measurements or 24-h recording. Others have studied patients on antihypertensive therapy, which may affect not only blood pressure but also, perhaps, nocturnal breathing pattern. Few studies stand up to rigorous review of their methodological standards.

Hla and colleagues [60] found an increased frequency of hypertension during 24-h monitoring in patients with SAHS compared with either snoring or non-snoring normal subjects. These differences persisted after controlling for age, sex and obesity. In a recent study, the same group have reported that blood pressure is correlated with

frequency of apnoea/hypopnoea and that even individuals with five apnoeas plus hypopnoeas per hour have a higher blood pressure than those with none, again when controlling for other variables [61]. This strongly suggests that irregular breathing at night produces clinically important effects on blood pressure that persist even after controlling for other risk factors. Other population-based studies have also found significant relationships between SAHS and hypertension, although these were explained by associations between hypertension and sex, age, body mass and alcohol consumption [62,63]; in both these studies blood pressure was only recorded on one occasion. Whether or not the 24-h blood pressure is significantly raised in patients with SAHS, there is no doubt that patients have hundreds of transient elevations of blood pressure every night associated with each arousal from a respiratory event [39]. Recurring every night for years or even decades, these could produce significant cardiovascular and cerebrovascular sequelae even in the absence of daytime hypertension.

### **Cardiovascular risk**

A retrospective study has shown that patients with myocardial infarction have a raised frequency of apnoeas during sleep [64]. A population-based study of 441 middle-aged subjects has indicated that patients with irregular breathing at night have a 3.5-fold increased risk of coronary artery disease; however, when adjustment was made for age, sex, body mass index, alcohol consumption and smoking, this ratio decreased to a non-significant 1.4 (95% confidence interval 0.4–3.5) [63]. Thus, the relationship between sleep apnoea and ischaemic heart disease is not yet clear.

### **Cerebrovascular disease**

Several studies have shown associations between snoring and cerebrovascular disease [65–68] and these findings persist after correction for age, smoking and obesity, although there are no data indicating whether SAHS *per se* predisposes to cerebrovascular accidents. However, there is evidence from a retrospective study that treatment for sleep apnoea decreases 'vascular' mortality, i.e. a combination of cerebrovascular and cardiovascular death [40]. Data suggest that the severity of snoring prior to a cerebrovascular accident is a predictor of outcome [68], indicating that nocturnal breathing may be important in the pathogenesis of cerebrovascular accidents.

### **Right heart failure/respiratory failure**

The development of chronic carbon dioxide retention, pulmonary hypertension and peripheral oedema in SAHS

usually requires an additional respiratory problem, most commonly chronic airflow obstruction [43,44,69]. Occasionally, other coexisting respiratory problems, such as extreme obesity or weakness of the respiratory muscles, may also produce these complications.

### **Sudden infant death syndrome**

There appears to be an increased frequency of sudden infant death syndrome (cot deaths) in the families of patients with SAHS [70,71]. This observation was made in the families of non-obese patients with SAHS. Families who had both SAHS and sudden infant death syndrome had retroposition of the maxilla and mandibles. A recent study indicates that victims of sudden infant death syndrome also have retroposed maxilla in comparison to age-matched control infants [72]. It is not yet clear how many, if any, cases of sudden infant death syndrome result from an SAHS-related mechanism.

### **Differential diagnosis**

Other causes of daytime sleepiness need to be considered [73].

### **Narcolepsy**

Narcolepsy occurs in 0.05% of the population and thus has a frequency about one-hundredth that of SAHS. Narcolepsy tends to present at 10–30 years of age, whereas patients with SAHS tend to present in middle age. The four characteristic features of narcolepsy are daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis.

Cataplexy is the sudden onset of muscle weakness when awake, almost always in response to amusement or some other strong emotion. It can vary between minor drooping of the head to total collapse. Hypnagogic hallucinations are vivid dreams at the onset of sleep and both these and sleep paralysis relate to the propensity for REM sleep suffered by these patients.

The diagnosis of narcolepsy is easy when sleepiness is associated with one of the other features of the tetrad but it commonly is not, in which case the demonstration of sleep-onset REM during multiple sleep latency testing [74] and the demonstration of HLA-DR2, DQw1 may be helpful as may a family history, although the latter is by no means always positive. Narcolepsy is best treated by a combination of simple advice (e.g. taking postprandial naps where possible, and avoiding dangerous situations if feasible) and stimulant medication. Drugs normally used include mazindol, methylphenidate, dexamfetamine (dexamphetamine) and modafinil. Tolerance to these drugs may develop and drug holidays may be required. Cataplexy can also be difficult to treat but drugs of

choice include clomipramine, imipramine, fluoxetine and phenelzine.

### **Idiopathic hypersomnolence**

Nocturnal sleep duration tends to be longer than usual and daytime naps are also longer than those found in sleep apnoea or narcolepsy, often lasting over 1 h. The morning is often the worst time of day for patients with idiopathic hypersomnolence, with morning drunkenness as a troublesome feature for some. Like narcolepsy, this condition usually presents first at 10–30 years of age, earlier than SAHS. Treatment is the same as with narcolepsy in terms of advice and stimulant drugs.

### **Periodic limb movement disorder**

Repetitive leg movements occur in many individuals during sleep, perhaps up to 30% by the age of 60 years. These leg movements occur around every 20 s during non-REM sleep but usually disappear totally during REM sleep. When these leg movements are followed by arousals, they may cause daytime sleepiness and treatment with either L-dopa or a benzodiazepine can be beneficial.

### **Post-traumatic hypersomnolence**

Persisting daytime sleepiness following head injury is well documented. This may also occur following cranial surgery or a cerebrovascular accident.

### **Kleine–Levin syndrome**

This rare syndrome causes recurrent episodes of hypersomnolence lasting several days or weeks at a time and recurring perhaps once or twice a year. The patient is often an adolescent and the episodes of prolonged sleeping may be associated with bouts of binge eating and hypersexual activity. Usually the condition gradually improves with time. Lithium therapy may be helpful.

### **Psychiatric illness**

Severe depression and psychotic illnesses may be associated with daytime sleepiness. Psychiatric referral should be considered for not only sleepy patients with overt psychiatric illness but also those in whom no medical cause for sleepiness can be found.

### **Psychological sleepiness**

Occasional daytime sleepiness may relate to anxiety or depression. More often these conditions are associated with insomnia rather than sleepiness.

### **Insufficient sleep**

Patients should always be asked about their normal sleep duration. Prospective sleep diaries may be helpful in this situation.

### **Shift work**

It can be very difficult to ascertain whether the patient's shift rota itself is causing the reported sleepiness and an accurate history is essential.

### **Drug abuse**

Hypnotics, sedatives and alcohol in excess can all cause sleepiness. Trials of withdrawal may prove helpful.

## **Diagnosis**

### **History and examination**

The diagnosis of SAHS cannot be adequately made from the history alone. While questions about intensity of snoring, witnessed apnoeas and falling asleep while driving are useful for selecting patients likely to have SAHS from the general population [75], they are of less value in patients presenting to a sleep clinic, many of whom have such symptoms. Several studies have attempted to distinguish which of the patients presenting to a sleep clinic may have SAHS on history alone but the results have been disappointing. Factors increasing the likelihood of sleep apnoea are witnessed apnoeas [76–78], nocturnal choking [76,77], sleepiness [78], being male [76,77], obesity [76–78], hypertension [77] and the presence of a narrowed pharynx with a large uvula [76]. However, none of these are sufficiently specific to be diagnostically useful, the most helpful being the presence of witnessed apnoeas in 75% of patients with SAHS; however, apnoeas are also reported in around 60% of patients referred to sleep clinics who are shown not to have SAHS [76,77]. Predictive equations can be built around these observations but their value in limiting the number of sleep studies required has yet to be proved.

### **Sleep studies**

The 'gold standard' for the diagnosis of SAHS was originally thought to be polysomnography, which involves the overnight recording of sleep, breathing patterns and oxygenation (Table 47.2). However, the need for this level of investigation in all cases and the associated expense has been questioned as a result of the limitation of healthcare budgets combined with the rapidly increasing numbers of patients being referred for investigation.

**Table 47.2** Variables recorder during polysomnography.

<i>Usual</i>
Neurophysiology
EEG
Electro-oculography
Electromyography: submental, anteriotibial
Respiratory
Airflow
Thoracoabdominal movement
Oxygen saturation
General
ECG
Body position
Sound
Optional
Oesophageal pressure
Blood pressure
Penile tumescence
Light intensity

The recording of sleep quality and duration appears to play little part in the routine clinical diagnosis of SAHS according to a study of 200 patients [79]. The re-examination of patients who either slept for less than 3 h per night or who had no REM sleep did not change the clinical diagnosis, and the identification of early REM sleep was also not diagnostically useful. The expense of sleep recording does not therefore appear to be justified in routine studies. However, there are occasional patients who genuinely do not sleep during either diagnostic or therapeutic sleep studies. Thus, if a technique is used that does not record sleep and the patient indicates that sleep was very poor, polysomnography should be considered to allow interpretation of the breathing pattern during sleep.

The major value of recording sleep may be to identify transient arousals; however, there is no agreement on the definition of such brief arousals [37,80]. Furthermore, even this may not be a reason for recording EEG, since arousals may be better detected by examining changes in cardiovascular or respiratory pattern. For example, each arousal is associated with a rise in blood pressure [81] and a shortening in pulse transit time [82] and most are associated with an increase in tidal volume and with the loss of flow limitation.

Many different respiratory sensors have been used to detect SAHS, including oximetry, airflow signals, thoracoabdominal movement, snoring detectors and oesophageal pressure. Oximetry alone can detect about two-thirds of patients with SAHS and this is best done by a trained observer examining the pattern of desaturation [79,83]. Current computerized systems designed to detect recurrent desaturations are highly specific when positive (specificity 97–100%) but are not adequately sensitive (sensitivity 30–40%). Thus, oximetry alone can be diagnos-

tic when positive although normal oximetry by no means excludes the diagnosis of sleep apnoea nor indeed can it even exclude severe sleep apnoea. It must be remembered that the magnitude of daytime impairment in patients with SAHS in terms of reaction time and driving ability relates to arousal frequency more than the degree of desaturation [37]. Thus, patients with recurrent respiratory-associated arousals who have either SAHS or the so-called upper airways resistance syndrome may show no desaturation during sleep but have severe symptoms and benefit greatly from continuous positive airway pressure (CPAP) or other treatment. These limitations of oximetry must be realized by those using this technique either on its own or as a key component in their diagnostic systems.

SAHS was initially diagnosed from recurrent episodes of flow cessation. More recently, it has been realized that events in which there is continued airflow but reduced thoracoabdominal movement (hypopnoeas) are also associated with recurrent arousals and similar clinical sequelae [8]. Indeed, even hypoventilation may not be necessary for the clinical features of the syndrome, some patients exhibiting repeated arousal following increases in upper airways resistance with no decrease in ventilation (upper airways resistance syndrome) [34,35]. There is widespread confusion about this terminology, with similar patients being diagnosed in some centres as having hypopnoeas, in others partial airways obstruction and in yet others upper airways resistance syndrome. This is of more than semantic importance since if upper airways resistance-induced arousals in the absence of any change in ventilatory pattern are common, then the diagnostic strategy must centre on proving the coincidence of an arousal with some relatively subtle respiratory change. These respiratory changes may be documented by invasive techniques such as oesophageal pressure along with EEG monitoring, or less invasively by detecting inspiratory flow limitation or changes in thoracoabdominal phase angle, or by using the static charge-sensitive bed.

There are many different techniques used to record thoracoabdominal movement, including inductance plethysmography, impedance pneumography, strain gauges, piezoelectric systems or charge-sensitive beds. Each gives different results and all users must be aware of the advantages and disadvantages of their system. Thoracoabdominal movement can be used to classify apnoeas into central or obstructive, although this may not be a useful classification since many apnoeas labelled as 'central' respond to CPAP [84]. This may be because the events are initiated with upper airway occlusion, which reflexly inhibits subsequent ventilatory efforts, or because relatively poor thoracoabdominal signals are obtained from some individuals, particularly the grossly obese. The rare true central apnoea can only be diagnosed by oesophageal manometry or respiratory muscle electromyography.

The major use of the thoracoabdominal signal is to identify hypopnoeas, which are better defined with inductance plethysmography than conventional flow sensors since temperature-based measurements do not provide a quantitative estimation of ventilation, there being little difference between the temperature of an expired volume of 100 mL and that of 1000 mL [8]. The conventionally used flow-based devices that record temperature, expired  $P_{CO_2}$  or tracheal sound are adequate to detect true apnoeas, although such apnoeas are detected adequately by inductance plethysmography and thus the need for a flow signal is unclear [85]. Flow signals based on true flow-measuring devices such as pneumotachographs or on the measurement of intranasal pressure may allow detection not only of apnoeas and hypopnoeas but also of flow limitation, thus providing a non-invasive method of diagnosing upper airways resistance syndrome [86]. This is an area of considerable research.

Many different devices have been developed to record snoring. However, the sensitivity of these for diagnosing SAHS based on snoring alone has been poor (around 27%), although specificity is high [87]. Thus, at present, these devices on their own cannot be recommended for excluding SAHS, although the addition of other monitors such as oxygen saturation greatly improves their diagnostic value [88].

There is a confusing array of limited sleep study devices that use various combinations of the above sensors. Unfortunately, most systems are poorly validated at present. It is imperative that the users of such equipment fully appreciate the potential for false-positive and false-negative results with their own system.

Ideally, all sleep studies should have the ability to detect the periodic limb movements found in at least 5% of patients referred to a respiratory sleep clinic [79]. These patients may benefit from treatment for this condition. Such limb movement can be detected either by electromyography, the classical method, or by piezoelectric, static charge bed or video techniques.

### Diagnostic strategy

Many factors determine the diagnostic strategy, including the availability of resources and equipment and the distances travelled by patients. Few centres can afford the luxury of polysomnography for all patients referred; indeed, it is not required for the clinical management of most patients. The diagnostic approach depends upon the patient's presenting features and in the author's view the following approach is reasonable.

#### Patients highly likely to have sleep apnoea

Patients who fall asleep at least once a day when not in bed, are loud snorers with witnessed apnoeas and have no

features to suggest periodic limb movement disorder or narcolepsy should have a limited sleep study performed either at home or in hospital without EEG documentation of sleep being obtained. If this overnight study is unequivocally positive, the patient may proceed to therapy but a negative study must result in further investigation.

#### Simple snorers with no features of sleep apnoea

Any patient who is considering dental splinting or surgery for snoring should have a limited overnight sleep study, which includes recording of snoring so that both the presence of snoring and the presence or absence of sleep apnoea can be documented. In some patients, several nights' recording of snoring may be required to establish whether there is a major problem warranting surgery, as many alleged 'habitual snorers' are found to snore rarely.

#### Patients with moderate likelihood of sleep apnoea

Our practice in such patients depends on their proximity to the sleep laboratory. Those living less than 80 km away have a limited sleep study performed at home. This saves time and money, although a conservative definition of abnormality has to be used since events occurring during wakefulness are included in the analysis and sensitivity and specificity may differ from that used during polysomnography [89]. Those living more than 80 km away tend to find it inconvenient to travel to and from the sleep laboratory twice in order to collect and return the equipment and overnight sleep studies in the laboratory are more satisfactory. As the costs of a hospital bed are incurred, it is imperative that the maximal amount of diagnostic information is obtained on this night and it is the author's practice therefore to perform overnight polysomnography on all patients living more than 80 km away who give a reasonable but not totally convincing story of SAHS. This stance may change with the development of better limited sleep study equipment.

#### Patients who may have other diagnoses

In patients with significant daytime sleepiness without obvious drug or psychological cause and who do not have a good history of SAHS, it is reasonable to perform overnight polysomnography, perhaps combined with the daytime multiple sleep latency test both to quantify the severity of the daytime sleepiness and to help with the diagnosis of narcolepsy through the documentation of early REM sleep [74].

This scheme is just one of many and will require modification as diagnostic equipment becomes more sophisticated and better suited to home use. It supposes access to limited sleep study equipment capable of measuring

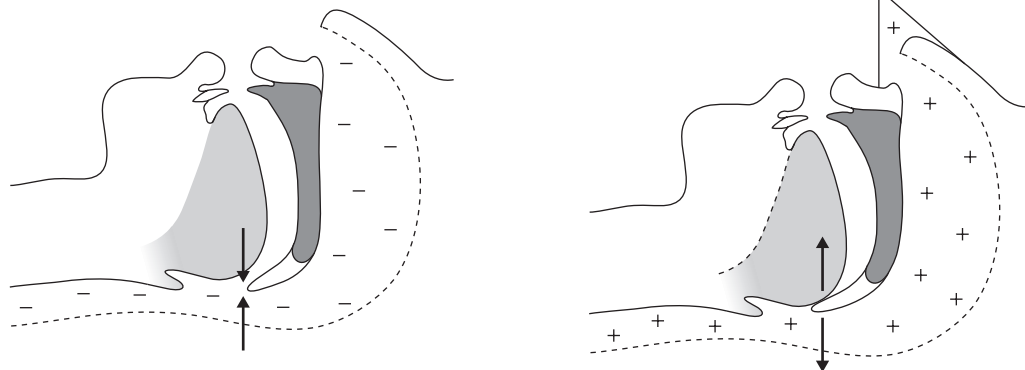
breathing pattern, snoring, oxygenation and leg movement in each hospital. It is reasonable for hospitals without such facilities to use oximetry for patients with a high probability of having SAHS since it is positive in two-thirds of patients with SAHS and a positive result allows rapid initiation of CPAP. However, all patients with negative or equivocal oximetry alone need to be referred for further investigation.

## Treatment

The threshold for benefit from treatment has yet to be established. Most patients with more than 15 apnoeas plus hypopnoeas per hour of sleep who are troubled by daytime sleepiness benefit from therapy [90]. However, there are a significant number of patients with fewer events who are troubled by daytime symptoms who also benefit from therapy [91]. At present, the author's policy is to offer treatment to all those with troublesome sleepiness who have more than 15 apnoeas plus hypopnoeas per hour of sleep or more than 15 respiratory-related arousals per hour in the context of the upper airways resistance syndrome.

All such patients should receive advice on weight reduction and alcohol avoidance as routine. Those with otorhinolaryngological symptoms or abnormal findings on examination should be referred in order to discover whether improvement of the nasopharyngeal airway might help. Any patients with craniofacial abnormality should be considered for surgical mandibular advancement, with or without maxillary advancement. These are highly skilled procedures that must be carried out in specialist centres.

**Fig. 47.5** Mechanism of action of continuous positive airway pressure. Left-hand panel shows mechanism of airway obstruction with the throat being sucked closed by the negative intraluminal pressure. Right-hand panel shows the throat being blown open by the continuous positive airway pressure applied by nasal mask.



## Continuous positive airway pressure

Those patients with severe symptoms and those not responding to the above measures require a trial of CPAP [92]. CPAP blows open the upper airway, thus preventing apnoeas, hypopnoeas, increases in upper airways resistance and snoring. CPAP is usually applied via an external nasal mask (Fig. 47.5), although some patients prefer intranasal devices. Therapy must be initiated with a careful explanation to each patient of the benefits and potential problems of CPAP. Educational videos are a useful adjunct to explanations by doctors and nurses. The patient must then be sized for an appropriate mask; each sleep centre should hold in stock at least 20 different sizes of masks from differing manufacturers so that an adequate fit can be achieved for each patient. Each patient should try CPAP for at least 30 min using the correct mask during the daytime to become accustomed to the sensation before returning for an overnight titration study. This sets the pressure required to keep the patient's airway patent and to minimize arousals: too high a pressure results in the patient being kept awake, while too low a pressure does not effect airway patency. 'Split night' studies, with the first part of the night for diagnosis and the second for CPAP titration, can be used in many patients with severe sleep apnoea but their role in milder disease is still unclear [93].

CPAP is one of the most satisfying therapies to deliver in that it can completely transform a patient's lifestyle. Patients who were unable to perform their job or drive safely because of sleepiness and who were subjected to considerable domestic strife can be returned to normality overnight, a situation rare in respiratory medicine. Randomized placebo-controlled studies have shown that CPAP improves symptoms, sleepiness, quality of life, mood, cognitive function, IQ and driving performance [90,91,94]. Uncontrolled data also suggest that CPAP may improve sleepiness [95], quality of life [96] and survival [48]. Recent evidence indicates that CPAP improves driving performance [97], decreases the rate and cost of



road traffic accidents [98], improves work efficiency and decreases time off work through ill-health [99].

Recently, the efficacy of CPAP has been challenged by Wright and colleagues [100]. At the time, these authors were correct in stating that there were few randomized controlled trials; however, many such studies have since been carried out and their results reviewed [101]. There is no real doubt that CPAP is effective in many patients, a conclusion shared by a recent systematic review [102], although there is a real need for further information on the cost-effectiveness and long-term use of CPAP.

Like all therapies, CPAP has side-effects. One of the major problems is the obtrusive nature of the device and careful education is the most important way of minimizing this problem. Despite careful mask fitting, local problems sometimes arise and mask sizes may need to be changed. The most common side-effects relate to nasal drying, rhinitis or dry mouth [99], all of which appear to be due to mouth leaks. Mouth leaks increase the flow of air through the nasopharynx, which may not only produce nasal drying and rhinitis but also increase airflow resistance, thus decreasing the effect of pressure delivered to the nasopharynx. Management should involve trying a chin strap but if this is not successful, then a heated humidifier may be necessary. Other problems include abnormal bloating that may be difficult to manage, although pressure reduction may prove satisfactory.

As with any other form of chronic therapy, including treatment for asthma [103], patient compliance with therapy is not as high as might be hoped. On average, patients on chronic CPAP use their machines for around 4–5 h per night but there is wide variation between subjects. Short-term trials yield slightly lower compliance figures [104], probably because those who use their machines early only rarely abandon the therapy subsequently. It is not yet clear whether symptoms or initial sleep study findings can be used to predict the subsequent use of CPAP by patients, the author's own data indicating no useful relationships [104].

Follow-up of patients on CPAP must include checking for side-effects, checking the function of the mask, tubing and machine, and monitoring objective use of therapy from the time clock built into the machine, since patients are frequently inaccurate in their estimate of use [104]. Annual electrical safety checks are standard for CPAP machines.

Bilevel ventilation via a nasal mask is an acceptable form of treatment for many patients with SAHS. However, it is significantly more expensive than CPAP and there is as yet no evidence that patient compliance or outcome is improved by using this method as opposed to CPAP [105].

Those patients who do not tolerate CPAP and in whom weight reduction is either not appropriate or unachievable should be considered for either dental devices or surgery.

## Oral devices

The role of dental devices in the treatment of sleep apnoea is unclear. These devices, which the subjects only use overnight, often advance the mandible and may decrease snoring and potentially also the frequency of apnoeas plus hypopnoeas [106]. Recent evidence from controlled trials suggests that oral devices may be effective in some patients with SAHS [107,108]. These data indicate that patients like oral devices and that these devices improve, but do not usually normalize, nocturnal breathing. Further studies investigating outcome measures and compliance with oral devices are awaited with interest before their role in the therapy of sleep apnoea can be stated with certainty. At present they have a role in patients who decline or do not comply with CPAP therapy, but whether they are as effective as CPAP as primary therapy remains to be seen.

## Otorhinolaryngological surgery

There is considerable controversy over the role of uvulopalatopharyngoplasty, whether carried out by conventional surgical techniques or by laser. Unfortunately, there are no objective data from controlled clinical trials that indicate high success rates [109,110]. In addition, the operation tends to be painful for around 2 weeks and has been associated with significant morbidity and very occasional mortality [111,112]. Casual readers of the literature should be careful not to be confused by differing definitions of success rates between studies, few of which use definitions of cure that involve returning the frequency of apnoeas/hypopnoeas and symptoms to normal levels. Furthermore, those patients who fail to benefit from uvulopalatopharyngoplasty and who then need CPAP have difficulty with pressure leaking out through the mouth, and have more side-effects and lower use of CPAP [113].

The theoretical problem with uvulopalatopharyngoplasty is that it addresses airway occlusion only at the palatal level, whereas obstruction generally takes place at both the retropalatal and retroglossal levels [15,16]. The earlier hope that localization of the prime site of obstruction as the retropalatal level would improve the success rate of uvulopalatopharyngoplasty has not been borne out [114,115]. There is dispute whether uvulopalatopharyngoplasty improves survival in patients with SAHS [48,116]. In selected centres, this operation has been augmented by partial glossectomy and significant success rates have been claimed to ensue.

## Faciomaxillary surgery

In a few centres around the world, mandibular plus maxillary advancement has been shown to benefit some

patients [117]. At present, patients who may benefit from this approach should be treated by surgeons who have experience in this area. Patients who should be considered for such procedures are those with abnormal cephalometric findings and narrowed upper airway. Further factors in favour of this approach include relatively younger patients, thinner patients and those not able to tolerate CPAP.

### Upper airway pacing

Pacing of the upper airway opening muscles by external or internal electrodes has been suggested as a possible treatment for SAHS [118]. Thus far, there is insufficient evidence available to recommend this approach.

### Tracheostomy

This option must be remembered as a possibility in severely ill patients intolerant of CPAP, although it is rarely needed.

### Central sleep apnoea

There is a small minority of patients who have true central apnoeas that do not respond to CPAP. Such patients generally have coexisting cardiovascular or cerebrovascular disease. When symptoms are troublesome, the best treatment in such cases is usually nocturnal intermittent positive-pressure ventilation via a nasal mask [41]. Aceta-

zolamide therapy has been shown to help some patients [119].

### Training

It is obviously essential that those dealing with any area of medicine are adequately trained in the clinical, diagnostic and treatment approaches relevant to that subspecialty. This is a particular problem in newly evolving areas of medicine such as the management of sleep disorders. Throughout the world, guidelines are being drawn up indicating the training requirements. The British guidelines, published by the Royal College of Physicians of London [120], indicates that trainees in respiratory medicine who wish to direct a sleep laboratory or to make sleep disorders a major component of their work should receive at least 12 months of specialist training in this area. In addition, it is recommended that all respiratory physicians in training should receive the equivalent of at least 3 months' education in a sleep laboratory during their training programme. These guidelines have yet to be rigorously enacted.

### Conclusions

Our understanding of SAHS is rapidly increasing. This is a clinically rewarding area that all respiratory physicians should understand so that they may identify potential patients and refer them for appropriate investigation and treatment.

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# HYPERVENTILATION SYNDROMES

ANTHONY SEATON

The symptom of breathlessness is one of the principal reasons for referral of a patient to a chest clinic and for acute admission into hospital. It is a symptom that everyone is familiar with from the effects of exertion but one that not uncommonly causes difficulties for individuals in distinguishing normal from abnormal breathlessness. The previously fit person who becomes unfit and fat from lack of exercise and overeating notices shortness of breath during activities that earlier had been carried out without difficulty, and may interpret this as indicating serious heart or lung disease. Similarly, anxious or obsessive people may seize upon an awareness of the process of respiration and interpret the pattern as abnormal. Once focused on such a symptom, it is easy to develop an obsessive interest in the suspected abnormal function of the organ, sufficient to prompt a visit to a doctor. Any subsequent indication by the doctor of uncertainty about the cause or implications of the syndrome is likely to reinforce the patient's anxiety and help perpetuate the complaint. It is therefore important that all chest physicians, to whom such patients are often referred, are aware of the syndrome of behavioural breathlessness, its causes and the methods of managing it.

The two important syndromes of behavioural breathlessness are hyperventilation, which usually occurs in attacks but rarely may become chronic, and sighing. Both types are described by patients as shortness of breath and need to be distinguished from breathlessness of organic aetiology. Hyperventilation in normal people causes a wide range of symptoms related to hypocapnia and alkalosis, vasoconstriction and stimulation of chest wall muscle receptors, and these symptoms may be interpreted by patients with hyperventilation syndrome as further evidence of organic disease.

## Control of respiration

This is discussed in Chapter 2. The involuntary system is based on rhythmical discharge of neurones in the pontine and medullary respiratory nuclei that respond to stimuli

from the carotid and medullary chemoreceptors; the receptors in the carotid bodies respond primarily to arterial hypoxia while those in the floor of the fourth ventricle respond to arterial and cerebrospinal fluid pH and  $P_{CO_2}$ . In addition, sensory stimuli from lung and airway receptors transmitted via the vagus nerve may modify the pattern of respiration. Inspiratory and expiratory neurones are found in the spinal cord, supplying the diaphragm via the phrenic nerve (C3–C5) and the intercostal, accessory respiratory and abdominal muscles through spinal nerves down to T12.

Voluntary control of respiration is possible because higher neural centres are able temporarily to override the brainstem control centres, by direct inhibition or stimulation of spinal motor nerves via corticospinal pathways or of brainstem control via corticobulbar pathways. It is with this voluntary control of respiration that this chapter is primarily concerned.

## Causes

Hyperventilation may be defined as ventilation sufficient to reduce  $P_{aCO_2}$  while maintaining a high  $P_{aO_2}$ . This excludes breathlessness due to diseases that impair gas exchange, such as pulmonary fibroses and cardiac failure, and those with airflow obstruction such as asthma. However, it should be noted that behavioural hyperventilation can occur in these conditions as readily as it can in an otherwise healthy person. The definition also excludes breathlessness due to exercise and to hypoxia. There are organic causes of hyperventilation as well as psychogenic, and the most important are shown in Table 48.1. In any case of suspected hyperventilation it is essential to reassure oneself that there is not an organic cause. This differential diagnosis is discussed below.

## Symptoms

Haldane and Poulton [1] first described the characteristic and varied symptoms associated with hyperventilation

**Table 48.1** Causes of hyperventilation.

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<i>Lung disease</i>
Asthma
Pulmonary embolism
Multiple arteriovenous fistulae
<i>Brain disease</i>
Midbrain tumour
Meningitis
Meningeal lymphoma
Langerhans' histiocytosis
Rett's syndrome
<i>Metabolic acidosis</i>
Renal failure
Renal tubular acidosis
Diabetic ketoacidosis
Lactic acidosis in shock
Gastrointestinal loss of bicarbonate
Metformin acidosis
Aspirin poisoning
Methyl alcohol poisoning
Ethylene glycol poisoning
<i>Psychogenic</i>
Panic attacks
Anxiety, depression
Hysteria

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and hypocapnia, and generations of medical students have since experienced a selection of these symptoms in their physiology practical classes. The most common are lightheadedness, dizziness and paraesthesiae, which may lead to syncope and tetany. Other symptoms include chest pain, palpitations and a range of feelings of psychological discomfort. Symptoms occur at around an end-tidal  $P_{CO_2}$  of 2.66 kPa (20 mmHg) on average, with a threshold of no higher than 3.86 kPa (29 mmHg) [2]. Various mechanisms probably contribute to their causation, including alkalosis, cerebral and peripheral vasoconstriction, stimulation of chest wall stretch receptors and falls in blood phosphate concentrations [3–7]. The subject has been well reviewed by Gardner [8].

## Behavioural breathlessness

### Hyperventilation

#### Clinical features

Patients with psychogenic hyperventilation complain of breathlessness disproportionate to the amount of exercise taken or any cardiopulmonary impairment detected [8–10]. Indeed, they frequently complain of episodic breathlessness at rest. Their symptoms often vary substantially from day to day and, if asked, admit that breathing in is harder than breathing out. Breathlessness may be,

though not always, associated with other symptoms. These may mimic cardiac disease with chest pain or palpitations, and in some patients hyperventilation may provoke coronary artery spasm and genuine attacks of angina [11,12]. Neurological disease may be mimicked, with dizziness, lightheadedness, syncope, tingling in the fingers and muscle cramps. Panic attacks may be a feature [13,14], and the author has seen one patient with an epileptic tendency in whom grand mal attacks were brought on by hyperventilation. The term 'hyperventilation syndrome' was introduced in 1937 to describe this condition, in the belief that the symptoms were the result of the hyperventilation [15].

Investigation of such patients has shown that a high proportion suffer from symptoms indicating a psychiatric illness [9]. Depression, not always clinically overt, is common as is anxiety. In a relatively few cases, hysteria or motivation by the prospect of gain, for example sympathy from a spouse or in pursuit of litigation, may be important factors. A careful history often indicates that the patient has an obsessional personality and that the perceived illness was provoked by a traumatic event such as bereavement, separation or divorce. Hyperventilation does not seem to be a feature of the chronic fatigue syndrome [16], although it might be expected to occur in some cases. Bad medical management has a way of making matters much worse, and resentment at either actual or perceived medical incompetence may be detected in patients with hyperventilation. Doctors involved in examining lawyers' clients as part of civil litigation proceedings frequently see patients with disproportionate breathlessness. Not all in this situation are deliberately exaggerating (though many are); some have been made genuinely anxious by a perceived gloomy prognosis, given by rather thoughtless or stupid doctors, relating to a trivial condition such as pleural plaques or mild asthma and have developed psychogenic breathlessness.

### Diagnosis

An essential step in making the diagnosis is to exclude an organic cause of the breathlessness. The syndrome is usually suspected strongly by the experienced chest physician from the history and from observation of the patient while taking it. A careful examination of lungs and heart is not only essential for diagnosis but is also of therapeutic value. It should be remembered that hyperventilation may occur in patients with organic lung or heart disease and is not uncommon in patients with asthma and other chronic airways disease [17,18]. In such subjects, a peak flow chart is of considerable value in allowing the dissociation between symptoms and flow rates to be demonstrated. Detailed lung function testing and ECG are similarly useful to reassure the patient about the absence of organic disease.

A simple exercise test, such as an 8-min run or brisk walk in or near the clinic, may be helpful as a means of indicating to the patient that exercise tolerance is unimpaired. However, many such patients complain of severe symptoms during exercise and formal testing has shown that inappropriate hyperventilation may occur on exercise as well as at rest [9].

Some physicians who have studied the syndrome find hyperventilation tests of value in diagnosis, by reproducing the patient's symptoms. Howell [9] recommended a simple test in which the patient is asked to take 20 deep breaths and to stop if he or she feels odd in any way. If this does not reproduce the patient's symptoms, the diagnosis of psychogenic breathlessness is unlikely to be correct, whereas if it does the diagnosis finds support. There is little to be gained clinically from more complex tests monitoring end-alveolar  $P_{CO_2}$ . There is no clear relationship between the rate of change in  $P_{CO_2}$  and symptoms [2], and it has been shown in a controlled study that patients with hyperventilation syndrome develop symptoms similarly with hypocapnic and isocapnic hyperventilation [19]. This study also demonstrated, by using ambulatory  $P_{CO_2}$  monitoring, that symptoms did not correlate with changes in  $P_{CO_2}$ . It seems therefore that hyperventilation producing hypocapnia is but one symptom of the underlying psychological illness, and not necessarily the cause of the other somatic symptoms. In support of this concept, other studies have shown symptoms to be provoked by psychological stress tests as readily as by hyperventilation [20].

### Differential diagnosis

The main problem of differential diagnosis arises in patients with genuine organic disease such as asthma or other chronic heart and lung disease [21]. In lung disease, demonstration of inappropriate breathlessness on formal exercise testing or on a chart recording both symptoms and peak flow rate is necessary. In the case of chest pain, reproduction by deep breathing in the absence of ECG changes is reassuring. If ischaemic changes do occur, further investigation by angiography and hyperventilation is obviously necessary. Two respiratory diseases in particular may cause hyperventilation with no other obvious chest signs: pulmonary embolism and multiple arteriovenous fistulae [22–24]. In breathlessness due to pulmonary embolism, anxiety is often quite justifiably present and it is not uncommon for the diagnosis of psychogenic hyperventilation to be considered.  $P_{aCO_2}$  is low but  $P_{aO_2}$  is also usually reduced and the alveolar–arterial oxygen gradient is increased. Arteriovenous malformations may be multiple and not obvious on chest radiography, although finger clubbing and often a sufficiently low  $P_{aO_2}$  to cause cyanosis are present.

Hyperventilation due to acidosis may still catch the unwary [25], but in contrast to psychogenic breathlessness

the patient with Kussmaul respiration may look remarkably unconcerned about what appears to be distressing breathlessness. Measurement of arterial blood gases together with blood sugar and urea quickly show the cause of the problem. The acidotic respiration of aspirin or methyl alcohol poisoning constitutes a well-known presentation in the emergency department, since these patients often look suitably anxious or depressed. Diagnostic confusion should not arise in the intensive care unit with breathlessness due to sepsis or blood loss [26]. Neurological disease is a relatively rare cause of hyperventilation, and may cause considerable diagnostic difficulties if it is not considered. A stroke in the region of the brainstem, multiple sclerosis, malignant meningeal infiltration by lymphoma, and Langerhans' cell histiocytosis (histiocytosis X) have all been described as rare causes [27–31]. In these syndromes, the hyperventilation is chronic.

Rett's syndrome is a brain disorder of young females, starting in infancy and progressing through the first two decades of life, characterized by autistic behaviour, abnormal hand movements, epilepsy, dementia, neurogenic scoliosis, and episodic hyperventilation and apnoea [32–34]. It is perhaps caused by a deficiency of dopaminergic neurotransmitters. The disordered control of breathing appears to result from higher cortical brain damage, since polysomnographic studies in such patients have shown a normal pattern during sleep [35].

### Management

The first step in the management of psychogenic hyperventilation is exclusion of organic disease and reassurance of the patient that none is present. In many cases this is possible at the time of the first consultation if a few simple tests as described above prove to support the diagnosis. This reassurance should be firm, as any doubt in the doctor's mind will be readily apparent to the anxious patient. An acute attack in an anxious individual is very easily recognized, and once seen is not forgotten; it is usually managed by asking the patient to rebreathe in a paper bag, thus allowing the symptoms generated by hypocapnia to be relieved and their cause demonstrated. Subsequent steps in management are still at the stage of individual preference based on experience, experience quite likely to be of application only to the sorts of patients that one physician sees. However, in general a sensible approach would seem to be as follows.

#### *Explain the breathlessness*

Having been told that there is nothing the matter with heart and lungs, the patient, though reassured, still wishes to have an explanation of the symptoms. It is necessary therefore to explain how breathing normally occurs involuntarily but that awareness of the process can cause alter-



ations in its pattern. A useful analogy is running downstairs, something that most people can do in a hurry but that can become awkward and even lead to a fall if too much thought is given to where one's feet should be placed on every step. It can then be explained that once one becomes aware of the process of breathing it is a small step to becoming anxious that it is not proceeding normally and this may lead to a vicious cycle of increasing anxiety and breathlessness. This explanation needs to be approached with care as some patients are quite resistant to the suggestion that their symptoms are non-organic and may interpret such an idea with denial or outright hostility. Clearly, the rapport established with the patient in the consultation is a determinant of success in managing this part of the process. The author prefers to discuss these mechanisms in a way that emphasizes their organic aspects—control by the brain, symptoms of hypocapnia (despite what was said above about this not necessarily being the cause of all the symptoms) and so on—and to explain that the syndrome is a common accompaniment of stress of one sort or another. The concept of 'stress' is now quite well appreciated by the general public and does not seem to be associated with the same amount of perceived stigma as a more psychiatric label such as depression. It is useful to point out that the syndrome is common and one with which chest physicians are quite familiar and which occurs particularly in perfectionists.

#### *Evaluate the effectiveness of reassurance and explanation*

In many less severe cases, this simple procedure is enough to give the patient sufficient insight into the condition to relieve anxiety and cure the symptoms. It is therefore sensible not to take the process any further initially but to arrange to review the patient after an interval in order to assess progress. It is apparent that overall cure depends on relief of the primary cause, and it may well be that the hyperventilation disappears but that other psychosomatic symptoms replace it. If this is the case, the psychological problem needs to be addressed, not necessarily by the chest physician.

#### *Discuss with the patient possible causative factors*

Again this requires a delicate approach and is often best done in terms of stress. The history may have revealed evidence of symptoms of depression or anxiety and of an obsessional or hysterical personality. Possible precipitating factors should be explored by asking tactfully about

any events that may have occurred about the time that the symptoms started. Apart from obvious factors such as marital difficulties and bereavement, common causes nowadays include stress in the workplace, loss of employment, troublesome children and financial worries.

#### *Treat the cause*

If there is an important environmental cause, such as domestic or work-related problems, these can be addressed by appropriate agencies and this should certainly be considered before starting drug treatment. In severe cases, treatment of the symptom of hyperventilation alone is unlikely to be of benefit without additional psychological treatment. However, various forms of re-education of breathing patterns have been reported to be successful in relieving the symptom [36,37].

#### *Take a positive attitude towards recovery*

It is the author's practice, based on experience, to be optimistic about recovery. If the patient proves able to complete a simple exercise test it is often possible to demonstrate that no harm has come from that exercise and to persuade the individual to initiate a personal exercise training programme that allows confidence to increase that no serious disease is present. Since many of these patients are slightly, or indeed very, obsessional, they may take well to such advice. One of the author's patients responded to the suggestion to go swimming regularly by doing so daily in the sea off Aberdeen throughout a Scottish winter. Fortunately she did not succumb to pneumonia before being advised that the local pool was perfectly adequate.

#### **Sighing breathlessness**

Sighing breathlessness is a minor variant of the hyperventilation syndrome but one seen quite commonly in outpatient clinics [38,39]. The patient complains of the need to take a deep breath or of being unable to get a really good breath. Sometimes sighing can be observed during the consultation, occasionally to the point that one has to stifle a feeling of annoyance that one's best efforts are so boring! The symptom is usually a manifestation of mild anxiety, and reassurance that there is no abnormality of lung function (after appropriate spirometry) is all that is needed. A simple exercise test is of particular value in demonstrating to these patients that all is well with their lungs.

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# DISEASES OF THE MEDIASTINUM

DOUGLAS SEATON

## Anatomy of the mediastinum

The mediastinum comprises those structures situated between the lungs at the centre of the thorax, the word being derived from the Latin *medius* meaning middle and *stare* to stand. It is bounded superiorly by the thoracic inlet, inferiorly by the diaphragm, posteriorly by the thoracic spine, anteriorly by the sternum and laterally by the parietal pleurae. For descriptive purposes anatomists have drawn an imaginary line on the mediastinal map from the fourth dorsal intervertebral disc (the point at which the paravertebral fascia attaches) to the sternal angle of Louis, thereby creating the superior mediastinum. The remaining inferior compartment is subdivided vertically by the heart to give anterior, middle and posterior mediastinal compartments (Fig. 49.1).

A knowledge of the normal contents of the four mediastinal compartments is helpful when considering the possible causes of a radiographic abnormality in the mediastinum or the likely consequences of its enlargement. All compartments contain vessels, lymph nodes, nerves, fat and connective tissue.

1 The superior mediastinum contains the aortic arch, its three large branches, the upper half of the superior vena cava and its two innominate tributaries. It is also traversed by the trachea, the oesophagus, the thoracic duct and the phrenic, vagus, cardiac and left recurrent laryngeal nerves.

2 The anterior mediastinum contains the thymus gland, which also extends into the superior compartment.

3 The posterior mediastinum contains the spinal nerve roots, which lie in the paravertebral gutters, the descending aorta, the oesophagus, the azygos and hemiazygos veins, the thoracic duct, the vagi and the splanchnic nerves.

4 The middle mediastinum contains the heart and pericardium, the ascending aorta, the lower half of the superior vena cava, part of the azygos vein, the pulmonary arteries and veins, the tracheal bifurcation, the phrenic nerves and inferior vena cava.

## Mediastinal tumours and cysts

Predictably, the reported series of mediastinal masses appear in the surgical literature and generally include those tumours and cysts requiring an invasive procedure for diagnosis. For detailed descriptive purposes, many lesions are conventionally omitted from such series although they remain important in the differential diagnosis of a mediastinal lesion. These include the following:

- 1 diaphragmatic lesions, including eventrations and herniae (commonly oesophageal hiatus, occasionally foramina of Morgagni, Bochdalek or post-traumatic), as discussed in Chapter 46;
- 2 oesophageal tumours and megaesophagus due to achalasia of the cardia;
- 3 mediastinal metastases and direct invasion of the mediastinum by tumour from other anatomical areas;
- 4 mediastinal lymph node enlargement as a manifestation of systemic disease, including lymphoma (see Chapter 42) and non-neoplastic granulomatous disease;
- 5 retrosternal extension of a thyroid goitre in the neck, except for a minority that cannot be removed by a cervical approach;
- 6 aneurysms of the aorta and its major branches;
- 7 ventricular aneurysms;
- 8 a minority of rare conditions, including tumours of the trachea and heart, skeletal lesions and paravertebral abscess.

## Incidence

The overall incidence of mediastinal cysts and tumours is not known. A series of 105 patients collected over a 10-year period in Edinburgh resulted in an estimated incidence of 1 per 100 000 per year. These lesions were seen approximately three times more commonly than bronchial adenomas over the same period. Conversely, for every case of primary mediastinal cyst or tumour, 30 cases of bronchial carcinoma and seven cases of oesophageal carcinoma were seen [1]. North American estimates for

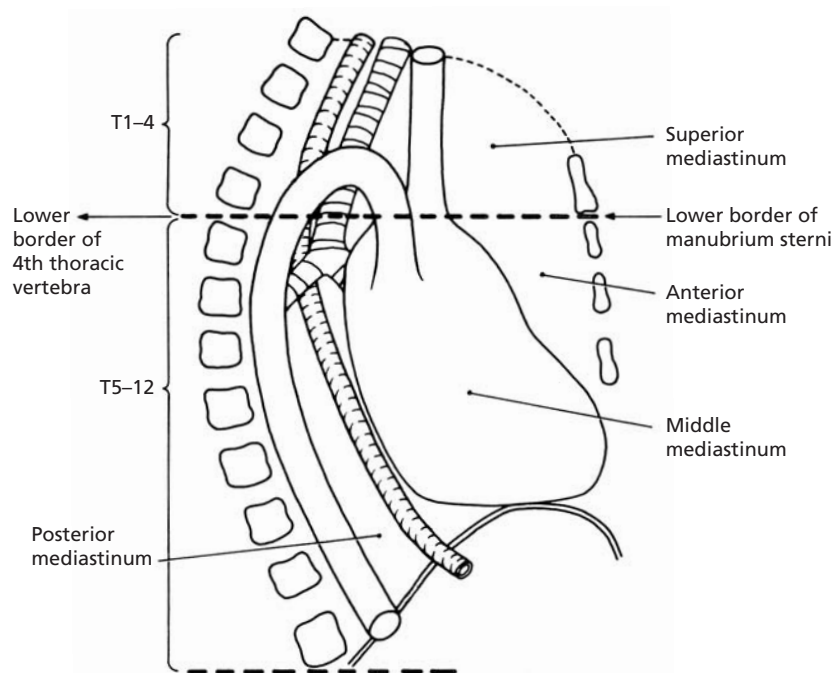


Fig. 49.1 Subdivisions of the mediastinum.

mediastinal lesions have ranged from 1 per 2500 to 1 per 3400 admissions to large medical centres [2,3].

The relative proportion of different mediastinal lesions varies according to individual series and must reflect both local patterns of referral and surgical practice. Four large series containing 974, 251, 209 and 202 cases all found that neural tumours were the most common mediastinal lesion, accounting for 20–27% of cases [4–7]. The two largest series placed thymic lesions a close second (19 and 26% respectively), with developmental cysts a close third (18 and 21% respectively) [4,5]. Thus for practical purposes, neural tumours, thymic lesions and developmental cysts can each be regarded as having a similar incidence of about 20%.

If the foregoing three groups of tumours vie for first place, then mediastinal teratomas and lymphomas compete for fourth. One series did not include cases of extrathymic mediastinal lymphoma (regarded as a mediastinal manifestation of a systemic disease) [5], but those that included this pathological group found that it accounted for approximately 12% of cases compared with about 11% for teratomas and other germ-cell tumours [4–7].

Neural tumours, thymic lesions, developmental cysts, teratomas/germ-cell tumours and lymphoma together account for approximately 88% of primary mediastinal masses, those lesions that remain being rare (Table 49.1). These frequencies are in broad agreement with the earlier calculations of Silverman and Sabiston [8].

The relative frequencies of primary mediastinal lesions differ in children in that neural tumours are more common, accounting for 40% of the total compared with

20% in adults. Conversely, thymic cysts and tumours, which make up 20% of adult lesions, are extremely rare in childhood. Most series place lymphoma as the second most common mediastinal lesion in children (20%), with teratomas and developmental cysts accounting for about 10–15%.

### Clinical features

About one-third to half of patients in whom mediastinal cysts or tumours are found are asymptomatic at the time of diagnosis [2,5,8–10]. These figures also apply to children [8,11]. If the practice of performing routine chest radiographs on apparently healthy subjects were to become more widespread, then this proportion would increase. This is illustrated by one series in which 72% of military personnel found to have mediastinal tumours on routine radiographic screening were symptom-free [12].

The absence of symptoms at the time of diagnosis is a good prognostic sign as about 90% of these patients have a benign lesion [1,10,12], whereas in patients who are symptomatic about half have benign and half malignant lesions. It follows that although malignant lesions are more likely to produce symptoms than benign ones, the presence of symptoms need not imply malignancy.

The symptoms most frequently encountered are cough, breathlessness and chest pain [1,2,8–10,13]. These are usually a consequence of compression or invasion of mediastinal structures. Malaise, anorexia, weight loss, weakness and fever may occur as the non-specific features of any malignant process. When cough is present it is often recurrent and the patient may receive repeated courses of

**Table 49.1** Classification of principal mediastinal tumours and cysts (see text).

<i>Neural</i>
Nerve sheath tumours
Schwannoma*
Neurofibroma*
Malignant peripheral nerve sheath tumour**
Autonomic nervous system tumours
Ganglioneuroma
Ganglioneuroblastoma**
Neuroblastoma†
Paraganglioma†
Aorticopulmonary*
Aorticosympathetic*
<i>Thymic</i>
Thymic hyperplasia
Thymoma†
Thymic cyst
<i>Thyroid</i>
Retrosternal goitre
<i>Germ-cell tumours</i>
Benign
Mature cystic teratoma*
Malignant
Seminoma**
Non-seminomatous
Teratocarcinoma**
Choriocarcinoma**
Endodermal sinus tumour**
Embryonal carcinoma†
Mixed varieties†
<i>Lymphoma†</i>
<i>Foregut duplications or cysts*</i>
Bronchogenic*
Gastroenteric*
Neurenteric
<i>Pleuropericardial cyst*</i>

\*Synonymous terms indicated in the text.

† Malignant neoplasm.

Note: other lesions, many of them rare, are discussed in the text.

antibiotic for supposed respiratory tract infection before referral to hospital. Haemoptysis may occur and sometimes the contents of a ruptured cyst are expectorated. Dyspnoea may be associated with wheeze and may lead to inappropriate treatment for asthma. Proximal airway compression is usually accompanied by stridor, which need not always imply a neoplastic cause [14]. Chest pain may be caused by either thoracic wall invasion or intercostal neuralgia and need not indicate inoperability.

Oesophageal compression results in dysphagia, while compression of the superior vena cava causes neck vein engorgement and facial swelling, a syndrome more often associated with malignancy than not. Mechanical traction

**Table 49.2** Some systemic and endocrine syndromes associated with mediastinal tumours (see text).

Syndrome	Tumour
Myasthenia gravis	Thymoma; thymic hyperplasia
Gynaecomastia, Klinefelter's syndrome	Non-seminomatous germ-cell tumour
Hyperparathyroidism	Parathyroid adenoma
von Recklinghausen's disease	Neurofibromas
Diarrhoea, sweating, tachycardia, headache, hypertension	Functioning autonomic nervous system tumours
Spinal cord compression	Neural (dumb-bell) tumours
Hypoglycaemia	Sarcomas, benign teratomas
Hypogammaglobulinaemia, hypoplastic bone marrow, connective tissue diseases, Whipple's disease	Thymoma
Haematological malignancies	Thymoma, non-seminomatous germ-cell tumours
Malaise, weight loss, pyrexia	Lymphomas, sarcomas, any malignant tumour
Cushing's syndrome	Thymic carcinoid tumour
Multiple endocrine neoplasia syndromes	Parathyroid adenomas

or compression produces neurological impairment less frequently, but may result in hoarseness due to left recurrent laryngeal nerve palsy, hemidiaphragmatic elevation due to phrenic nerve palsy, or incomplete ptosis and a constricted pupil due to involvement of the upper thoracic sympathetic nerves. Spinal cord compression may result from the dumb-bell type of neural tumour (see Fig. 49.3c, p. 1275). Anterior or middle mediastinal tumours may rarely result in pericarditis and cardiac tamponade or heart failure due to obstruction of the right ventricular outflow tract [10]. Pleural effusion is occasionally present and may be chylous because of involvement of the thoracic duct or as a consequence of lymphangiomias [15,16].

In infants and small children compression of the upper airways, superior vena cava and oesophagus may develop with great rapidity as a result of the rapid expansion of a foregut cyst or other lesion in the close confinement of the superior mediastinum. In adults a similar life-threatening situation may rarely arise from the sudden expansion of a retrosternal goitre as a result of haemorrhage into its substance.

Apart from symptoms and signs arising as a result of the compression or invasion of adjacent mediastinal structures, there are several systemic or endocrine syndromes associated with mediastinal tumours. These are listed in Table 49.2 and discussed individually under the appropriate

ate pathological headings that follow. All of them are rare, with the exception of myasthenia gravis occurring in association with thymic lesions.

### Mediastinal neural tumours

Mediastinal neural tumours (Table 49.3) are usually but not exclusively found in the posterior mediastinum in both adults and children and comprise the largest single group of tumours in this compartment. They account for about 20% of mediastinal lesions in adults [17]. Over three-quarters of neural tumours in adults are benign, whereas about half are malignant in children [18]. The terminology surrounding these tumours may confuse as the literature is stiff with synonyms. The embryogenesis of the cell types from which neural tumours are derived is a controversial field. However, it has been claimed that during the folding of the primitive dorsal neural plate, certain ectodermal cells separate from it and migrate so that they come to lie apart from the developing neural tube in the embryo. These have been called neural crest cells and it is supposed that they subsequently differentiate via primitive blast cells into different types of mature neural cell, including peripheral nerve cells (or neurocytes) and peripheral nerve sheath (or Schwann) cells.

Peripheral nerve cells (neurocytes) are those from which sympathetic ganglia, including the spinal sympathetic ganglia, are formed. It is from these cells or from more primitive neuroblasts that mediastinal nerve cell, neurocytic or autonomic tumours develop. Benign mediastinal

neurocytic tumours arising from the sympathetic ganglia in the thorax are called ganglioneuromas. The malignant counterparts of these tumours are ganglioneuroblastomas, in which histological ganglionic differentiation remains strong, and the more aggressive neuroblastomas, which are in fact undifferentiated ganglioneuroblastomas in which ganglion cells are no longer an easily recognizable feature. Some earlier authors referred to neuroblastomas as sympatheticoblastomas [19], while others regarded this as a histological subtype [10]. All tumours belonging to this group may produce catecholamines and they are more common in children.

Mediastinal paragangliomas are very rare neurogenic tumours that arise, as the name implies, from the paraganglia, the cellular precursors of which are likely to have migrated from the embryonic neural crest to their final destination juxtaposed to the ganglia of the autonomic nervous system. They are found in the posterior mediastinum in the costovertebral sulcus and also in the region of the aortic arch. These tumours, which tend to occur in adults, may also be hormonally active, producing catecholamines. Hormonally inactive paragangliomas of the chemoreceptor system have been called chemodectomas, while those near the aortic arch have been called aortic body tumours. Hormonally active mediastinal paragangliomas have previously been classified as phaeochromocytomas because they may be morphologically indistinguishable from the adrenal paraganglioma of that name. Indeed all these mediastinal tumours are paragangliomas, so it is best to drop the terms 'chemodectoma' and 'aortic body tumour' and reserve the term 'phaeochromocytoma' for paragangliomas occurring in the adrenal medulla. The anatomical site of mediastinal paragangliomas can be described as aorticopulmonary for those found in the region of the aortic arch and aortic sympathetic for those found in the costovertebral sulcus of the posterior mediastinum [20]. It used to be thought that the presence or absence of chromaffin substance in paragangliomas correlated closely with hormonal activity, those that were chromaffin-positive being active (e.g. phaeochromocytoma) and those that were chromaffin-negative being inactive. However, it is now appreciated that the chromaffin reaction may be capricious [20] and that some chromaffin-negative paragangliomas may be hormonally active [21] and vice versa [22,23]; thus paragangliomas should be described as 'hormonally active/functioning' or 'hormonally inactive/non-functioning', without attaching complete reliance to their chromaffin status.

Nerve sheath cells give rise to both the Schwann cells and the perineural and endoneural fibrous tissue. Schwannomas (syn. neurilemmoma) are tumours that arise from Schwann cells, previously known as lemmocytes. It was thought that neurofibromas arose from perineural or endoneural fibrous tissue but it now appears

**Table 49.3** Mediastinal neural tumours (see text).

Currently favoured term	Synonyms
Benign peripheral nerve sheath tumours	
Schwannoma*	Neurilemmoma
Neurofibroma*	
Malignant peripheral nerve sheath tumour	Neurosarcoma, neurofibrosarcoma, neurogenic sarcoma, malignant schwannoma, malignant neurinoma
Granular cell tumour	Granular cell myoblastoma
Autonomic nervous system tumours	Nerve cell or neurocytic tumours
Ganglioneuroma*	
Ganglioneuroblastoma	
Neuroblastoma	Sympatheticoblastoma,
Paraganglioma	
Aorticopulmonary	Chemodectoma
Aortic sympathetic	aortic body tumour
	Mediastinal
	phaeochromocytoma, chromaffinoma

\* Benign neoplasm.

that they too arise predominantly from Schwann cells, although they contain all elements of the nerve. The fact that both these neoplasms may occur in the same patient and sometimes even within the same tumour mass lends further credence to a common cell of origin. Both schwannomas and neurofibromas were referred to collectively in the older literature as neurofibromas. They may be regarded as benign although neurofibromas and rarely schwannomas have potential for undergoing change to their malignant counterpart, the malignant peripheral nerve sheath tumour (MPNST). Earlier authorities used the terms 'malignant neurilemmoma' or 'malignant schwannoma' synonymously with MPNST [24]. A third and extremely rare type of nerve sheath tumour thought to be derived from either Schwann cells or their precursors is the granular cell tumour, originally thought to be of muscle cell origin and called granular cell myoblastoma [25,26].

### Peripheral nerve sheath tumours

There are three major neoplasms in this category, the benign schwannoma and neurofibroma and MPNST.

#### Benign: schwannoma and neurofibroma

##### *Relative frequency and pathological features*

In adult series, benign nerve sheath tumours constitute the largest single group of neural neoplasms in the mediastinum [4,5], although in children they are much less common than autonomic nervous system (syn. nerve cell or neurocytic) tumours [11]. Several authors have reported that neurofibroma is the more common tumour [2,5,13,27–29]. However, the majority of workers find that schwannoma is by far the most common and review of 10 different series reporting 398 cases of these two tumour types finds that 70% of them were schwannomas [2,4,6,9,13,27,28,30–32]. Histologically mixed forms have been reported in which the pattern varies between sections in the same tumour [28] and this may account for some differences in histopathological reporting. Most neural tissue in the mediastinum is situated posteriorly in the paravertebral gutters and for this reason benign nerve sheath tumours in common with other neurogenic tumours are often found in this location, although they may also arise from other intrathoracic nerves.

Schwannomas are rounded tumours that are well encapsulated and easily removed surgically [28]. They arise from the lateral aspect of their parent nerve, which is usually spinal although occasionally the sympathetic chain or rarely the vagus, phrenic or recurrent laryngeal nerves may be involved [32–34]. They have an organized architecture that may assume a pallisaded or reticular pattern of growth, referred to as Antoni types A and B respectively

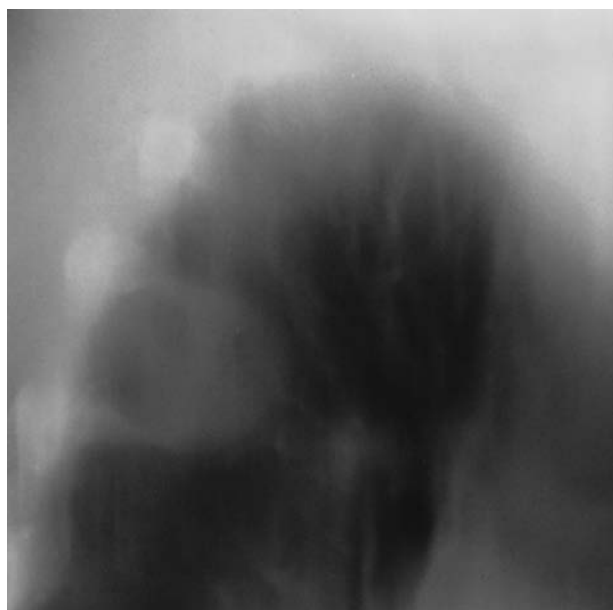
[8,35]. Neurofibromas are also nearly always rounded with a similar gross appearance and although usually unencapsulated are generally easily removed [28]. They tend to expand from within the parent nerve, which is usually spinal [31], and present a different histological picture of a less orderly arrangement of tangled and reticular fibrous tissue in which all elements of the nerve trunk may be represented [9]. Both benign nerve sheath tumours enlarge slowly [32,36]; during this process cellular degenerative changes may occur in schwannomas but not neurofibromas [6]. Neurofibromas may be multiple and rarely take on a plexiform configuration in which the tumour assumes a serpentine shape, insinuating itself around the various mediastinal structures so that complete excision may be impossible [5,28,36]. In such cases, the patient is likely to have von Recklinghausen's disease (neurofibromatosis) type 1, and plexiform neurofibromatous proliferation in a limb or elsewhere may produce massive enlargement (elephantiasis neuromatosa). The reported frequency of type 1 (or peripheral) von Recklinghausen's disease in patients from whom neurofibromas are resected varies widely between series but approaches 30% on average [4,6,28,30,31]. Patients with this type of neurofibromatosis, which is inherited as an autosomal dominant, may have neurofibromas at every conceivable site, usually presenting with cutaneous lumps and multiple *café-au-lait* spots plus the common finding of a thoracolumbar scoliosis. Such patients may also have some schwannomas.

##### *Clinical features*

Schwannoma and neurofibroma are approximately equally distributed between the sexes. They may both occur at any age but are usually diagnosed between the ages of 30 and 60 years [4,32,36]. The majority are asymptomatic and are discovered following a routine chest radiograph (Fig. 49.2). When symptoms do occur they fall into the general pattern produced by any benign lesion that occupies space in the mediastinum (see above). Spinal cord compression as a result of a dumb-bell or hourglass tumour straddling the intervertebral foramen is a rare but well-recognized complication of both schwannomas and neurofibromas. Segmental pain may be caused by spinal nerve involvement. The radiographic appearances are of a solitary, sharply defined, rounded mass, usually occupying a paravertebral sulcus (Fig. 49.3a,b). The ribs may sometimes be splayed by lesions of sufficient size and the adjacent intervertebral foramen may be enlarged, particularly in the case of a dumb-bell tumour, the presence of which may be confirmed by spinal magnetic resonance imaging (MRI) (Fig. 49.3c). Posterior mediastinal opacities in patients with von Recklinghausen's disease are very occasionally caused by an intrathoracic meningocele, which may easily be mistaken for a neurofibroma on a chest radiograph. In this case the dura may herniate



through an intervertebral foramen, the meningeal sac coming to lie in the paravertebral gutter. Associated scalloping of the posterior margins of two or three adjacent vertebral bodies with splaying of the overlying ribs are characteristic findings, as is widening of the corresponding intervertebral foramen. The nature of this problem may be shown by MRI. If intervention is required, the sac may be excised and its neck closed at thoracotomy [37].

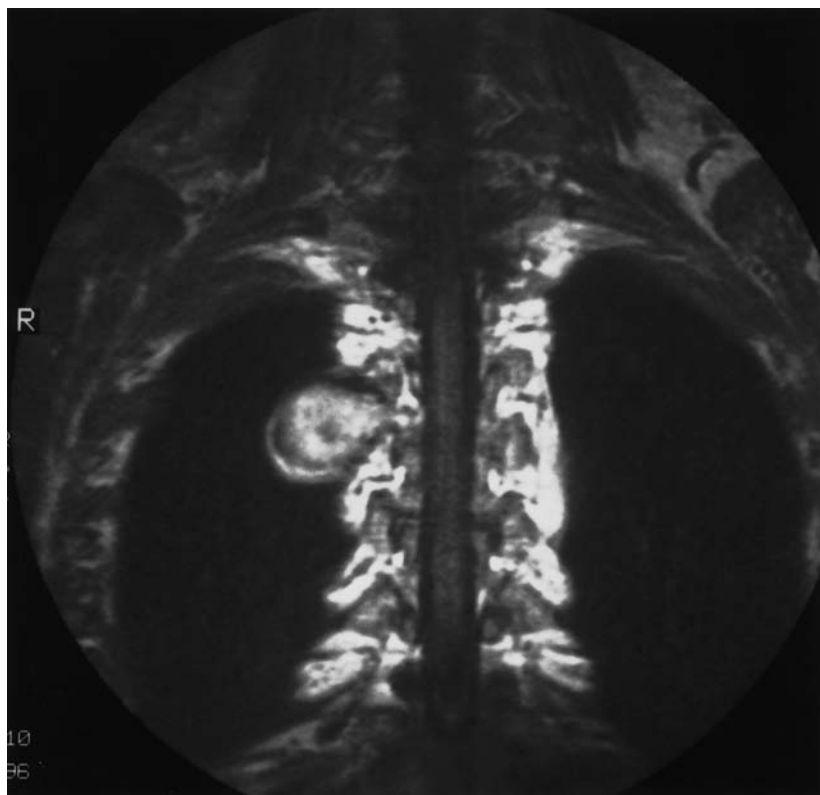


(a)

Both schwannomas and neurofibromas may very rarely occur intratracheally, in which case they may be treated by either endoscopic or laser resection [38,39]. Two cases of mediastinal schwannoma apparently occurring in association with nephrotic syndrome have been described in the literature [40]. Sudden, presumed dysrhythmic death has been reported in a young man with type 1 von Recklinghausen's disease, who was found at postmortem to have a massive neurofibroma involving the vagus nerve [33]. Uncomplicated benign neural tumours in the posterior mediastinum are conventionally removed by posterolateral thoracotomy, although more recently 'three-hole' thoracoscopic removal has been used. The latter procedure takes longer and may be difficult with large tumours but patients tend to have a shorter hospital stay and may return to work sooner [41]. Dumb-bell tumours are dealt with by a joint neurosurgical and thoracic approach (see below).

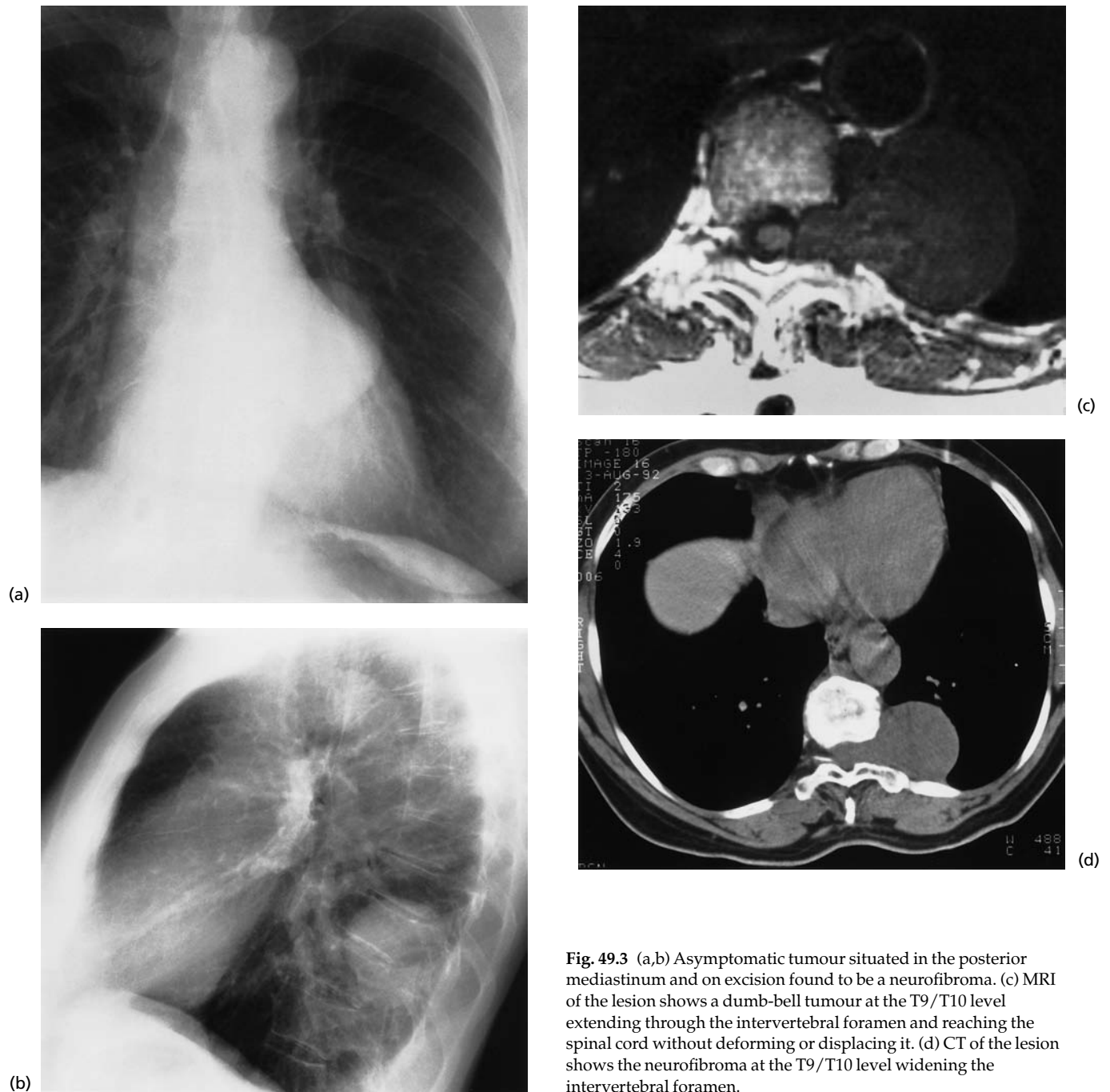
#### Malignant: MPNST

Although MPNST is now the usual term, there are the inevitable synonyms including neurosarcoma, neurofibrosarcoma, neurogenic sarcoma, malignant schwannoma and malignant neurinoma. About half of all cases are thought to occur *de novo*, the remainder developing in a neurofibroma or rarely in a schwannoma. They are more



(b)

**Fig. 49.2** (a) Asymptomatic right upper mediastinal tumour that on excision proved to be a neurofibroma. (b) MRI of the neurofibroma showing no evidence of spinal cord compression or displacement.



**Fig. 49.3** (a,b) Asymptomatic tumour situated in the posterior mediastinum and on excision found to be a neurofibroma. (c) MRI of the lesion shows a dumb-bell tumour at the T9/T10 level extending through the intervertebral foramen and reaching the spinal cord without deforming or displacing it. (d) CT of the lesion shows the neurofibroma at the T9/T10 level widening the intervertebral foramen.

likely to occur in patients with type 1 von Recklinghausen's disease and it has been estimated that 10–15% of these individuals harbour tumours that undergo malignant transformation. When this transformation occurs in this group of patients, the site is usually a large nerve trunk in the neck or an extremity, whereas mediastinal or superficial neurofibromas in the periphery rarely become malignant [5,29,42]. MPNST is rare at any age and in nine combined series containing about 400 nerve sheath tumours accounted for 5% [2,6,9,13,27,28,30–32]. In a

small paediatric series of eight nerve sheath tumours only one was an MPNST [11]. As with other neurogenic tumours, the majority are situated in the posterior mediastinum. In addition to the usual symptoms of space occupation in the mediastinum (see p. 1270), MPNST may also produce the general systemic and metastatic features of any malignancy. Nausea and vomiting have been recorded in nerve sheath tumours of the vagus [34,43], and as with other sarcomatous tumours hypoglycaemia may occur. There may be extrathoracic evidence of

neurofibromatosis, such as cutaneous *café-au-lait* patches. The prognosis with MPNST is poor because of its tendency to both invade locally and metastasize.

Some MPNSTs of the mediastinum display metaplastic changes and those that contain well-developed skeletal muscle are sometimes referred to as malignant triton tumours [44].

### Autonomic nervous system tumours

These arise from autonomic nerve cells, principally the ganglia of the sympathetic chain. They span a spectrum of gradual histopathological change, from the benign ganglioneuroma to the highly malignant neuroblastoma, with ganglioneuroblastoma occupying an intermediate histopathological stage. These mediastinal sympathetic nervous system tumours tend to show greater differentiation than their retroperitoneal counterparts and as a group carry a better prognosis. The benign lesions tend to be seen in older children and adolescents, whereas the malignant lesions tend to occur in younger children. Paragangliomas, as the name suggests, arise from autonomic paraganglionic tissue.

### Ganglioneuroma

This is the most common of the three mediastinal sympathetic tumours in both adults and older children but occurs in a younger age group than nerve sheath tumours, most patients being less than 20 years of age [4]. Ganglioneuromas may be found on a chest radiograph taken for some other reason and are usually large before they cause symptoms. They contain nerve fibres and varying numbers of large mature ganglion cells. They are nearly all situated in the posterior mediastinum and in common with other neural tumours occasionally straddle the intervertebral foramen in dumb-bell fashion (see p. 1278), having similar radiographic features to the nerve sheath tumours described above (see Figs 49.2 & 49.3). Their sex incidence is equal and they are benign, encapsulated and slow-growing, lending themselves to curative surgical removal, which is indicated both for diagnostic purposes and because they may have malignant potential [2]. Although von Recklinghausen's disease is typified by the presence of neurofibromas, ganglioneuromas, like schwannomas, may also occasionally occur in this condition [2]. As with all autonomic nervous system tumours, ganglioneuromas may be metabolically active, producing catecholamines, although these hormones are less likely to produce symptoms than is the case with neuroblastoma.

Treatment is by surgical removal. Uncomplicated benign neural tumours in the posterior mediastinum are conventionally removed by posterolateral thoracotomy, although more recently 'three-hole' thoroscopic removal has been used. The latter procedure takes longer

and may be difficult with large tumours but patients tend to have a shorter hospital stay and may return to work sooner [41].

### Ganglioneuroblastoma

Mediastinal ganglioneuroblastomas are rare tumours in adults. A review of 80 cases found that 50% occurred in the first 3 years of life, while only three were found in patients aged over 20 years [45]. Their sex incidence is equal. As with neuroblastoma, the overall majority occur primarily in the adrenal medulla. Half of all mediastinal cases are diagnosed following a routine chest radiograph and the most common symptoms in the remainder are respiratory. They show histological features intermediate between ganglioneuroma and neuroblastoma, being characterized by ganglion cells with immature forms in a background of differentiating neuroblasts. Their intermediate position may result in some being classified as 'malignant ganglioneuromas' or 'differentiating neuroblastomas'. The vast majority of those occurring in the thorax arise posteriorly from the sympathetic chain. Insinuation into the intervertebral foramina in dumb-bell fashion has been described as with other neurogenic tumours (see Fig. 49.3c). They are often large pear-shaped or lobulated tumours and although the majority are encapsulated they must be regarded as malignant, with a propensity to invade locally more often than spreading by metastasis. Despite this, cure by excision is often possible and this approach, combined in some cases with radiotherapy, has achieved a 5-year survival rate of almost 90% [36]. The outlook is therefore much better than for its more malignant cousin the neuroblastoma, ganglioneuroblastoma being similar in its clinical behaviour to ganglioneuroma. Diagnosis at a young age (<3 years), a localized situation and a high degree of histological differentiation are all good predictive factors. The prognosis of mediastinal ganglioneuroblastoma is better than for abdominal forms, and if bony metastases are found a primary adrenal sympathetic tumour should be suspected.

The tumour is biochemically active in about 10% of cases, producing catecholamines whose metabolites, vanillylmandelic acid, homovanillic acid or cystathionine, may be detected in the urine. These findings may be helpful in a diagnostic sense and are also useful tumour markers, a failure of the levels to fall or a subsequent rise indicating persistent or recurrent tumour. Biochemical activity may account for the symptom of chronic diarrhoea that occurs in some cases.

### Neuroblastoma

Neuroblastomas are the third most common tumour in children after acute leukaemia and intracranial neoplasms [46]. They occur only rarely in adults, 50% presenting

within the first 2 years of life [47,48]. The sex incidence is equal [48]. Most neuroblastomas are retroperitoneal, usually occurring in the adrenal medulla, although 20% are found in the thorax and nearly all of these arise in the posterior mediastinum from sympathetic neural cells. This malignant autonomic tumour tends to be less well radiographically defined than its more benign counterparts, although in other respects its appearance is similar. In contrast with the preceding two members of this group, patients are usually unwell with anorexia, fever and cough. They occasionally display symptoms such as flushing, sweating, tachycardia, hypertension and diarrhoea that result from catecholamine synthesis, as may occur less frequently with the other members of this group of tumours [11,49]. Spinal cord compression due to dumb-bell forms may occur in common with other neural tumours and paraplegia may result [11]. Horner's syndrome, dyspnoea and dysphagia may also occur [17].

Histology shows small round immature cells that may be arranged in rosettes and there may be a variable degree of differentiation within the same neoplasm [8,48]. These tumours are highly malignant and form fleshy masses with ill-defined margins that may attain a large size. They are both locally invasive and prone to metastasize but are notable for their infrequent but well-documented propensity either to regress spontaneously or to mature into benign ganglioneuroma forms [50]. Tumour regression may even occur in the presence of metastases and probably accounts for some 'cures' [51–54]. This behaviour may be due to a phenomenon known as immunological coercion [55].

In those rare cases that occur in adulthood, the natural history of neuroblastomas is rapid in comparison with other malignancies so that survival for 2 years after diagnosis and treatment is an accepted definition of cure, provided there is no evidence of persistent or recurrent disease at that point [48]. Treatment is by surgery, to remove the tumour if possible (if not, to relieve pressure symptoms by debulking) and to obtain histological confirmation [48,56]. Radiotherapy and chemotherapy may provide additional benefit [57]. The main prognostic determinant is the age of the patient at diagnosis; a cure rate of 87% in patients aged under 2 years compared with 34% for those aged 2–12 years has been reported [48]. Localized disease carries a better prognosis, although cures may be achieved with metastatic disease provided there is no radiographic evidence of bony destruction.

### Paraganglioma

These tumours are very rare, accounting for 1–5% of neural tumours in the mediastinum [4,30,31]. They arise from autonomic paraganglionic tissue in two principal sites.

1 Most arise in the chemoreceptor tissue around the aortic

arch and pulmonary artery, which gives rise to so-called aorticopulmonary paragangliomas. These are the mediastinal counterpart of the carotid body and glomus jugulare tumour. Generally, they are hormonally non-functioning and chromaffin-negative, and in the literature are also referred to as chemodectomas, non-functional non-chromaffin paragangliomas and aortic body tumours [58]. They tend to occur in young adults with an equal sex distribution.

2 The second important site is close to the ganglia of the sympathetic chains in the paravertebral gutters, in which case they are referred to as aorticosympathetic paragangliomas [59]. These tend to be hormonally functioning and chromaffin-positive, producing catecholamines in about 50% of cases. They are sometimes referred to in the literature as chromaffinomas, functional chromaffin paragangliomas or mediastinal phaeochromocytomas, although it is now usual to reserve the term 'phaeochromocytoma' for the corresponding paraganglioma arising in the adrenal medulla [58,60].

There are a few reports of both functioning and non-functioning paragangliomas arising in relation to the heart, presumably from the cardiac plexus [61–63]. They may also very rarely occur as a primary intratracheal tumour [64]. The heart and great vessels may both be invaded and obstruction of the superior vena cava has been described [65].

Mediastinal paragangliomas have been recorded in both adults and children and in both sexes, the aorticosympathetic paraganglioma being more common in males, usually occurring in the third to fifth decades [29,66,67].

Paragangliomas are usually encapsulated, yellowish in colour and haemorrhagic; multiple tumours have been described [22,68]. Paragangliomas are highly vascular and the cellular characteristics of those occurring in the usual mediastinal sites are similar [8,22]; furthermore, the usual histological criteria for determining malignant potential cannot be readily applied to them [8,10,31] since they may recur locally or metastasize despite a benign appearance [69].

Aorticopulmonary paragangliomas rarely metastasize but tend to cause significant morbidity and mortality as a result of local spread and recurrence despite the fact that they grow only slowly [8,60]. Although they are traditionally regarded as chromaffin-negative and hormonally inactive, evidence exists to show that they may produce catecholamines in about 3% of cases [21,70].

Aorticosympathetic paragangliomas are usually hormonally active and account for about 2% of catecholamine-producing tumours, the vast majority of which are intra-abdominal, about 80% arising in the adrenal medulla [66]. Very few of these mediastinal tumours are malignant as evidenced by distant metastases [8,10,71]. They may present with episodic hypertension,

palpitations, sweating and headache, or they may not produce catecholamines in sufficient quantities to produce symptoms and are discovered as a posterior mediastinal opacity on a routine radiograph. Any suspicion that hypertension is secondary to a catecholamine-producing tumour can be substantiated by assay of blood or urine for catecholamines or their metabolites (vanillylmandelic acid, homovanillic acid or cystathionine) and by performing a phentolamine test if these other tests are equivocal [21,72]. Localization of the tumour first involves abdominal CT to exclude a primary adrenal site followed by a combination of thoracic CT and radioactive isotope scanning using a labelled norepinephrine (noradrenaline) analogue, such as <sup>131</sup>I-metaiodobenzylguanidine [66]. Thoracic aortography has also been found useful in localizing mediastinal paragangliomas because of their vascularity [36,73].

The treatment for paragangliomas is surgical and they are relatively radioresistant. Less than half of those in the aorticopulmonary area can be completely resected because of their close association with great vessels; thus they are ultimately fatal, although prolonged survival is still possible as these tumours are usually slow-growing [4,18]. The assay of catecholamine metabolites may prove a useful monitor of disease activity postoperatively in functioning tumours [71].

### Clinical problem of dumb-bell tumours

As implied above, the term 'dumb-bell' refers to the shape of neural tumours of various histological types, about 10% of which may straddle an intravertebral foramen and have both intrathoracic and intraspinal components (see Fig. 49.3c) [74]. These tumours are usually but not invariably of nerve sheath origin and are also sometimes referred to as hourglass tumours. They are important to recognize since their removal may be beyond the competence of either a thoracic surgeon or a neurosurgeon alone, the expertise of both being necessary. These tumours should be suspected preoperatively if any long tract signs are present or if the radiographs show either a widened intervertebral foramen or erosion of vertebral pedicles or lamellae. The lesions may be well shown by CT (see Fig. 49.3d), although MRI produces better images with regard to spinal cord displacement. Spinal aortography to identify the artery of Adamkiewicz (which arises from a posterior intercostal artery to supply the inferior portion of the anterior spinal artery) is recommended if the tumour is situated in the lower thoracic region in order that this vessel is not compromised during surgery.

There are considerable advantages in removing the tumour at a single combined neurosurgical/thoracic operation, with a posterior hemilaminectomy to free tumour within the spinal canal and a posterolateral thoracotomy [30,74–76]. This reduces the possibility of cord

damage caused by undue traction at the intervertebral foramen or of uncontrolled haemorrhage in the same area.

### Other mediastinal tumours of possible neural progenitor cell origin

Some migrating neural crest progenitor cells may differentiate into so-called APUD cells capable of *amine precursor uptake and decarboxylation*; tumours that may have arisen from APUD cells have been functionally grouped as APUDomas or neuroendocrine tumours. These include carcinoid tumours (of both 'typical' and 'atypical' histological types), small-cell carcinomas and large-cell neuroendocrine carcinomas. These tumours are found in the lung, where large-cell neuroendocrine carcinoma is often classified as large-cell undifferentiated carcinoma. Carcinoids may occur as primary thymic tumours, as may small-cell carcinoma, although it may be difficult to exclude spread from the lung in the latter case. Atypical carcinoid tumours are more aggressive and may themselves be mistaken for small-cell carcinoma on small biopsies due to sampling error. The capacity for these precursor cells to be chemically active accounts for the propensity of some APUDomas to be hormonally active. Melanocytes are also thought to originate from the neural crest. However, the malignant melanomas that arise from these cells are nearly always cutaneous. Although primary visceral melanomas may occur, they have not been described in the mediastinum other than in the oesophagus [77], those melanomas found in the vicinity of the mediastinum being secondary; two-thirds of patients dying of disseminated melanoma are found to have cardiac metastases [77,78].

### Disorders of the thymus

Thymic lesions comprise the largest group of anterior mediastinal masses [2,4,36] (Table 49.4). The thymus gland is a lymphoreticular organ that develops as a pair of solid buds arising predominantly from the third branchial pouch at about the sixth week of embryonic life. It migrates caudally during intrauterine development to lie

**Table 49.4** Disorders of the thymus.

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Thymic hyperplasia
Thymic cysts
Thymoma
Thymic carcinoma
Thymic carcinoid tumour
Thymolipoma
Germ-cell tumours
Ectopic parathyroid adenomas
Lymphoma
Secondary neoplastic disease

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retrosterally in the upper part of the anterior mediastinum. Sometimes this migration is incomplete or bizarre so that it occupies a cervical or some other ectopic site [79]. The thymus has two lobes bound together by fatty tissue and contained in a capsule of loose connective tissue, from which septa arise dividing the gland into lobules. Each lobule has a cortex packed with small lymphocytes and a medulla comprising reticular cells and Hassall's corpuscles, which are zones of squamous cells surrounded by epithelial cells.

In infancy, the thymus gland is large relative to the size of the mediastinum, weighing perhaps 15 g. It doubles in size by puberty and thereafter gradually involutes, returning to its original infantile weight.

### Thymic hyperplasia

It is difficult to decide whether a thymus gland that appears to be enlarged on a chest radiograph in early childhood represents one extreme of a wide range of normal variation or whether it contains tumour (Fig. 49.4). In a number of cases coming to surgery with a preoperative diagnosis of thymoma no tumour is present but the gland is grossly hyperplastic and these patients are nearly always infants or small children [4,80]. Thymic hyperplasia may also sometimes occur in adults after successful treatment of malignant disease elsewhere with chemotherapy [81].

The histological criterion of lymphoid follicular hyperplasia of the thymus is the presence of germinal centres in the medulla [5,82]. This may occur without the gland increasing in size, whereas for true thymic hyperplasia to be present the gland itself must increase beyond the upper limits of normal for age. Thymic hyperplasia is not usually

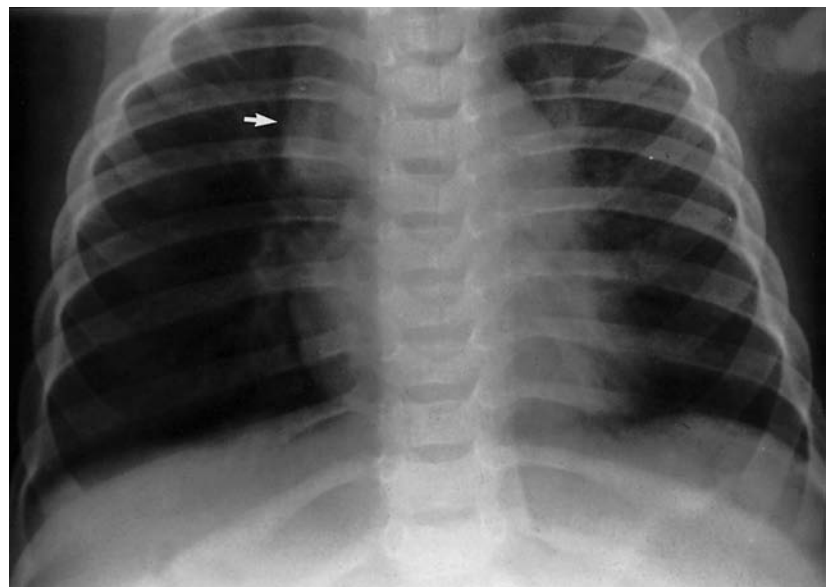
associated with symptoms [11] but when symptoms do occur they are seen in small children and are nearly always respiratory [5,6]. The thymus may involute in childhood during any form of stress, including illness and injury, and upon recovery the phenomenon of 'rebound hyperplasia' may occur with resultant pressure symptoms [83]. Thymic involution has also been noted to be pronounced in human immunodeficiency virus infection [84]. Both thymic hyperplasia and thymoma may occur in patients with myasthenia gravis, the former accounting for 50% of thymic abnormalities found after thymectomy in one series of 10 myasthenics [85]. Thymic hyperplasia may also occur in other autoimmune disorders, such as systemic lupus erythematosus and thyrotoxicosis [80]. Thymic hyperplasia cannot normally be differentiated from an intrinsic thymic tumour by radiography, including CT [86].

When an enlarged thymus is found in infancy, steroids have been given as a diagnostic test since they may reduce the size of the hyperplastic gland. Lymphoma, which might also regress with the same therapy, is unusual before the age of 18 months [87]. When surgery has to be undertaken to relieve pressure symptoms, the histological nature of the disorder should be confirmed at operation; resection should be subtotal and confined to that part of the hyperplastic gland causing compression [5].

### Thymoma

#### Pathology

Thymoma is used to refer to tumours of epithelial origin arising in the thymus gland and containing a non-



**Fig. 49.4** Chest film of infant showing normal thymus as a right upper mediastinal mass (arrowed).

neoplastic lymphocytic component, representing functioning thymic tissue. They comprise about 20% of all mediastinal tumours and cysts and are the most common anterior mediastinal tumours [8]. Three principal histological groups were described in early classifications [88–90]: (i) the epithelial type, in which up to 80% of cells are epithelially derived (subgroups of this class are sometimes referred to as spindle cell, oval cell or epidermoid); (ii) the lymphocytic type, in which up to 80% of cells are lymphocytically derived; and (iii) the mixed or lymphoepithelial type, in which neither cell type predominates. However, these cellular characteristics do not appear to influence prognosis and although more recent histological classifications have related aggressiveness to the appearance of the neoplastic epithelial cell component and their numerical predominance over lymphocytes [91], this remains a controversial area. Prognosis appears to be mainly governed by clinical stage. Thymomas in which the capsule is intact, with no gross or microscopic evidence of invasion, tend to behave in a benign fashion and this is the case in two-thirds to three-quarters of cases [92], whereas those with gross or microscopic invasion through the capsule are regarded as malignant. These have a tendency to invade local structures and also to metastasize [93–95]. Clinical staging is therefore important and all thymomas should be regarded as potentially malignant [96–99].

### *Clinical features and diagnosis*

Thymomas may occur at any age but nearly all present in adult life and are rare before the age of 20 years. There is probably a slight overall male predominance [83,85,96]. Symptoms are present at the time of diagnosis in about 60% of patients, chest pain, dyspnoea, dysphagia and other mediastinal pressure effects having been described. There is in addition a large number of associated immune-mediated systemic syndromes, the most common of which is myasthenia gravis [92,100–103]. Pure red cell hypoplasia is unusual, occurring in about 5% of cases of thymoma [104,105]. Hypogammaglobulinaemia may also occur as may a number of other conditions, the majority of which are rare associations [92,106–108] (see Table 49.2).

The usual chest radiographic features are those of an anterosuperior mediastinal mass (Fig. 49.5) and this impression may be confirmed by CT (Fig. 49.6) [86,109]. Thymomas may rarely occur ectopically in the neck or lung or as a pleural tumour [110]. It is impossible to reliably discriminate between thymic tumour and hyperplasia by imaging techniques. Cystic changes may sometimes occur. The diagnosis of thymoma may be confirmed preoperatively by fine-needle biopsy [96], although this is not usually necessary and should be avoided if surgery is to be undertaken in any case as it runs the risk of tumour implantation [111].

### *Treatment*

The treatment of choice is surgical removal of both the tumour and the entire surrounding gland [96,112,113]. Every effort should be made to keep the capsule intact, although this may not be possible with large tumours such as that illustrated in Fig. 49.6. Surgery is by median sternotomy or thoracotomy or by a transcervical approach. Fortunately, most patients present with localized disease and routine postoperative irradiation following surgery for thymomas with an intact capsule does not improve survival, which is already good [113]. Radiotherapy is usually reserved for cases in which excision has been incomplete, and it may be a useful adjunct for these locally invasive thymomas [112,114,115]. In cases where local invasion prevents complete excision, more extensive surgical debulking procedures, as opposed to simple biopsy, appear to confer no advantage in terms of survival when both are followed by radiotherapy [116,117]. When thymoma does behave in malignant fashion it is usually by local invasion, sometimes with pleural seeding, or by local recurrence. Distant metastases, although less common, are well described and may occur as a late phenomenon, so that long-term follow up is advisable [100,118–120]. The role of chemotherapy in the management of invasive or recurrent thymoma is more controversial and has yet to be properly determined. Suffice to say that thymoma is chemosensitive and remissions have been obtained in small series with combinations of cisplatin, doxorubicin, vincristine and cyclophosphamide, sometimes as an adjunct to surgery and/or radiotherapy, although prospective randomized controlled trials are lacking [112,121,122].

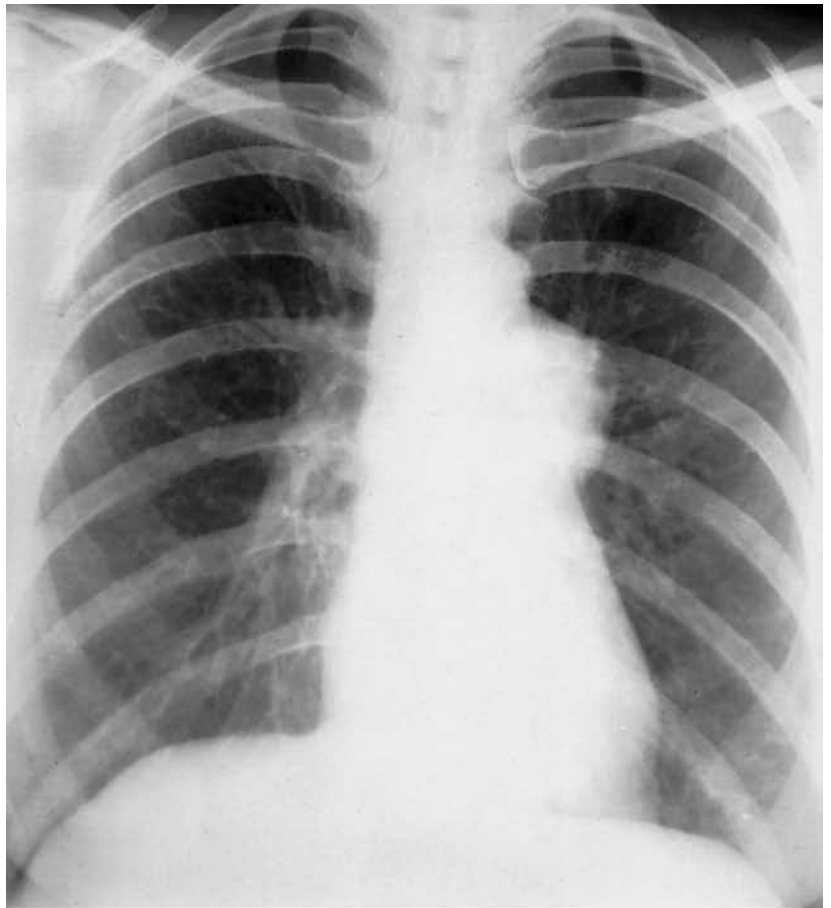
### *Prognosis*

The most important factor contributing to long-term survival is complete surgical resection of tumour with an intact capsule, and when this is achieved the prognosis is excellent. An early large North American surgical series reported the survival rate for patients with non-invasive tumours to be not much dissimilar to that of the general population, whereas more invasive tumours produced a 15-year survival rate of 12.5% [123]. Series where the extent of tumour has been staged report a 5–10-year survival of over 80% for thymomas without evidence of extracapsular invasion, falling to a 10-year survival of 23% where such invasion was evident [124,125].

### **Myasthenia gravis and thymic disease**

Myasthenia gravis is an autoimmune disease, as indicated in nearly all cases by the presence of circulating autoantibodies that bind to acetylcholine receptors in the motor end-plates [126]. It is thought that T lymphocytes



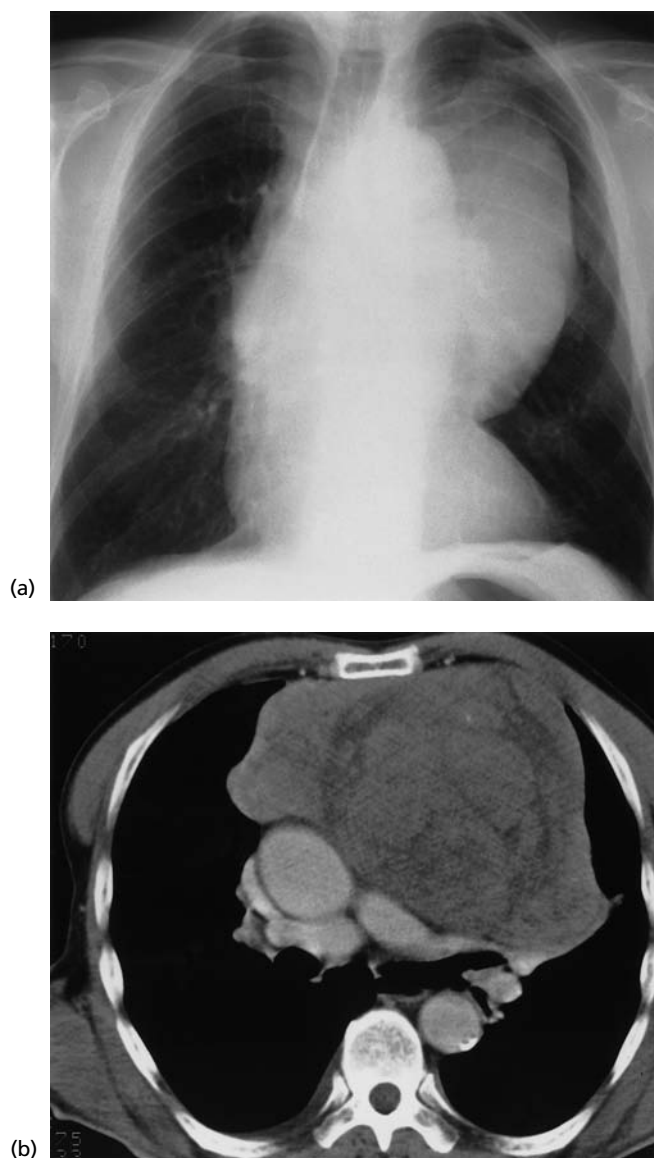


(a)



(b)

**Fig. 49.5** (a) Posteroanterior film showing enlargement over left hilum. (b) Left lateral film showing lesion occupying the anterior mediastinum. On excision it proved to be a thymoma.



**Fig. 49.6** (a,b) A large anterior mediastinal mass that did not enhance with contrast on CT in a 77-year-old man. It was removed at thoracotomy and found to be a thymoma.

elaborated by the thymus interact with B lymphocytes in order to produce these antibodies, which then result in the depletion of functioning acetylcholine receptor sites at the postsynaptic membranes.

An association between myasthenia gravis and thymic tumours was recorded in 1901 [127]. The reported frequency of thymoma in patients with myasthenia gravis is variable, approximately 10–20% [5,128]. Conversely, 35–40% of patients with thymoma develop myasthenia gravis, sometimes after the tumour has been removed [98,129]. In patients with myasthenia gravis in whom the thymus is removed, the gland is seldom found to be histologically normal and thymic hyperplasia is common, particularly in younger patients, occurring in about 65% of

cases [91]. A thymoma is more likely when a patient with myasthenia gravis is older than 50 years, and this is particularly true in males [130]. A thymoma may therefore be diagnosed before, at the time of or after the onset of myasthenic symptoms. Myasthenia gravis may occur in association with any histological type of thymoma. It remains unclear if or how the pathogenesis of myasthenia gravis is related to the presence of thymomas [92]. It has been shown that the presence of striated muscle antibodies in patients with myasthenia gravis correlates with the presence of a thymoma; these antibodies were absent in over 90% of myasthenic patients without a tumour [86,131].

Thymectomy has an important role in the treatment of myasthenic patients whether a thymoma is present or not [126,132]; indeed symptomatic response may be better when the gland is found to contain follicular hyperplasia rather than thymoma or normal tissue. The results are best in younger patients with a short history of severe myasthenia, although thymectomy may be employed in any patient with deteriorating myasthenia gravis of sufficient severity despite optimal medical treatment [133,134]. Thymectomy in such patients requires close cooperation between the thoracic surgeon, neurologist and anaesthetist. The operation may be carried out successfully using a suprasternal approach, although a sternotomy is often preferred [135]. Preoperatively the dose of anticholinesterase is reduced to a minimum before complete omission in the postoperative period, when the patient is ventilated mechanically and narcotic analgesics need to be administered. Weaning from the ventilator is controlled by blood gas analyses and measurements of ventilatory capacity. Difficulties may arise in distinguishing between weakness as a result of a stress-related myasthenic crisis and a cholinergic crisis due to overdosage with anticholinesterases, the distinction being made by using the edrophonium test. Some work has indicated that high-dose corticosteroid therapy postoperatively may assist in the weaning process [136].

The standards of postoperative care of these patients have improved to such an extent that the presence of myasthenia gravis no longer adversely influences the prognosis of thymoma [96,137]; indeed, paradoxically, patients with thymomas and myasthenia gravis may survive better because their neurological symptoms result in the early detection of the tumour. Although the results from thymectomy are best in young females without tumour, those who do have thymomas may also benefit from an improvement in their myasthenic symptoms, although continued anticholinesterase therapy is the rule in this group.

### Thymic cysts

Unilocular or multilocular cystic spaces containing clear fluid or pasty material may occur in otherwise normal

thymic tissue. These thymic cysts occur with equal frequency in adults and children [138]. Some are likely to be congenital and these tend to be unilocular, being found anywhere along a line running from the angle of the mandible to the manubrium sterni. Others may be acquired, probably as a result of an inflammatory reaction in thymic tissue; these tend to be multilocular and fibrotic. Although the presence of cysts may be predicted by CT, certain differentiation from thymoma can only follow histological examination, particularly as thymic tumours of various types may cavitate [92]. Cysts are usually asymptomatic but occasionally become very large (Fig. 49.7), in which case they may produce symptoms due to mediastinal compression, including in extreme cases cardiac tamponade [139]. They are otherwise benign but because of the inevitable preoperative diagnostic uncertainty, treatment is by surgical excision. Thymic cysts in association with Hodgkin's disease are rare but well described and also tend to cause diagnostic difficulties (see p. 1290) [140,141]. It has been suggested that they may form as a result of the degeneration of treated lymphomatous tissue within the thymus but this is seemingly not always the case and their pathogenesis is uncertain.

### Other thymic tumours

The thymus gland may be the site of other tumours, although these are all encountered less frequently than thymoma. Thymic carcinoma is a rare group of tumours distinct from thymomas and seemingly unassociated with myasthenia gravis or the other immune-mediated disorders listed in Table 49.2. Various cell types have been described, including squamous, small-cell and undifferentiated carcinomas [142]. Care should be taken to ensure that these are not secondaries from lung as these and other primary tumours elsewhere may occasionally metastasize to the thymus.

Lymphomas of both Hodgkin and non-Hodgkin type may involve the thymus (see p. 1290) and are occasionally confined to it. The diagnosis can reliably be made by open or excision biopsy and treatment depends upon the extent of disease as determined by formal staging.

Carcinoid tumours may rarely arise in thymic neuroendocrine cells and the morphology of most of them is similar to that of the 'atypical' type of bronchial carcinoid tumour. They appear to be more frequent in males, are unassociated with myasthenia gravis and behave in a much more aggressive manner than thymomas, with a tendency to both recur locally and to metastasize [143,144]. A minority of them are associated with endocrine abnormalities, such as Cushing's syndrome and multiple endocrine neoplasia types 1 or 2a [145–147].

Thymolipoma (syn. lipothymoma) is a rare, benign, slowly growing tumour that has the gross appearance of a lipoma but which contains both thymic and fatty elements

[148–150]. This tumour may become enormous and is sometimes mistaken for cardiomegaly on plain films because of its propensity to mould itself about the mediastinal structures in a plastic fashion. The use of CT shows it to have the density of fat and may help to make the proper distinction.

Germ-cell tumours, both benign and malignant, may arise in the thymus gland and these are discussed in the following section. Secondary neoplastic disease in the thymus is not uncommon and may sometimes respond to surgery [151]. Occasionally ectopic parathyroid adenomas may be found embedded in the substance of the thymus (see p. 1298).

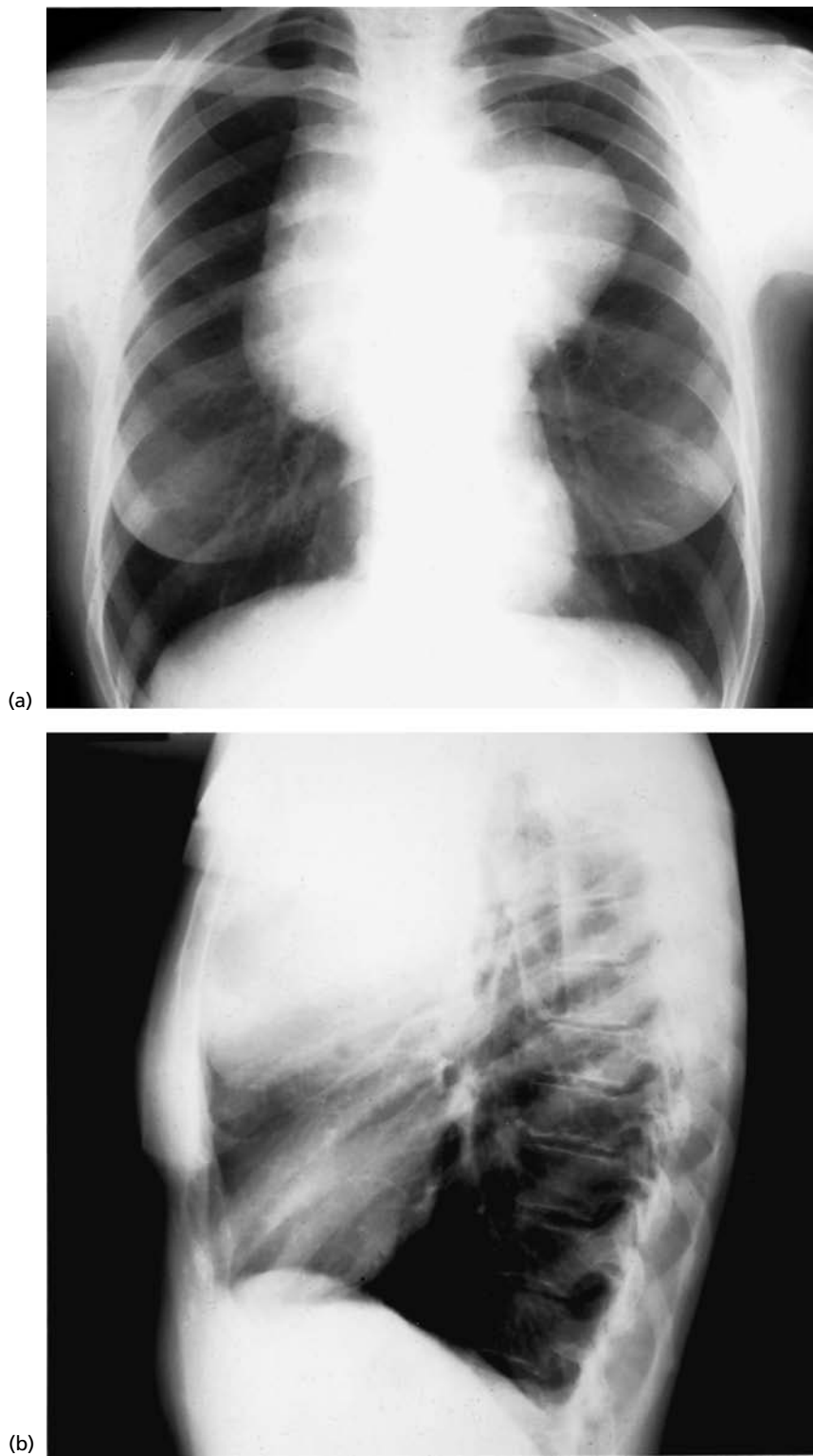
### Miscellaneous thymic disease

Thymic masses have been reported in children with Langerhans' cell histiocytosis (histiocytosis X) [152], in patients with Churg–Strauss syndrome [153] and in giant lymph node hyperplasia (Castleman's syndrome), a condition of uncertain pathogenesis that some regard as hamartomatous, the diagnosis being made after excision biopsy [154,155].

### Mediastinal germ-cell tumours

The histogenesis of mediastinal germ-cell tumours remains controversial but it seems probable that these tumours arise as a result of the proliferation of primitive extragonadal germ cells that have the potential to differentiate into various cell types of ectodermal, mesodermal and endodermal origin [36,156,157]. The anterior mediastinum is the most common adult extragonadal site for these tumours, which for some undetermined reason arise in relation to the thymus gland but which are histologically entirely distinct from thymomas. In children, extragonadal germ-cell tumours occur with greater frequency in the sacrococcygeal area [36]. Mediastinal germ-cell tumours may be benign or malignant. The terminology of germ-cell tumours is confusing because of uncertainties surrounding their pathogenesis and because of the wide histological variety that may be encountered. A plethora of synonymous terms have been used and are found scattered in the literature, nomenclature inevitably changing as wise men ponder and as the years go by (Table 49.5).

The most common mediastinal germ-cell neoplasm is mature cystic teratoma (syn. teratoma, benign or mature teratoma, dermoid cyst or tumour, teratodermoid). This tumour is benign and accounts for approximately 80% of germ-cell neoplasms, affecting both sexes equally. The term 'teratoma' was defined by Willis [158] as 'a true tumour comprised of multiple tissues foreign to the part in which the tumour is found'. This term is well entrenched in medical literature and its use will continue but is best



**Fig. 49.7** Posteroanterior (a) and left lateral (b) chest films of asymptomatic patient with huge thymic cyst.

reserved for benign tumours, the term 'teratocarcinoma' being applied to a malignant counterpart containing a combination of benign teratomatous components and embryonal carcinoma (see below and Table 49.5).

Five distinct subtypes of malignant germ-cell tumour

are described: seminoma (affecting males exclusively), teratocarcinoma, embryonal carcinoma, choriocarcinoma and endodermal sinus (or yolk sac) tumour, all of which have a strong male predilection, although rare cases have been reported in females. It is important to realize that the

**Table 49.5** Germ-cell tumours of the mediastinum (see text).

Currently favoured terms	Synonyms
Benign germ cell tumour	
Mature cystic teratoma*	Teratoma, benign teratoma, mature teratoma, dermoid cyst, dermoid tumour, teratodermoid
Malignant germ-cell tumour	
1 Seminoma†	Germinoma, dysgerminoma
2 Choriocarcinoma†	Trophoblastic teratoma
3 Endodermal sinus tumour†	Yolk-sac tumour
4 Embryonal carcinoma†	
5 Mixed germ-cell tumour† (of types 1–4)	
6 Teratocarcinoma*	Malignant teratoma
7 Immature teratoma* (age-dependent malignant potential)	

\* Tissue non-specific.

† Tissue specific.

histological boundaries between these tumours may be indistinct and that they may occur both in mixed and pure form. The reader should be aware that some authors have used the term 'malignant teratoma' subgenerically to include all the above malignant germ-cell tumours, although this practice is not recommended.

Both mature cystic teratomas (benign teratomas) and teratocarcinomas, in common with all germ-cell tumours, arise from immature or primordial germ cells during development. However, in the case of benign teratomas and teratocarcinomas these immature germ cells are pluripotent and still capable of producing a regionally diverse cellular output that results in different lines of embryonal tissue (epithelial, mesenchymal and neural), whereas the remaining pure histological types of germ-cell tumour (seminoma, embryonal carcinoma, choriocarcinoma and endodermal sinus tumours) possess tissue specificity [5,159]. These tissue-specific germ-cell tumours arise in an organ-formative field or 'blastoma' in which the immature germ cells are restricted to single regionally determined patterns of cellular output. Tissue-specific germ-cell tumours are all malignant and although their response to treatment is variable some are curable. The management of these neoplasms has altered significantly in the last 20 years, especially with the introduction of cisplatin-based combination chemotherapy which been found capable of curing advanced disease [160].

The histogenesis of mediastinal germ-cell tumours is controversial. Some investigators have claimed that the tissue-specific germ-cell tumours found in this site represent metastases from occult primary gonadal tumours

[161]. This is improbable for various reasons. Firstly, several studies have excluded a gonadal primary by multiple testicular sectioning [162–164]; secondly, in the case of mediastinal seminoma the disease can be cured by local therapy to the chest [165]. Furthermore, mediastinal metastases from known testicular primary seminomas are rare [166]. Extragonadal germ-cell tumours are all found near the midline and it has been suggested that they arise from primordial germ cells that fail to migrate from the urogenital ridge to the gonads during embryogenesis [162].

## Benign germ cell tumours

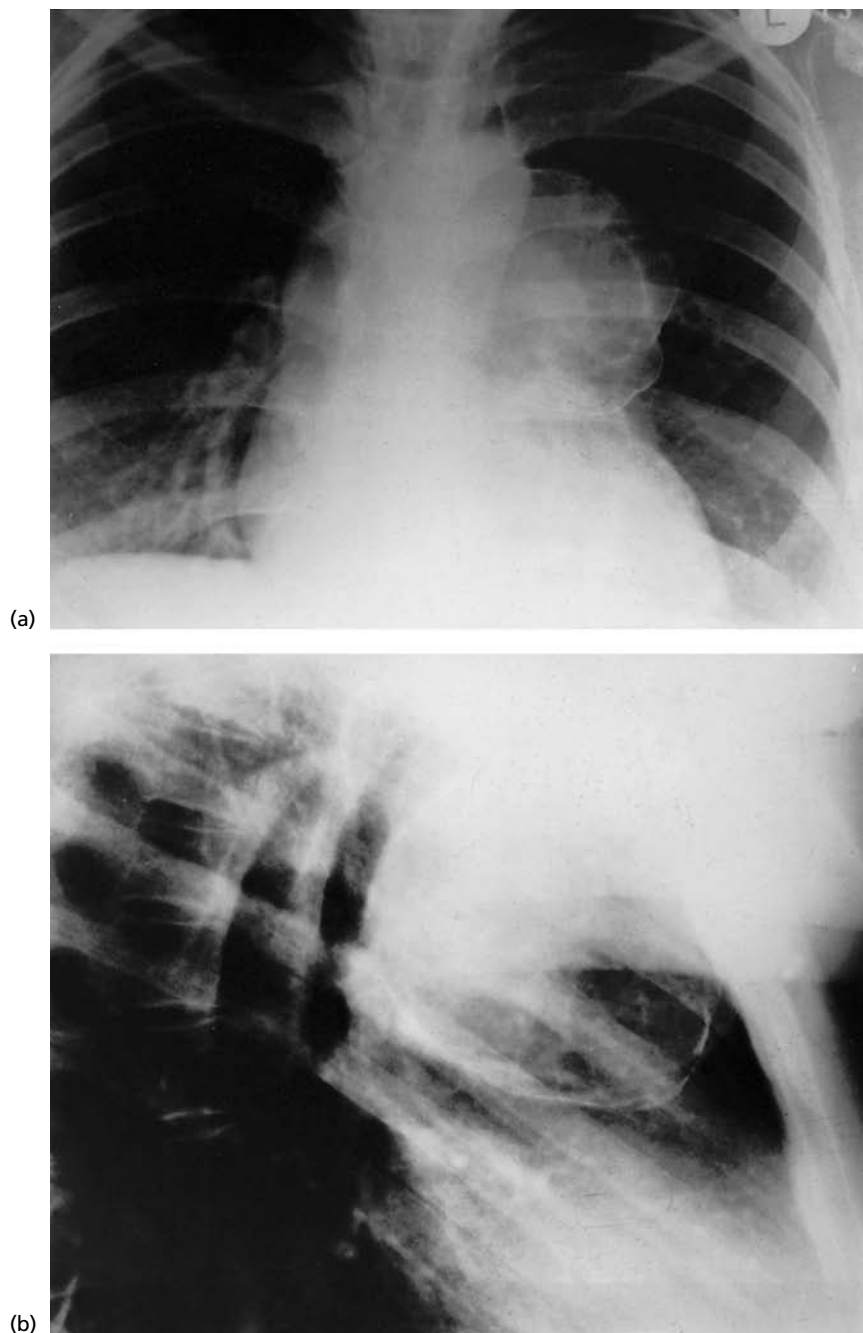
### Mature cystic teratoma

Mature cystic teratomas account for approximately 80% of all mediastinal germ-cell tumours and about 8% of mediastinal tumours of all types [4,5,36]. With very few exceptions indeed they are situated in the anterior or anterosuperior mediastinum, although they are less common anterior mediastinal masses than thymomas and lymphomas [167]. Rare cases have been described in the posterior mediastinum and at more than one intrathoracic site [168–170].

### Pathology

Macroscopically, benign germ-cell tumours of the mediastinum are rounded or lobulated and well-encapsulated tumours. They vary very widely in size, the average diameter in a large North American series being about 8 cm [167]. As the name suggests, they are often cystic or loculated and are commonly found at operation to be closely associated with the thymus and adherent to surrounding tissues.

Microscopically, mature tissue from all three germ layers is represented. Ectodermal elements predominate and of these the most common is skin, the cysts being lined by stratified squamous epithelium, hence the old term 'dermoid'. The other common ectodermal elements are hair and sebaceous glands (pilosebaceous units). The most common mesodermal element is smooth muscle followed by fat, cartilage and less frequently bone. Respiratory epithelium is the endodermal component most often found, followed by gut epithelium [167]. Pancreatic tissue may be found and can be enzymatically active, leading to the suggestion that digestive enzyme activity may account for the dense adhesions with surrounding tissues that characterize this tumour [171]. Islet of Langerhans components may also occur, giving mature cystic teratomas the potential to produce hypoglycaemia. A wide variety of other tissues are identifiable, including neural components and occasionally formed teeth. Calcification may also occur in the wall of this tumour (Fig. 49.8), which is



**Fig. 49.8** Posteroanterior (a) and right lateral (b) chest films of asymptomatic patient with calcified anterior mediastinal teratoma. The tumour was found to contain hair.

histologically similar to the more common mature cystic teratoma of the ovary.

Benign mediastinal teratomas may be found at any age but most series show a diagnostic peak in early adulthood [167]. They affect both sexes more or less equally [4,167,172,173], in contrast with malignant germ-cell tumours of the mediastinum that affect males almost exclusively. They are usually a chance radiographic findings in a subject with no respiratory symptoms and there is evidence that asymptomatic diagnosis has become more common [167,172]. Symptoms are more often present in

children than adults, pain in the sternal region, back or shoulder and dyspnoea with cough being usual [4,5,167,172]. Uncommonly, symptoms may occur as the result of the erosion of a teratoma into surrounding structures. Bronchial erosion may lead to haemoptysis, with the expectoration of sebaceous material or even hair (trichoptysis). The release of fatty material into the bronchial tree may cause lipoid pneumonia and its spillage into the mediastinum may incite a granulomatous reaction. Rupture into the pericardium may cause pericarditis or tamponade and rupture through the chest wall or into the

pleura, aorta and superior vena cava have been recorded [174–176], although all these complications are becoming increasingly uncommon [167]. In subjects with large tumours, evidence of obstruction of the superior vena cava, splaying of ribs, dullness to percussion, wheeze or a pulmonary systolic murmur may sometimes be found, but more commonly physical examination reveals no localizing signs.

### *Investigations*

Chest radiography characteristically shows a well-circumscribed or lobulated anterior mediastinal mass that may extend into one or other lung field (see Fig. 49.8). Flecks of calcification in the wall or substance of the mass and sometimes bone or tooth may be found in 15–40% of cases [167,172,177]. The presence of an air–fluid level may indicate a bronchial communication. Ultrasound examination or CT may show cystic changes with areas of fat density [178], although the diagnosis can only be established with certainty by pathological examination after surgical removal.

### *Treatment*

The treatment of choice is total excision via either thoracotomy or sternotomy. This operation is advisable because of the diagnostic uncertainty that would otherwise exist and also because of the possibility of complications, including very rare malignant change [179,180]. Although these benign germ-cell tumours may be ‘shelled out’ easily [5], removal is often difficult because of dense adhesions between the lesion and surrounding structures, such as the pericardium, lung, great vessels, thymus and chest wall [172]. Lobectomy may be necessary when a teratobronchial fistula is present. Surgical removal achieves total cure even if excision has been incomplete because of adherence to mediastinal structures [172].

### **Immature teratoma**

Immature teratoma of the mediastinum may be regarded as the potentially malignant counterpart of mature cystic teratoma. It contains immature elements of the three germ layers but unlike teratocarcinoma (see below) contains no component of embryonal carcinoma. The behaviour of this tumour is age-dependent (parallels with neuroblastoma) so that in infancy and early childhood it acts mainly as a space-occupying lesion, whereas after the age of about 14 years it behaves as a malignant tumour invading adjacent structures and metastasizing widely [159].

### **Malignant germ cell tumours**

Approximately 20% of germ-cell tumours of the medi-

astinum are malignant [5]. Therapeutically and prognostically it is very important to distinguish between those malignant germ-cell tumours that are pure seminomas and those that contain any non-seminomatous elements [165]. Seminomas and non-seminomatous germ-cell tumours are therefore considered separately.

### **Non-seminomatous tumours**

#### *Classification*

Immature teratoma, which straddles both groups, has already been discussed above and this section therefore includes (i) teratocarcinoma (syn. malignant teratoma), which comprises embryonal carcinoma surrounding foci of benign teratoma with elements of immature teratoma, and (ii) three other tumours of more specific cellularity: choriocarcinoma (syn. trophoblastic teratoma), endodermal sinus (or yolk-sac) tumour and embryonal carcinoma, the latter being the least differentiated of this group but having the potential to transform into the other non-seminomatous cell types. Many malignant germ-cell tumours contain mixtures of the specific cell types within this group and one or more of the non-seminomatous tumour cell types may also occur in combination with seminomatous elements, so-called mixed germ-cell tumours in which all individual cell types should be specified. Occasionally, sarcomatous elements may occur in malignant mediastinal germ-cell tumours, a finding that worsens the prognosis as these components are less susceptible to chemotherapeutic agents [181].

#### *Clinical features*

Non-seminomatous germ-cell tumours of the mediastinum occur most commonly in the third decade of life and are extremely rare in females [5,165]. With the exception of immature teratoma in infancy and early childhood, they behave in a highly malignant fashion, with local invasion and a tendency to metastasize, and are usually associated with symptoms at the time of diagnosis. Chest pain, cough and dyspnoea are common and may be accompanied by systemic symptoms [5,165]. Obstruction of the superior vena cava may occur. Gynaecomastia is commonly present in these patients, especially in those with choriocarcinoma, presumably due to the elaboration of human chorionic gonadotrophin (hCG) from trophoblastic elements of the tumour [182,183]. There is also a well-recognized association between the development of malignant non-seminomatous germ-cell tumours and the presence of Klinefelter’s syndrome; indeed germ-cell tumours may be 30–40% more common in this group of patients than in the population as a whole [184–188]. There is also an association between non-seminomatous mediastinal germ-cell tumours, particularly those with a



yolk-sac component, and various haematological malignancies including acute leukaemias and malignant histiocytosis [189,190].

### *Investigation*

Chest radiography shows an anterior mediastinal mass that may cause mediastinal displacement and there may be evidence of metastatic intrathoracic spread. A more accurate disposition of the tumour is demonstrated by CT, which shows the neoplasm to be more solid than mature cystic teratoma but with areas of heterogeneity, corresponding to haemorrhage and necrosis. The tumour is also less likely to contain areas of fat density than benign teratoma [191]. An accurate diagnosis may be obtained by the submission of a generous surgical biopsy in order to facilitate identification of the tumour type and to enable immunohistochemical and genetic studies to be carried out. Occasionally such genetic studies reveal a chromosome marker that confirms the germ-cell origin in a tumour of otherwise uncertain histology, a finding that may be therapeutically important in terms of indicating appropriate cisplatin-based chemotherapy [192]. CT- or ultrasound-guided percutaneous needle biopsy may result in an inaccurate diagnosis in these tumours.

Diagnosis is also assisted by the detection of two protein tumour markers in the patient's serum [193]:

1 the  $\beta$  subunit of hCG may be detectable at any surgical stage and in 40–60% of patients with metastatic non-seminomatous malignant tumours but only 15–20% of metastatic seminomas;

2  $\alpha$ -fetoprotein (AFP) may also be present at any surgical stage and in 40–60% of non-seminomatous metastatic malignant tumours [160,183,194,195].

AFP has never been detected in pure seminomas and its presence in a patient with a germ-cell tumour is always taken to indicate a non-seminomatous element, a finding of crucial therapeutic and prognostic importance. Of the non-seminomatous germ-cell tumour components, AFP is specifically produced by embryonal carcinoma and endodermal sinus (yolk-sac) tumours. AFP concentrations may also be raised in inflammatory or toxic liver damage, hepatomas and other gastrointestinal tract tumours [196]. hCG is not as specific but high levels are suggestive and one or other, or both, of these two markers is present in about 90% of malignant non-seminomatous germ-cell tumours. Serum lactate dehydrogenase may also be raised in both seminomatous and non-seminomatous germ-cell tumours [160].

### *Treatment and prognosis*

The extent of disease is determined as for seminoma. The possibility of spread from an occult testicular tumour is considered in all extragonadal presentations of malignant

germ-cell tumour since a testicular primary may be very small even though metastases have occurred (see section on seminoma). Unfortunately, invasion of adjacent mediastinal structures or metastases are usually present at the time of diagnosis in non-seminomatous germ-cell cancers and surgery has ceased to be a primary treatment, complete removal having been found to be most unusual though not unheard of [165]. Patients with mediastinal non-seminomatous germ-cell cancer are considered 'poor-risk', with a low likelihood of cure, and are usually relatively insensitive to radiotherapy, the mainstay of treatment being chemotherapy [160]. The management of non-seminomatous germ-cell tumours, as with seminomas, has been the subject of much research and collaborative effort and is a matter for the expert.

Trials to improve the effectiveness of treatment in poor-risk germ-cell cancer are ongoing, one current approach comprising four cycles of conventional-dose bleomycin, etoposide and cisplatin. Some patients die within a year, although success has been achieved using cisplatin-based chemotherapy as primary treatment [197,198]. One early study achieved a median survival time of 14 months using this approach provided that cisplatin and bleomycin were included in the regimens [165]; more recent series have reported a 2-year survival of 53% (median 28 months) in 64 patients [197] and a median survival of 55 months in a small group of 11 patients [198]. Surgery may have a role in debulking residual disease after chemotherapy, once normal levels of tumour markers have been achieved. Although these tumours still carry a poor prognosis compared with their testicular counterparts, about half should be cured with modern chemotherapy [199].

The serum levels of tumour markers are used as an essential tool in monitoring the response of disease to treatment, AFP and hCG being measured and monitored before, during and after treatment. A sustained rise or increasing levels of either AFP or hCG or both may be taken to indicate active disease, even in the absence of symptoms, signs or radiographic change, and may lead to therapeutic intervention. The levels decline after treatment and a failure to do so is indicative of residual active disease [200]. Furthermore, there is evidence to suggest that a bulky tumour need not indicate a poor prognosis in the absence of high tumour marker levels [201].

## **Seminoma**

### *Clinical features*

Seminoma (syn. germinoma, dysgerminoma) is the most common single malignant mediastinal germ-cell tumour, accounting for approximately half of all these neoplasms [165]. They affect young men, 95% occurring between the ages of 20 and 40 years [202], so that sperm banking should be considered prior to chemotherapy. Mediastinal

seminomas almost always arise within the thymus gland. They are histologically indistinguishable from testicular seminomas. Only one-third of patients are asymptomatic, in contrast with benign mediastinal germ-cell tumours, the most common symptom being chest pain [165,202]. Dyspnoea and obstruction of the superior vena cava sometimes occur. It is not unusual for these tumours to metastasize.

### Investigation

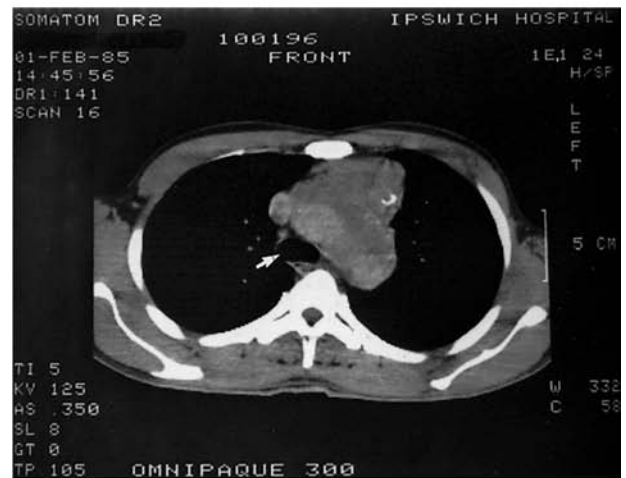
The chest radiograph shows a lobulated, usually non-calcified anterior mediastinal mass (Fig. 49.9). More accurate disposition of the tumour is confirmed by CT, which often shows the neoplasm to be large, lobulated, more solid and less likely to contain fat than benign mature teratomas [191]. Diagnosis is established by the removal of a generous piece of tumour in order to identify the tumour type and to enable immunohistochemical and genetic studies to be carried out. CT- or ultrasound-guided percutaneous needle biopsy may result in an inaccurate diagnosis in these tumours. Further evidence that the tumour is free of non-seminomatous germ-cell tumour elements, whose presence would alter management, is provided by a normal serum level of AFP. hCG is also usually absent, occurring in only 7–10% of pure seminomas and 15–20% of patients with metastatic seminoma [160,165]. Other tumour markers for seminoma, such as serum lactate dehydrogenase, are being evaluated but are less specific, also being found in non-seminomatous germ-cell tumours. For practical purposes, a seminoma is only diagnosed if the histology shows pure seminoma and if the serum level of AFP is not raised [203].

The possibility of metastasis from a testicular tumour should always be considered in any malignant germ-cell tumour, although primary mediastinal seminoma is a sufficiently well-recognized entity for surgical exploration of the testis to be unnecessary provided that (i) physical examination provides no evidence of testicular swelling or atrophy, (ii) ultrasound examination of the testes is normal and (iii) no evidence of retroperitoneal lymph node involvement is found by CT of the abdomen and pelvis [163,164,166].

The ultrasonographic findings of testicular germ-cell tumour include one or more discrete hypoechoic masses or more diffuse abnormalities with microcalcifications.



(a)



(b)



(c)

**Fig. 49.9 (Right.)** (a) Posteroanterior film of young man with seminoma in anterior mediastinum. (b) CT shows irregular mass of tissue displacing trachea (arrowed) to right. (c) Posteroanterior film after radiotherapy showing regression of tumour.

### *Treatment and prognosis*

Seminomas carry a better prognosis than non-seminomatous germ-cell tumours and it is important to make the diagnosis accurately. As with germ-cell tumours in general, the management of seminomas has been the subject of national and international collaborative research and is a matter for the expert. Although seminomas are highly radiosensitive (and indeed complete cure may be obtained by radiotherapy) [165,166], the treatment of choice for seminoma has shifted from radiotherapy to chemotherapy, irradiation tending to be reserved for bulky tumours. Although cure has been achieved in the past when all gross evidence of tumour has been removed by surgery [5], operative attempts to remove tumour other than for histological diagnosis have generally been incomplete and are usually no longer indicated. Currently, chemotherapy takes the form of four cycles of standard etoposide and cisplatin or three cycles of bleomycin, standard etoposide and cisplatin [160]. Patients with an incomplete remission and those who relapse may be given second- and third-line 'salvage' chemotherapy, from which a significant number of cures have been obtained [160]. Such treatment may include high-dose chemotherapy with autologous bone marrow (stem cell) rescue [204]. A 2-year survival rate of 86% was reported in a series of 23 patients with pure mediastinal seminomas, most of whom were treated (between 1983 and 1990) with cisplatin-based chemotherapy, although some had been primarily treated with radiotherapy [197]. In a small series of seven patients with pure mediastinal seminomas treated with cisplatin-based combination chemotherapy and in some cases additional radiotherapy, 100% disease-free survival was reported at a median follow-up time of 41 months [198]. With modern cisplatin-based chemotherapy and radiotherapy, long-term survival or cure can be expected in around 80% of this group [199].

## **Other mediastinal tumours and tumour-like conditions**

### **Mediastinal lymphoma**

Any type of lymphoma can involve any lymph node, including those in the mediastinum as well as those radiographically more obvious nodes in the hila. The thymus gland may also be the seat of a lymphoma, although whether the disease originates in this site is not clear. Lymphomatous involvement of the lungs is described in Chapter 42. The mediastinum is involved in over 50% of patients with Hodgkin's disease [205]. Mediastinal Hodgkin's disease is considered 'massive' if the ratio of the maximal horizontal width of the mediastinal mass to the maximum intrathoracic diameter on a standard chest radiograph exceeds one-third [205]. Most cases of

Hodgkin's disease found in the mediastinum are of the nodular sclerosing type. The correct diagnosis (as with other mediastinal tumours) is clearly important since lymphomas are eminently treatable and in many cases curable. The temptation to establish the diagnosis of a mediastinal tumour by CT- or ultrasound-guided percutaneous needle biopsy, although attractive in avoiding a more invasive surgical biopsy, runs the risk of misdiagnosis in cases of lymphoma, for which the pathologist requires a block of tissue so that a full morphological and immunohistochemical analysis can be carried out (as is the case with germ-cell tumours, see above). Failure to do this may result in some treatable non-Hodgkin lymphomas being mistakenly labelled as anaplastic carcinomas [206,207], with prognostic consequences.

Treatment may be with intensive chemotherapy regimens or primary radiotherapy or both, depending on the type, stage and bulk of the disease [205,206,208,209], and is a matter for experts in this field. Management dilemmas may sometimes be created by the persistence of cysts in the substance of the thymus following the treatment of thymic lymphoma, as there may be uncertainty about whether such cysts represent residual or recurrent disease or indeed whether they are benign. In such cases it is probably best to withhold further treatment unless pathological confirmation of active disease is obtained [141]. Similar dilemmas arise when imaging shows residual opacities in lymph node areas following treatment; indeed these are found in over 60% of patients with mediastinal disease, particularly when the original lymph node mass was large [205]. Persistent gallium isotope uptake or positron emission tomography may be helpful in distinguishing disease activity from non-malignant tissue in doubtful cases and may lead to further biopsy [205,206,209].

Patients with stage II massive mediastinal Hodgkin's disease have relapse rates of 50–74% when treated with nodal radiotherapy alone, while chemotherapy alone has been found to have relapse rates of 33–50% [205]. Improved survival may be obtained by using a combined approach, and some workers have favoured chlormethine (mustine)/vincristine/procarbazine/prednisolone (so-called 'MOPP') or doxorubicin/bleomycin/vinblastine/dacarbazine (DBVD) followed by radiotherapy [205]. The prognosis for non-Hodgkin's lymphoma varies according to the histology and stage. For well-localized high-grade tumours, disease-free survival rates of 60–80% may be achieved at 5 years. Where disease is widespread and treated with chemotherapy, the rates are 30–40%. Low-grade non-Hodgkin lymphoma runs a more indolent course, with a median survival of 7–8 years [210]. The freedom-from-relapse rate at 5 years for primary mediastinal large-cell and immunoblastic lymphoma was found to be 45% in a study of 57 patients, and the presence of pleural effusion at presentation was associated with an extremely poor outcome [209].

### Mediastinal amyloid

Amyloidosis is the term used for a group of diseases characterized by the extracellular deposition of fibrillar proteins consisting of fragments of immunoglobulin light chains. There have been a number of case reports of tumorous or lymph node deposits of amyloid in the mediastinum. The diagnosis of this very rare condition can only be made by histological examination of biopsy material, which shows a characteristic amorphous eosinophilic substance that stains positive with Congo red and which shows characteristic apple-green birefringence under polarized light microscopy [211,212]. An aspirate of subcutaneous abdominal fat may also stain similarly if other involved tissue is inaccessible. Monoclonal proteins are usually detected on electrophoresis of serum or urine. The prognosis depends upon the type and extent of disease, length of survival varying from months to years. Treatment is generally supportive but experience is accumulating with the use of colchicine, melphalan and, in certain cases, organ transplantation [213].

### Mediastinal mesenchymal tumours and tumour-like lesions

Mediastinal mesenchymal (connective tissue) tumours form a diverse group of rare neoplasms that account for only about 6% of mediastinal tumours [18]. They arise from mesenchymal or connective tissue elements, including lymphatic tissue, blood vessels, fat, smooth and skeletal muscle [92]. Some are regarded as hamartomatous malformations, others as true neoplasms, either benign or their malignant (sarcomatous) counterpart. Their morphology may be heterogeneous, depending on the differentiation of the primitive mesenchymal cell, so that different cell lines are sometimes found in the same tumour. The precise diagnosis depends upon histological examination following surgical biopsy or excision, only fatty tumours lending themselves to more confident pre-operative diagnosis because of their characteristically low attenuation values on CT.

Benign tumours such as lipomas are usually asymptomatic findings but may produce compressive symptoms and signs if they attain a large size. Their malignant counterpart, the liposarcoma, is more likely to produce dyspnoea and chest pain but may also be asymptomatic at the time of diagnosis [214]. This may arise in any mediastinal compartment but possibly favours the anterior mediastinum, where it may also arise within the thymus [215]. Surgical excision may be curative but these tumours have a tendency to run an aggressive course with local recurrence, although distant metastases are not a common feature.

A series of 10 surgically resected malignant smooth muscle tumours (leiomyosarcomas) reported seven in the

posterior and three in the anterior mediastinum. Most of those patients with posterior lesions were asymptomatic, whereas the anterior ones tended to produce compressive symptoms. Survival was related to histological grade and surgical staging [216]. Malignant skeletal muscle tumours (rhabdomyosarcomas) may arise in the anterior mediastinum of younger adults and behave in a highly aggressive manner [217]. Rhabdomyosarcomatous elements may also occur focally within non-seminomatous germ-cell tumours [199].

Benign tumours of blood vessels (haemangiomas) tend to be diagnosed in children and young adults but may occur at any age. They favour the anterior mediastinal compartment and range in size from small to very large. Two types are described: one is more solid and lobular, the so-called capillary haemangioma; the other, known as cavernous haemangioma, has larger dilated vascular spaces. The most common presenting symptoms in a series of 18 cases were dyspnoea, cough and chest pain [218]. These tumours tend to enhance on CT [219]. Haemangiosarcoma is an even rarer tumour in this location and has been treated by radical excision and postoperative radiotherapy [220].

Mediastinal lymphangiomas are probably hamartomatous malformations rather than true neoplasms and may result from a localized failure of the developing lymphatic system to communicate with its venous counterpart. Cystic forms of lymphangioma (so-called cystic hygroma, see below) most commonly arise in the neck of infants and sometimes extend into the superior mediastinum [221]. Solitary lymphangiomas arising exclusively in the mediastinum rather than extending from the neck are most commonly found in adults [221]. They are benign localized lesions up to several centimetres in diameter, comprising endothelial-lined spaces with a supporting connective tissue stroma that may contain smooth muscle. They are morphologically similar to haemangiomas but may contain straw-coloured fluid or chyle rather than blood [221]. They may occur anywhere in the mediastinum and although benign can infiltrate along tissue planes in a serpiginous fashion, proving difficult to remove completely at surgery. They may produce symptoms as a result of pressure on surrounding structures and are sometimes complicated by chylous pleural effusions but are often completely asymptomatic [16,221]. Lymphangiomas sometimes occur in multiple form as part of a generalized maldevelopment of the lymphatic system, so-called lymphangiomatosis, in which the tumours may be found in the mediastinum and the lungs as well as in abdominal viscera and the retroperitoneal space [222–225]. Lymphangiomatosis may also involve bones, producing cystic endothelium-lined spaces [222].

Mediastinal lymphangiomas should not be confused with lymphangiomyomas (previously called lymphan-

giopericytomas), which are true neoplasms seen only in females, the tumour consisting of intimately mingled lymph vessels and smooth muscle elements with particular immunohistochemical characteristics [92]. Lymphangiomyomas may occur in localized form, often in association with the thoracic duct or its tributaries in the mediastinum or retroperitoneal space and sometimes result in chylothorax. There is a generalized or systemic form of this condition known as lymphangiomyomatosis (or lymphangioleiomyomatosis) that occurs in postpubertal women. This condition is characterized by a proliferation of immature smooth muscle derived from associated lymphatics [226,227]. This smooth muscle infiltrates the walls of alveoli and bronchi with resultant air trapping and impaired gas transfer that may mimic emphysema. These women tend to present in their thirties with slowly progressive breathlessness and radiographic and CT changes that alter from a reticular infiltrate to 'honeycombing' with diffuse cystic change, so that pneumothoraces are a common feature [228]. The myoproliferative process may involve pulmonary blood vessels and lymphatics, resulting in haemoptysis and chylothorax respectively (see Chapter 42). There are close histological parallels between lymphangioleiomyomatosis and the

pulmonary manifestations of tuberous sclerosis, although this hereditary condition affects both sexes and also has cutaneous and cerebral manifestations. The pathogenesis of lymphangioleiomyomatosis remains obscure but the condition is probably a hamartomatous malformation of smooth muscle [229].

Cystic hygromas rarely develop in the superior mediastinum but more usually present as a poorly defined swelling in the neck, usually posterior to the sternomastoid muscle. However, these may extend into the mediastinum in about 10% of cases [221,230,231]. Even in this situation they are rare in adults, the vast majority being diagnosed within the first 2 years of life. They are thin-walled endothelially lined cystic tumours that contain lymph and are usually multilocular. The term 'cystic hygroma' is used synonymously with 'cystic lymphangioma' [232] and they are regarded as congenital hamartomatous malformations that may arise as a result of a bud of lymphatic tissue becoming pinched off during early development [233]. They are soft and yielding structures and although they may increase in size in adults as a result of the accumulation of lymph and the enlargement of their spaces, they do not usually produce pressure symptoms unless distended by haemorrhage into the cyst (Fig. 49.10)



**Fig. 49.10** Barium swallow in patient who presented with stridor showing mediastinal displacement to left. At operation, the tumour proved to be a cystic hygroma into which an acute bleed had occurred.

or by infection [234]. The diagnosis in adults usually follows the finding on the chest radiograph of a well-defined, rounded, homogeneous density with a sharp border in the superior mediastinum. CT shows the lesion to be cystic and of low density [234]. Treatment is by surgical excision, which may be difficult as cystic hygromas tend to mould themselves to the contours of the mediastinal contents so that a plane of cleavage may not be easy to establish [5,235].

## Developmental mediastinal cysts

Congenital cysts of the mediastinum account for an average of 16% of all mediastinal cysts and tumours [2–4,6,10,30,36]. Foregut duplications are the largest group followed by pleuropericardial cysts. Congenital cysts may also occur in the thymus as described above (see Fig. 49.7) and also in relation to the thoracic duct and occasionally in ectopic thyroid or parathyroid tissue (see below).

### Foregut cyst or duplication

#### *Classification*

The term 'foregut duplication' (or reduplication) may be applied to cysts, diverticula and fistulae that have resulted from developmental malformations of the primitive foregut in the embryo. Such cysts therefore contain tissues derived from primitive endoderm and mesoderm. The term 'bronchogenic cyst' is often used synonymously with 'bronchial cyst' for foregut duplications that are clearly related to the airways, especially the trachea and main bronchi, a common site being posterior to the carina. Those closely related to the gut are variously referred to as gastric, enteric or gastroenteric cysts, depending on their principal histological constituents; those where there is an associated vertebral abnormality are often called neurenteric cysts.

#### *Pathogenesis*

The pathogenesis of foregut duplications is incompletely understood, although several different mechanisms are likely to be operative [236].

1 One possible mechanism is the defective separation of the tracheobronchial bud from the foregut proper so that a bud or diverticulum becomes pinched off, creating a cystic space that may be found between the trachea or a major bronchus and the oesophagus or stomach. Such a cyst may be connected by a fibrous strand to the gut, the tracheobronchial tree or both and may be referred to as a tracheobronchial foregut duplication. When one of the connecting strands remains patent, then the 'cyst' is in fact a diverticulum of either the gut or the tracheobronchial tree; if both

connections are patent, then a tracheobronchial fistula results.

2 A second mechanism may involve the defective coalescence of chains of vacuoles that form during epithelial proliferation within the developing tracheobronchial tree, giving rise to solitary or multiple intralobar bronchogenic cysts or oesophageal cysts embedded in the oesophageal wall.

3 A third mechanism may give rise to so-called neurenteric cysts, in which a tract of abnormal development runs between a part of the upper gastrointestinal tract and the skin surface, usually over the upper thoracic spine. This anomaly is presumably initiated at an embryonic stage when the cellular precursors of the spine and the upper gastrointestinal tract are still contiguous, the neural tube and foregut being connected by the primitive neurenteric canal [237]. The persistence of this may result in a fistulous tract running from the alimentary canal to the surface of the skin [238]. This canal or its remnants may divide both the spinal cord and a corresponding vertebral body and has therefore been referred to as the split notochord syndrome [239]. Reabsorption of parts of this fistula may give rise to incomplete forms of the split notochord syndrome but upper thoracic spine anomalies are a common feature.

Intrathoracic foregut duplications may be intrapulmonary or extrapulmonary and, as suggested above, usually occur in relation to the oesophagus, the trachea or a major bronchus. They are reportedly more common in the right hemithorax than the left [5,236,238,240]. They are more likely to be diagnosed in infancy rather than adult life because their expansion in a limited space exerts pressure effects on surrounding structures [36,241].

#### *Pathology*

Macroscopically, foregut duplications appear as rounded or oval saccular structures. Bronchogenic cysts are usually spherical and thin-walled, containing gelatinous mucoid green/blue material with an average diameter of about 4 cm [92]. Their wall may be lined by ciliated columnar epithelium or pseudostratified epithelium of respiratory type and may contain bronchial glandular elements as well as cartilage and neural tissue. These walls may undergo calcification. Oesophageal cysts may be found in the wall of that viscus and characteristically contain a double layer of smooth muscle in their own wall. They are occasionally tubular, traversing the long axis of the entire thorax and may contain thick mucus [238]. Rarely there may be a communication with the parent organ and exceptionally they may be multiple [5,238,242]. Gastroenteric and neurenteric cysts usually occur in the posterior mediastinum paravertebrally and are associated with vertebral, spinal cord and skin abnormalities, the cysts sometimes communicating with the skin surface through a

spina bifida [238,239,243]. Microscopically, gastroenteric and neurenteric cysts have walls simulating stomach or intestine. Those with gastric features may contain parietal cells and the latter may form peptic ulcers [241]. Some cysts contain ectopic pancreatic tissue [244]. The histological findings are not always specific enough to allow differentiation between these various foregut duplications and overlap may occur.

### *Clinical features*

The majority of children with intrathoracic foregut cysts are symptomatic, with dyspnoea, stridor or persistent cough; one-third of those with neurenteric cysts may present with a motor or sensory neurological deficit, back pain or an abnormality of gait resulting from spinal cord involvement [241,245]. In adults the majority of foregut cysts are asymptomatic and are chance radiographic findings on a routine chest film [246]. Large cysts may cause cough, stridor or dysphagia. Complications include recurrent lower respiratory tract infection due to pressure, and perforation due to either infection of the cyst itself or peptic ulceration in the case of gastric or gastroenteric cysts. Perforation may occur into the lung, pleural or pericardial cavities, causing haemoptysis, empyema or septic pericarditis [247,248]. Adenocarcinoma has been reported in a foregut cyst but is an exceptional complication [249,250].

### *Chest radiography*

The chest radiograph may show a rounded opacity sometimes with a hair-line margin (Fig. 49.11). The majority exceed 5 cm along their longest axis [5]. The cyst occasionally contains a fluid level, indicating communication with the respiratory or gastrointestinal tract [251]. Calcification is sometimes seen in the wall of the cyst, if not with plain radiography then with CT. The presence of spinal abnormalities, such as fused vertebral bodies or a dorsal scoliosis, implies that the cyst is neurenteric and is an indication for spinal MRI, which may reveal an intraspinal cystic abnormality even in the absence of neurological symptoms or signs [241,243,252]. Radioactive technetium-99m scanning may be positive in cysts lined by gastric mucosa [253].

### *Treatment*

Treatment is by surgical excision, which both establishes the diagnosis and avoids the possibility of future complications. In an acutely breathless child, emergency needle aspiration of a tense cyst offers temporary relief. When a coincidental intraspinal cystic component is discovered, neurosurgical removal is recommended because of the possible subsequent development of a neurological deficit [241]. Ulceration of a mediastinal cyst into the lung may necessitate both excision of the cyst and lobectomy. The



**Fig. 49.11** Large right-sided foregut cyst that caused tracheal compression and stridor.



prognosis for these cystic malformations is generally excellent, although incompletely resected foregut duplications may recur.

### **Pleuropericardial cyst**

Synonyms for pleuropericardial cysts abound and include pericardial cyst, coelomic cyst, springwater cyst, serosal cyst, mesothelial cyst, parapericardial cyst, simple cyst and hydrocele of the mediastinum! They are usually reported in surgical series as the second most common form of mediastinal cyst after foregut duplications, although it is possible that they may be seen more commonly in a physician's practice. Le Roux [254] estimated that one pericardial cyst was diagnosed per year for every 100 000 of the population studied.

### **Pathology**

Pleuropericardial cysts are usually considered to be developmental anomalies whose origin is uncertain. It has been suggested that they arise as a result of the persistence of the ventral parietal recess of the primitive intraembryonic coelomic cavity, from which the pericardial, pleural and peritoneal cavities develop [255,256]. The coelomic cavity itself may be formed by the fusion of multiple disconnected lacunae in the primitive mesenchyme and a failure of one of these lacunae to fuse with the continuum may result in the formation of a pleuropericardial cyst [257].

Of these cysts, 70% occur in the right cardiophrenic angle and are usually situated anteriorly, tending to be loosely adherent to the pericardium and diaphragm [258,259]. Most of the remainder occur in the left cardiophrenic angle but are occasionally found in unusual locations such as the superior or posterior mediastinal compartments [260–262].

The sex incidence is approximately equal and they may occur from infancy to old age [255]. They may vary widely in size, from 5 to 25 cm in diameter [263]. They are soft and are usually unilocular, their walls being thin, consisting of a single layer of flattened mesothelial cells supported by a connective tissue stroma [255,258]. They characteristically contain crystal-clear 'springwater', although this is occasionally a more brackish yellow. The fluid is acellular and contains little protein, having the features of a transudate. They are usually truly cystic, although a small proportion communicate with the pericardial or pleural cavities via a tubular connection and in such cases are therefore diverticula [5,255].

### **Clinical features**

Between 60 and 80% of pleuropericardial cysts are asymp-

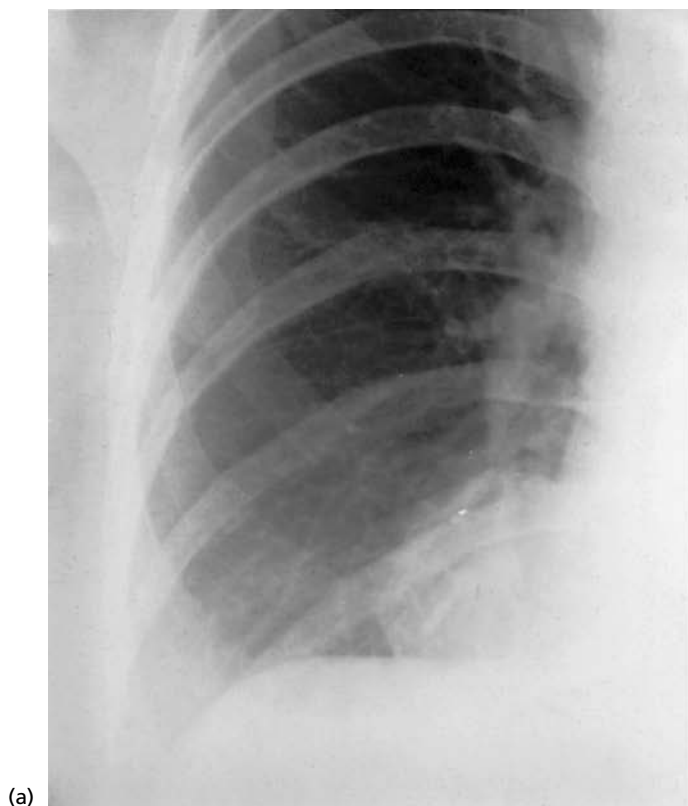
tomatic, presenting as a chance chest radiographic finding [5,255,258]. When symptoms are a feature, chest pain is most common, occurring in about 20% of cases. Pericardial cysts may compress the right middle lobe bronchus, causing cough and dyspnoea but this is unusual as they are under low pressure.

### **Diagnosis and treatment**

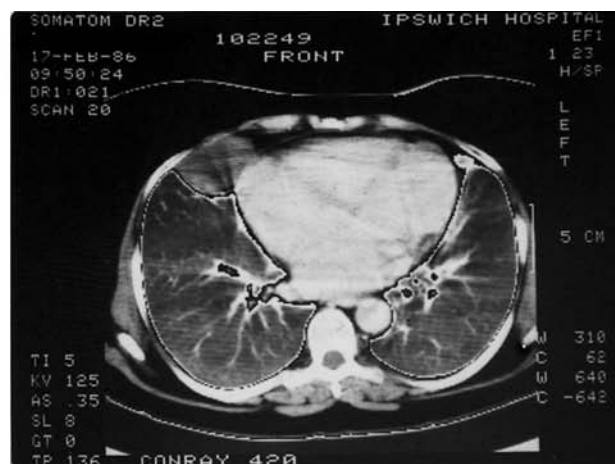
The provisional diagnosis is usually made following posteroanterior and lateral chest radiographs on the basis of a sharply demarcated, smooth-edged, rounded 'mass' shadow of uniform density situated anteriorly in the right, or less commonly the left, cardiophrenic angle and abutting the heart, diaphragm and anterior chest wall (Fig. 49.12a). Pericardial cysts have been observed to increase in size over a number of years on serial radiographs and a previously normal chest film does not exclude the diagnosis [255,258,264]. It is unusual for the rim of the cyst, which is very thin, to calcify. The absence of pulsation may be noted at fluoroscopy, as may the propensity of the cyst to alter shape during respiration and with postural change [257]. Echocardiography confirms the cystic nature of the lesion by showing a typical echolucent area that is anatomically distinct from the cardiac cavities [264]. CT shows a mass of fluid density that does not enhance following intravenous contrast [265–267] (Fig. 49.12b). The presence of a fluid-containing cyst may be confirmed by fine-needle thoracentesis of the lesion under ultrasound or CT control [268].

The most usual differential diagnoses are a prominent pericardial fat pad, an anterior diaphragmatic eventration and a diaphragmatic hernia through the foramen of Morgagni, which may contain gut or extraperitoneal fat. Less commonly, a pericardial cyst may be mimicked by a ventricular aneurysm and rarely by a rounded tumour of the middle lobe, pleura or diaphragm, or by a hydatid cyst, all of which may abut the heart or occupy the cardiophrenic angle. The differential diagnosis is much wider where a pericardial cyst is atypically situated elsewhere in the mediastinum or hilar regions.

The diagnosis may be confirmed and treated in symptomatic patients at thoracotomy or video thoracoscopy, in which case the pericardial cyst is excised [5,255,269,270]. This course of action removes doubt about the validity of the preoperative diagnosis, which has been shown to have been misplaced in earlier literature in up to 50% of cases [258]. Nowadays the diagnosis is more usually made using non-invasive imaging techniques and asymptomatic patients are managed conservatively [257,258,271,272]. CT may not always reliably differentiate between pericardial cysts and other cystic or low-density lesions, so that the uncertainty and anxiety of extended follow-up may be best removed by active surgical inter-



(a)



(b)

**Fig. 49.12** (a) Characteristic appearance of pericardial cyst in right cardiophrenic angle. (b) CT shows pericardial cyst at right cardiac border anteriorly.

vention [255,272,273]. Aspiration, although usually safe, carries a small risk of dissemination of disease or anaphylaxis in the rare case of hydatid cyst, which should be serologically excluded prior to needling if this is a concern. When aspiration is used the fluid often reaccumulates [258].

The prognosis following surgical excision is excellent and there have been no reported cases of malignant change [255]. Symptoms are not always relieved by cyst excision, implying that they are often coincidental [5].

### Thoracic duct cyst

These solitary cysts are a very rare intrathoracic finding and probably arise as a result of a developmental defect or weakness in the wall of the thoracic duct, of which they are really diverticula. They may be found accidentally on a routine chest radiograph that reveals a posterior mediastinal mass shadow, although symptoms of oesophageal or tracheal compression may sometimes be produced [274–276]. Ascending lymphangiography may be diagnostic if the condition is considered preoperatively [275]. Treatment is by surgical excision, which confirms the diagnosis and which should be curative. At operation a thin-walled, unilocular ‘cyst’ that contains chyle and which communicates with the thoracic duct is found. Chylothorax is a potential complication of operative treatment, although it should be possible for the surgeon to avoid this

by identifying and ligating the neck of the diverticulum as it arises from the thoracic duct [276].

### Retrosternal goitre and associated lesions

An extension of a cervical goitre into the thorax is probably the most common mediastinal tumour [5]. However, its true proportion is unknown as it is often managed by general rather than thoracic surgeons and its frequency therefore tends to be underestimated in surveys of mediastinal masses that appear in the thoracic literature. It is reported in one large series that 6% of cervical goitres have a retrosternal extension [277], whereas the finding of a retrosternal goitre in the absence of a goitre in the neck is rare.

#### Developmental features

Enlarging cervical goitres may expand into the thorax as a result of the anatomical restraints imposed by the cervical musculature and fascia, and also as a consequence of the effects of gravity and negative intrathoracic pressure. The usual pathological change in such intrathoracic extensions is nodular hyperplasia. Less commonly, thyroid tissue may find its way into the mediastinum during embryological development. A hollow diverticulum arises from the floor of the primitive pharynx in the fourth week of life at a site marked in the adult by the foramen caecum of the

tongue. The thyroid rudiment is formed in this process and it migrates caudally on a tube that becomes the thyroglossal duct. During the unfolding of the embryo, this rudiment may be dragged caudally in relation to the primitive aorta so that truly ectopic thyroid tissue may be found anywhere along a track extending from the tongue through the superior and anterior mediastinal compartments to the pericardium and heart [278,279].

### *Pathology*

Macroscopically, intrathoracic goitres nearly always extend from the lower pole of a lateral lobe, anterior to the trachea and immediately behind the sternum, although about 10% are situated posterior to the trachea and oesophagus. The histological features are no different from those of a cervical goitre and they are usually non-toxic.

### *Clinical features*

Retrosternal goitre occurs more commonly in females and in the middle-aged and elderly [277]. An Australian epidemiological study carried out during a mass radiography campaign found the incidence to be 1 in 2000 in females over the age of 45 years compared with 1 in 5000 for the whole of the population that was screened [280]. When symptoms occur, they usually come on insidiously as growth is generally slow. Dyspnoea is the most common symptom and may be accompanied by cough and stridor due to tracheal compression. Other symptoms are less frequently encountered and include dysphagia, hoarseness due to recurrent laryngeal nerve palsy and,

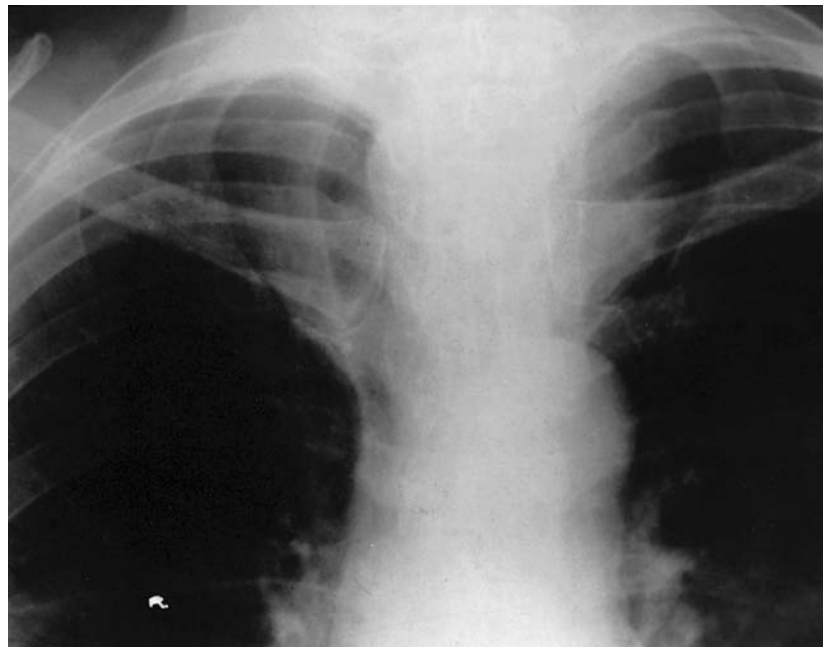
occasionally, those of thyrotoxicosis. Obstruction of the superior vena cava may occur [277]. A goitre is usually palpable in the neck but this sign may be easily missed in an obese patient. A retrosternal extension should always be suspected in a breathless patient with a cervical goitre or a thyroidectomy scar. Patients with ectopic thyroid tissue in the absence of a goitre in the neck are usually free of symptoms, the diagnosis being made at thoracotomy following the finding of an anterior mediastinal mass shadow on a routine chest radiograph taken for some other purpose.

Intrathoracic goitres may be complicated by haemorrhage into the substance of the gland, which can produce sudden severe dyspnoea that constitutes a surgical emergency. Malignant change was found in 16% of one surgical series of retrosternal goitres and is no less likely if the goitre is long-standing [277].

### *Investigation and diagnosis*

Posteroanterior and lateral chest radiographs show a rounded opacity occupying the anterior and superior mediastinal compartments. The upper border is usually indefinable because of extension into the neck. The shadow is often more prominent on the right and may displace the trachea (Fig. 49.13). Calcification is occasionally visible.

A positive radioactive iodine isotope scan is diagnostic of the presence of functioning thyroid tissue in the neck and mediastinum and is found in over half of all cases of retrosternal goitre. However, a negative scan does not exclude goitre since the thyroid tissue may be non-functioning [281]. Technetium-99m is sometimes used but



**Fig. 49.13** Retrosternal goitre showing marked displacement of trachea to the right.

although more convenient is less reliable, occasionally giving negative results where iodine-131 uptake is positive.

CT is capable of demonstrating the anatomical continuity of a retrosternal goitre with the lower pole of cervical thyroid; where there is no such continuity, the presence of ectopic thyroid may be suspected [282]. The iodine content of thyroid tissue may give higher attenuation values than would be expected from a soft tissue mass of non-thyroid origin. A barium swallow may be carried out when dysphagia is present and thyroid function is assessed biochemically.

The differential diagnosis includes any superior or anterior mediastinal tumour, particularly thymic masses and germ-cell tumours. Sometimes an aortic aneurysm may be suspected, in which case MRI, CT with contrast or aortography may be used.

### *Treatment*

It is a general rule that intrathoracic goitres should be surgically removed provided that the patient is fit enough to undergo the operation. The reasons for this are obvious in a symptomatic patient, although removal is still justified in symptom-free subjects in order to avoid the development of rare potentially life-threatening complications, such as haemorrhage into the substance of the gland [277]. The vast majority of thoracic extensions are removed using a cervical approach. Where an anterior mediastinal component is very large, the collar incision may need to be extended by a sternotomy [4].

### **Parathyroid adenomas and cysts**

Mediastinal parathyroid adenomas are sometimes found when surgical exploration of the neck in a patient with hyperparathyroidism fails to reveal a tumour in the usual location. The occasional ectopic position of these adenomas is explicable in terms of the common embryological development of the inferior parathyroid gland and the thymus, both of which arise from the third branchial pouch, so that ectopic parathyroid lesions may be found embedded in the thymus gland. One series found 7% of parathyroid adenomas to be situated in the mediastinum [283]. In another series of 400 patients with hyperparathyroidism, 21% had mediastinal adenomas [284]. The majority of these could be removed via a cervical incision and only 19 required a sternotomy. About 65% of mediastinal parathyroid adenomas are situated in the anterior part of the superior mediastinum and the remainder in the posterior part [285]. They often go unnoticed preoperatively because they are often small and nodular, although they may grow larger than their counterparts in the neck without exciting attention. Attempts may be made to identify small tumours by CT, MRI, radioisotope scintigraphy,

selective arteriography and venous sampling with parathormone assay [286–289]. Hormonally inactive mediastinal parathyroid cysts occasionally occur and may be large enough to manifest themselves on plain chest radiographs [290]. They have been known to cause symptoms of tracheal compression and recurrent laryngeal nerve palsy [291].

### **Aortic aneurysm**

Aortic aneurysms enter the differential diagnosis when a widened mediastinum is found on the chest radiograph. They have been defined as a permanent localized dilatation of the aorta that results in a diameter at least 50% greater than normal [292]. The possible causes range from degenerative change associated with cystic medial degeneration and atherosclerosis, to congenital disorders such as Marfan's syndrome and Ehlers–Danlos syndrome to connective tissue disorders, trauma and infection [293]; the most important single risk factor for dissection is hypertension.

### *Clinical features*

Frequently, thoracic aortic aneurysms are asymptomatic at the time of detection. However, pressure on adjacent structures may occur during the course of enlargement, with dysphagia, stridor or dysphonia due to compression of the oesophagus, trachea and left recurrent laryngeal nerve. Compression of the superior vena cava may also occur. Aneurysms of the aortic arch may cause pain referred to the neck and jaw, and those involving the descending thoracic aorta may cause interscapular or left chest pain. The sudden onset of such pain may indicate an acute aortic dissection or intramural bleed [293]. Other symptoms may result from heart failure in connection with associated aortic regurgitation or may be the result of the occlusion of aortic branches. Aneurysms of the brachiocephalic (innominate) and left common carotid arteries may also produce superior mediastinal 'mass lesions' on the chest radiograph and symptoms of tracheal compression [294].

### *Investigation*

Although often first suspected following chest radiography, plain chest films may miss significant retrosternal aneurysmal dilatation and cannot always differentiate a vascular opacity from other mediastinal masses [295]; indeed thoracic aortic aneurysms have sometimes been unwittingly subjected to percutaneous needle biopsy with alarming results for all concerned. MRI provides the best images of thoracic aortic disease, particularly dissections, and does not require contrast; however, it is difficult to perform on iller patients who may be attached to

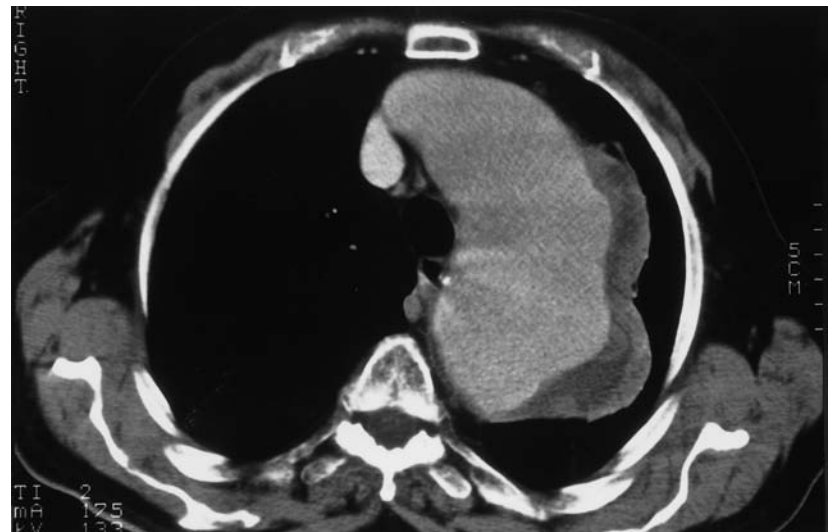
monitoring devices and CT is still widely used [294] (Fig. 49.14). CT or MRI may be carried out serially in order to monitor the size of aneurysms so that decisions can be made about when to intervene surgically, although aortography is still usually required before elective surgical intervention.

### *Treatment*

Surgical treatment is intended to reduce complications and in particular to prevent death from rupture. Series of patients with thoracic aortic aneurysms who did not undergo surgery showed that rupture of the aneurysm



(a)



(b)

**Fig. 49.14** (a) Chest radiograph showing a large suprahilar mass, which CT contrast imaging (b) showed to be a hugely dilated aneurysmal aortic arch containing mural thrombus in its lateral aspect.

was the most common cause of death, rates ranging from 42 to 70% [293,296]. The risk of rupture is increased for dissecting aneurysms and is also much greater for aneurysms exceeding 6 cm in diameter [296]. The earliest successful cardiothoracic surgical replacements of the ascending aorta and aortic arch were carried out over 40 years ago, since when there have been considerable improvements in both surgical and cardiopulmonary bypass techniques. At present, in asymptomatic patients consideration is given to replacing thoracic aortic aneurysms with grafts when the diameter of the aneurysm exceeds 5–6 cm, although these figures may well be reviewed as experience accrues. All patients with acute dissections of the ascending aorta should be considered for surgery, without which about 90% die within 3 months. A mechanical aortic valve prosthesis may be incorporated into the ascending aortic graft if this is necessary and the coronary arteries are implanted into the graft. The aortic arch may also be replaced with a graft where necessary and this may be indicated in acute dissection where an intimal tear has occurred in the arch. Most acute aortic dissections affecting the descending aorta may be managed medically at first, blood pressure being controlled with drugs such as nitroprusside.

## Diaphragmatic herniae

Hiatus herniae are a common cause of a double retrocardiac 'shadow' that often contains a fluid level, the lateral radiographic projection confirming the physician's suspicion. These are often incidental findings on a radiograph taken for some other reason and patients with surprisingly large hiatus herniae may have no symptoms referable to them, in which case surgical intervention is seldom justified. Symptoms of oesophageal reflux may occur and can usually be dealt with medically. There is a small risk of paraoesophageal herniae becoming incarcerated and strangulating and when this does happen it creates an acute surgical emergency. Surgical intervention may also be needed to dilate oesophageal strictures should these arise. Diaphragmatic herniae may also occur posteriorly through the foramen of Bochdalek or anteriorly through the foramen of Morgagni. Bowel or omentum or both may be contained in the hernial sac. These and other diaphragmatic lesions that may sometimes abut the mediastinum are described more fully in Chapter 46.

## Mediastinitis

### Acute mediastinitis

#### Causes

The commonest cause of acute mediastinitis is oesophageal perforation [297]. This may occur as the result of a difficult endoscopy. Attempts to dilate a stric-

ture or to insert a tube or stent for palliative purposes in carcinoma may have the same effect and a carcinoma may itself perforate spontaneously. Other causes of oesophageal perforation include accidental blunt or penetrating injury of the chest, surgery to the oesophagus or adjacent structures and ingestion of a foreign body. Forceful vomiting commonly causes a Mallory–Weiss mucosal tear but it is unusual for the entire wall of the oesophagus to rupture (Boerhaave's syndrome).

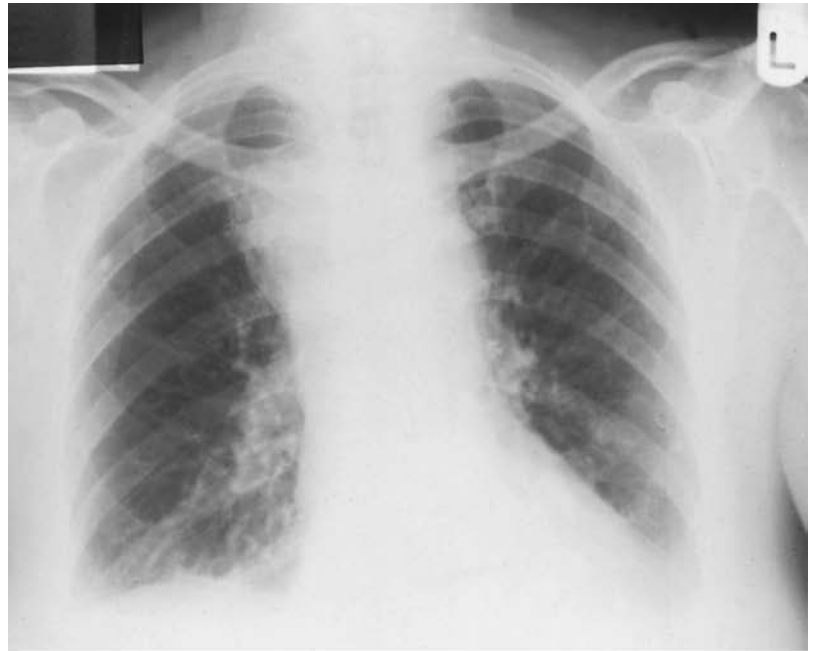
Infection may also track down to the mediastinum from higher levels, particularly along the so-called 'danger space', a potential cavity created by a fascial plane that runs from the upper cervical level as far caudally as the diaphragm [298]. Infection from the mouth, neck or retropharyngeal space may extend into this space, between the prevertebral fascia posteriorly and the alar fascia anteriorly, and result in acute mediastinitis. The portal of entry is occasionally a small oropharyngeal mucosal tear resulting from a difficult endotracheal intubation. Other less common causes include the extension of infection from the lung, pleural or pericardial cavities, with or without abscess formation. The spread of such infection may be direct or it may be carried by lymphatic drainage, with subsequent suppuration of mediastinal nodes. Osteomyelitis of the cervical or dorsal spine, ribs or sternum may also spread directly to the mediastinum. Surgical incisions in the neck and thorax may become infected with subsequent mediastinitis, particularly following tracheostomy and sternotomy. Infection may also reach the mediastinum from central venous cannulation sites in the neck. Tuberculous mediastinitis is now rare as is haematogenous spread of infection from remote sites.

### Clinical features

The patient usually feels ill and is febrile. There may be rigors. Swallowing often produces pain so that food is refused. Movements of the neck may produce discomfort if infection has tracked down from this area, so that the anxious patient may look fixedly to the front. A cough may indicate tracheal involvement. Mediastinal and subcutaneous emphysema may occur, particularly if the oesophagus is perforated, and a pleural effusion, empyema or pyopneumothorax may sometimes be produced. Retrosternal pain may be present and sternal tenderness may be elicited.

### Investigation

The chest radiograph may be normal or if fluid or pus are collecting in the mediastinum, a smooth-walled convex opacity may be seen bulging laterally beyond the mediastinal boundaries with displacement of the trachea and oesophagus (Fig. 49.15). Gas may be seen in the



(a)



(b)

**Fig. 49.15** (a) Posteroanterior film of patient with mediastinal abscess following faulty placement of central venous canula showing mass to right of upper mediastinum. (b) Right lateral view showing opacity surrounding trachea and displacing it forwards.



mediastinum or fascial planes of the neck, this being a feature of a mixed anaerobic infection in which organisms have gained entry from the oropharynx. There may be evidence of a pleural effusion or pyopneumothorax. Lateral soft tissue radiographs of the neck may show an increase in width of the retropharyngeal soft tissue. CT may show retropharyngeal inflammatory changes and gas, with possible extension to the mediastinum. This examination should be performed early as it may well show abnormalities at a time when plain radiographs are normal or show only subtle changes. The presence of a mediastinal abscess may also be shown by CT. Leakage through an oesophageal or pharyngeal tear may sometimes be demonstrated if a water-soluble non-ionic contrast (e.g. lopamidol, Gastromiro) examination of the oesophagus is undertaken. High-osmolality contrast media such as Gastrografin tend to be avoided as any 'spillover' into the lung in the presence of dysphagia may result in pulmonary oedema.

### **Treatment**

The patient should be monitored closely as acute mediastinitis is potentially fatal. Treatment consists of a broad spectrum of parenteral antibiotics, including cover for anaerobic bacteria [299]. Initial combinations might include penicillin and metronidazole plus an aminoglycoside, or clindamycin also with an aminoglycoside. Surgical drainage is essential where there is radiographic evidence of an accumulation of pus in the neck and/or mediastinum, in which case early thoracic and otorhinolaryngological opinions are necessary. Both these territories may require separate drainage and a thoracotomy may be required to achieve adequate mediastinal drainage [298]. Any pleural collections that may be present also require adequate drainage. The degree of intervention depends upon the nature and extent of the underlying disease process, so that a foreign body may be removed endoscopically, a postmetic oesophageal rupture repaired, and an advanced and inoperable oesophageal carcinoma managed conservatively. A literature review of necrotizing mediastinitis found a mortality rate of 31%, despite the availability of antibiotics [298].

### **Chronic mediastinitis**

Chronic mediastinitis may be caused by low-grade infection and in such cases the responsible organisms may be fungal or mycobacterial. It is possible that John Hunter's mid-eighteenth century description of mediastinal fibrosis (see below) may have been caused by tuberculosis or even syphilis [300]. More recent series from North America have implicated *Histoplasma capsulatum*, this organism having been found to be responsible for 26 cases of mediastinal granuloma or fibrosis in the series of Goodwin, the

remaining 12 cases being thought to have been caused by *Mycobacterium tuberculosis* [301]. The condition may also sometimes occur with nocardiosis [302], actinomycosis [303], blastomycosis [304], coccidioidomycosis [304] and aspergillosis [305]. Patients may be asymptomatic, coming to attention following the finding of mediastinal widening on a chest radiograph taken for some unrelated reason. They may also present with symptoms of cryptogenic mediastinal fibrosis, into which chronic mediastinitis imperceptibly merges. Where an infecting agent is identified, appropriate antimicrobial therapy can be tried but usually fibrotic change predominates so that any therapeutic distinction from cryptogenic mediastinal fibrosis is problematical. Antifungal agents have been tried when histoplasmosis was suspected as the cause but evidence of benefit is somewhat anecdotal and no controlled trials have been carried out [306].

### **Cryptogenic mediastinal fibrosis**

The different names that have been attached to this condition are a reflection of both its rarity and a general sense of ignorance about its cause. These names include fibrosing mediastinitis, sclerosing mediastinitis, chronic fibrous mediastinitis, chronic mediastinal fibrosis and idiopathic fibrosis of the mediastinum. All these terms are intended to convey the slowly progressive envelopment of mediastinal structures in fibrotic tissue.

### **Possible causes**

The first description has been attributed to John Hunter in 1757 [300]. Although such early reports may well have included cases due to tuberculosis or even syphilis, which were highly prevalent at the time, more recent descriptions have failed to identify a cause in over 80% of cases, hence the use of the term 'cryptogenic'. Those few cases where the aetiology is known should be referred to as chronic mediastinitis or mediastinal fibrosis due to whatever causal agent has been identified (as above). Infection with *H. capsulatum* is a recurrent theme in North American reports of fibrosing mediastinitis [307,308]. This infection is highly endemic in parts of the central USA, where residence produces almost invariable infection that is of no clinical consequence in the vast majority [309]. It has been proposed that immune stimulation may result from the seepage of material from infected lymph nodes; however, cultures and silver stains are usually negative in these cases and although there is a strong suspicion of an association between *Histoplasma* infection and consequent mediastinal fibrosis, clear proof is often lacking. It has also been suggested that the mediastinal fibrosis in these cases results from a delayed hypersensitivity reaction to mycobacterial, fungal or other unidentified antigens [301]. It is notable that histological reports where histoplasmosis

is the supposed cause refer to the presence of granuloma formation and caseation, hence the term 'mediastinal granuloma', whereas these are not regarded as typical features in European reports of the cryptogenic form [310,311].

A retrospective series of 18 patients collected at one British centre over the space of 23 years obtained a history of previous pulmonary tuberculosis in half of them but with no evidence of active infection at the time of diagnosis [311]. Cryptogenic fibrosing mediastinitis is occasionally associated with retroperitoneal fibrosis and both these conditions may sometimes coexist with Riedel's thyroiditis, sclerosing cholangitis, orbital pseudotumour and sclerosing mesenteritis. The histological similarities between all these conditions have been noted and have given rise to the term 'multifocal fibrosclerosis', which implies a systemic disorder with a possible common aetiology [310]. There have been reports of hypergammaglobulinaemia and hypercomplementaemia, as well as a prominent plasma cell infiltration, in patients with cryptogenic fibrosing mediastinitis and this has stimulated speculation that there may be an immune basis for the disorder [312]. Practolol and methysergide have been associated with peritoneal and retroperitoneal fibrosis. The former, a  $\beta$ -blocker, has been withdrawn from use and neither of these drugs, the second of which is used as prophylactic treatment for severe migraine, has been shown to cause mediastinal fibrosis, although pleural effusions, pleural friction rubs and microscopic evidence of pulmonary fibrosis have been described in a few patients receiving methysergide therapy [313].

### *Pathology*

Masses of ill-defined sclerotic tissue encase and may compress the mediastinal structures. Any part of the mediastinum may be involved and tissue planes are not respected. Histology shows that the predominant feature is the presence of bundles of intertwining hypocellular collagenous tissue containing an infiltrate of mainly plasma cells with some lymphocytes, polymorphs and fibroblasts, the process extending into surrounding connective tissue and fat [310,312].

### *Clinical features*

The diagnosis is most commonly made in the fourth decade of life, although the condition may occur at any age. It is found with equal frequency in men and women. It may be identified following the finding of mediastinal widening on the chest radiograph of an asymptomatic individual or it may present with the insidious onset of symptoms of obstruction of the superior vena cava, so that the patient may notice swelling of the face, neck and arms, particularly in the mornings, at which time there may be

headache and difficulty in buttoning the shirt collar [314]. Conjunctival oedema and anterior chest wall and neck vein engorgement may become evident and the patient may have a suffused complexion. These symptoms do not inevitably progress, presumably due to either the cessation of the fibrotic process or the opening up of collateral vessels [304]. Other symptoms may include dyspnoea and dysphagia, since both tracheobronchial and oesophageal compression may occur.

In some cases the fibrotic process may be limited to one or both hilar regions, with possible narrowing of the hilar vasculature and bronchi [315]. Bronchial compression may cause cough, breathlessness and recurrent lower respiratory tract infection. Pulmonary arterial hypertension may be produced if compression is bilateral. Haemoptysis may be produced by infection, bronchial invasion or as a result of pulmonary venous hypertension. It has been suggested that this distribution of fibrosis is more likely to be found in younger age groups but this may be an oversimplification [315,316].

### *Radiographic features*

These are non-specific. There may be widening of the mediastinal shadow and the mediastinum may be displaced towards the side of the most dense fibrosis. Either hilar shadow may be prominent. Calcification within the fibrotic mass may sometimes be seen. An affected pulmonary artery may be small. There may be cardiomegaly and compressed pulmonary veins may produce Kerley's B lines. A barium swallow or bronchoscopy may demonstrate areas of compression or distortion. There may be confusion with chronic thrombotic pulmonary arterial occlusion in those cases with pulmonary arterial hypertension, and this may be compounded by similar appearances on ventilation-perfusion lung scanning and pulmonary arteriography [317]. CT and MRI of the mediastinum may help to delineate the extent of the disease process [318,319], although biopsy is necessary to provide a tissue diagnosis and to exclude a neoplastic process, particularly as a fibrotic reaction may be associated with some tumours including lymphoma. This is best done surgically, usually by mediastinoscopy or anterior mediastinotomy provided that the patient is fit enough, and several blocks of tissue should be obtained. It is important that the diagnosis is confirmed histologically, since in the days before CT 'blind treatment' with radiotherapy on the assumption that a carcinoma was responsible for obstruction of the superior vena cava has been known to produce a later myelopathy with a tragic and permanent neurological deficit.

### *Treatment*

Medical treatment has nothing to offer, corticosteroids

having proved ineffectual and penicillamine having been of no demonstrable benefit [320]. Occasionally, fibrotic tissue may be localized and is surgically removable but usually it is diffuse and cannot be cleared. A bypass graft may relieve obstruction of the superior vena cava in severe

cases that do not develop an adequate collateral drainage [311,321]. Oesophageal strictures may require dilatation. Attempts to dilate bronchial strictures have been known to cause severe bleeding.

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# DEVELOPMENTAL DISORDERS OF THE LUNGS

DOUGLAS SEATON AND ANTHONY SEATON

Developmental disorders of the lungs are for the most part congenital, i.e. they exist from birth, being the consequence of disordered organogenesis following conception. As the development of the respiratory tract occurs according to a strict timetable (see Chapter 1), abnormalities present at birth may be accurately dated to disturbances of intercellular relationships that have occurred at fixed points in intrauterine life. Although major structural abnormalities of the respiratory tract and its adnexae are usually fatal, such effects are now frequently diagnosed before birth or early in postnatal life so that corrective surgery may be applied in certain cases. Other developmental anomalies may not manifest themselves until much later in life and although rare are of considerable interest to the practising physician.

A number of genetically based and ultrastructural disorders, including ciliary abnormalities, cystic fibrosis,  $\alpha_1$ -antitrypsin deficiency and skeletal dysplastic syndromes or chondrodystrophies, are considered elsewhere in this book. Hamartomas of the lung (mesenchymomas) are considered as benign neoplasms in Chapter 42.

## Tracheobronchial anomalies

The lower respiratory tract shares its embryological origin with the primitive foregut, arising from its ventral surface in the fourth week of intrauterine life as an epithelial laryngotracheal bud or 'respiratory primordial pouch' [1–3]. The subsequent development of the tracheobronchial tree and oesophagus proceeds concurrently, with the result that congenital abnormalities of one frequently involve the other, over 50 such anomalies having been recorded [4]. Respiratory tissues comprising airways and spaces distal to the terminal bronchioles are derived from mesoderm and are developmentally connected to epithelially derived proximal conducting airways in order to form a normal gas-exchanging pathway. Developmental errors of the tracheobronchial tree cannot arise after the 16th week of intrauterine life, since by this time its formation is complete [5].

## Tracheal agenesis

Tracheal agenesis or aplasia refers to the absence of growth in the trachea or in part of it. It has a male to female preponderance of 2:1 and is often incompatible with life [6,7]. Three main anatomical patterns are recognized [8].

Type 1, in which there is agenesis of the proximal trachea, accounts for 20% of cases. The distal trachea is present and is often connected to the oesophagus by a fistulous communication.

Type 2, in which the main bronchi join in the midline and communicate with the oesophagus by a single fistula, is the most common variety accounting for 60% of cases.

Type 3, in which the left and right main bronchi join the oesophagus independently, accounts for the remaining 20% of cases.

Occasionally, the coexistence of a tracheo-oesophageal fistula permits air to enter the lungs so that the infant may survive for a period. In these circumstances, early diagnosis may allow temporary measures to sustain respiration and later reconstructive surgery to be undertaken [9–11].

Sometimes the trachea, though patent, is shortened owing to the absence of a number of cartilaginous rings, as in congenital brevicollis or the 'short neck syndrome', most commonly associated with Klippel–Feil syndrome, and characterized by a triad of short neck, decreased neck mobility and low occipital hairline [8,12].

## Tracheo-oesophageal fistula

The H-type tracheo-oesophageal fistula (Fig. 50.1), in which both the trachea and oesophagus remain patent, may be sufficiently small to go undetected until adult life, despite the presence of recurrent symptoms from infancy [13,14]. Aspiration of oesophageal contents into the airways may cause choking, with cough and cyanotic episodes after feeding. The passage of air through the fistula and into the oesophagus in the reverse direction

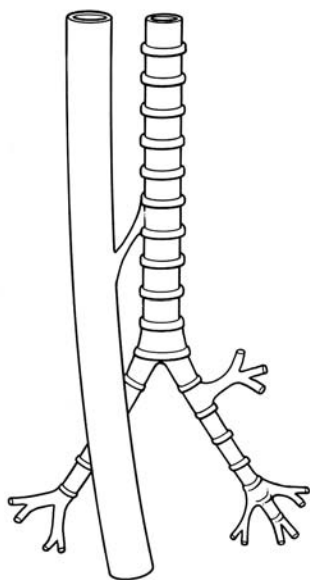


Fig. 50.1 H-type tracheo-oesophageal fistula.

may cause abdominal distension. Recurrent pneumonia is common [15]. Tracheo-oesophageal fistula may occur in partial tracheal agenesis [8] and also in oesophageal atresia, typified by a blind proximal pouch and distal fistulous communication between the lower oesophagus and trachea [16]. Tracheo-oesophageal fistula may also occur familiarly [17].

### Tracheal stenosis

Tracheal stenosis (Fig. 50.2) is diffuse in 30% of cases, the pars membranacea being absent so that the trachea is encircled by 'napkin-ring' cartilages, the total number of which may exceed the usual complement of 22. More commonly (50% of cases) the stenoses are segmental and may occur with equal frequency in the upper, middle and lower parts of the trachea. In 20% of cases the stenosis is carrot or funnel-like and this is associated with the 'sling' left pulmonary artery syndrome, described below [18,19]. Tracheal stenoses are associated with tracheo-oesophageal fistulae, and accessory bronchi arising from the trachea may also be found [20]. An association with Down's syndrome has been reported [21]. The condition usually presents in infancy with stridor and respiratory insufficiency. Surgical treatment may be necessary, and various plastic tracheal reconstruction procedures have been described [22–24].

### Tracheal narrowing due to extrinsic pressure

Congenital tracheal narrowing due to extrinsic pressure generally results from the close proximity of unusually large or abnormally placed vessels that have arisen as the

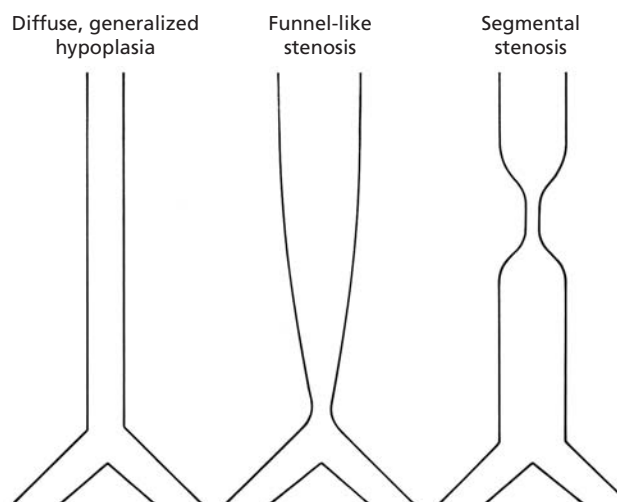


Fig. 50.2 Three types of tracheal stenosis.

result of faulty development of the primitive system of branchial arches (see Chapter 1). These anomalies are, in order of frequency, double aortic arch (47%), right aortic arch with left ligamentum arteriosum (20%), retro-oesophageal right subclavian artery (14%), anomalous innominate artery (11%), anomalous left carotid artery (4%), retrotracheal or 'sling' left pulmonary artery (3%) and right aortic arch with aberrant left subclavian artery (1%) [8,25]. Occasionally, the combination of anomalous vessels with congenital tracheal stenosis requires surgical repair [26].

### Tracheomalacia

This term is used to indicate excessive weakness and collapsibility of the tracheal walls as a result of abnormally soft or pliable cartilages. It may occur in localized form as the result of a deficiency of cartilage in a short segment of trachea [27]. This condition may be mistakenly diagnosed in the presence of obstructive airways disease in which high intrathoracic pressures are produced during expiration, with resultant compression of even the normal upper respiratory tract. It should be noted that acquired forms of tracheomalacia occur as a result of prolonged endotracheal intubation and in the rare systemic disorder of cartilage known as relapsing polychondritis (see Chapter 45). Tracheomalacia may be associated with other tracheo-oesophageal anomalies and presents in childhood with expiratory airflow obstruction and apnoeic episodes. In severe cases surgical intervention with aortopexy and various tracheal splinting procedures may be necessary [28,29].

### Tracheobronchomegaly

Tracheobronchomegaly [30–33] is a rare disease character-

ized by unusual width of the trachea and main bronchi and, because of the ineffectiveness of cough, often complicated by lower respiratory infection and bronchiectasis [34]. The cough may have a loud booming quality. The disease is probably congenital and may be inherited as an autosomal recessive; it has been recorded in association with Ehlers–Danlos syndrome. Most reported cases have been in young adults but it has been found in children. There is an atrophic or congenital defect of the connective tissues of the trachea and main bronchi. The condition may be missed on the plain chest film but is obvious on the tracheo-bronchogram and on CT or magnetic resonance imaging [35]. There is gross variation in diameter of the trachea with respiration and there may be other distortions and irregularities.

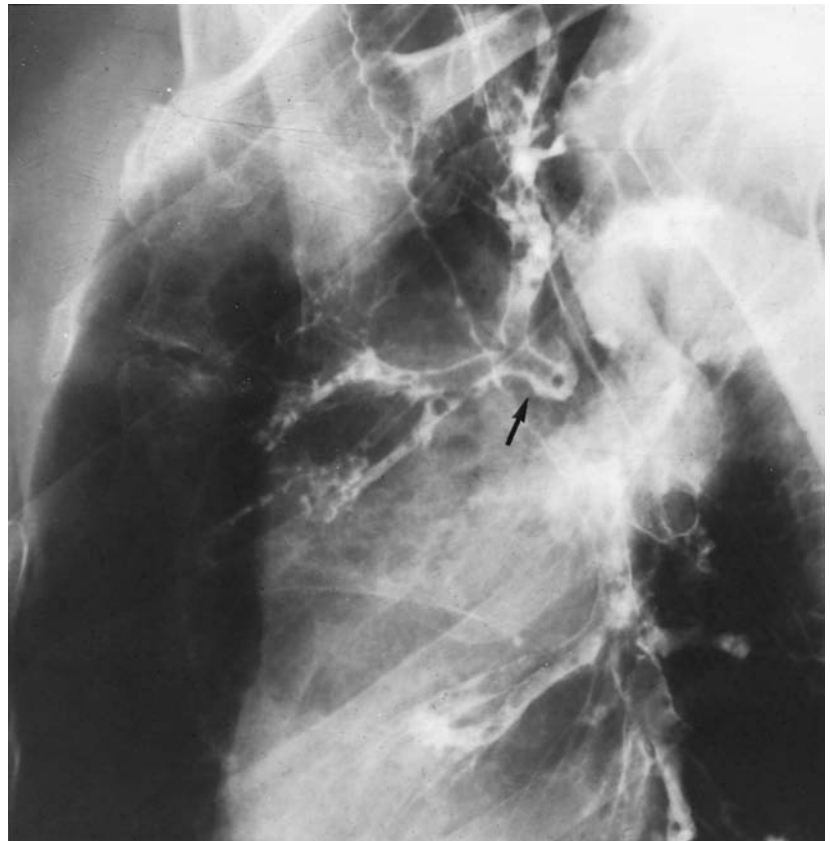
Those of the foregoing conditions that cause either a structural or functional narrowing of the trachea may produce clinical features, including wheezy dyspnoea, respiratory distress during feeding, recurrent lower respiratory tract infection, stridor, tugging inspiratory effort with intercostal muscle retraction, cyanosis and apnoeic episodes.

#### **Abnormal patterns of bronchial branching**

These are usually found at bronchoscopy and are seldom

of clinical significance, other than when resective surgery is being undertaken for some other reason. The abnormalities are more often additive than subtractive and, as might be anticipated, more variability is found at segmental level than in larger proximal bronchi. The most common major anomaly is a supernumerary right upper lobe bronchus [36], which may arise anywhere from the trachea or right main bronchus (Fig. 50.3). The frequency of tracheal origin is estimated at 0.9% and of double origin from the right upper lobe bronchus at 0.4% [37]. Sometimes the origin of an upper lobe bronchus may be displaced so that it arises only from the trachea with no separate main bronchial origin. Absence of an upper lobe bronchus is the most common of the major subtractive abnormalities (0.3%). The most common segmental anomaly is a double-stem apical lower lobe segmental bronchus that occurred in 7% of one series [37], the incidence being slightly higher on the right than on the left. Unusually, an apical upper lobe segmental bronchus may arise from the trachea in either displaced or supernumerary fashion.

Bronchial isomerism is a term applied to a rare group of developmentally anomalous syndromes in which the normal pattern of bronchial branching in either the left or the right lung is mirrored in the contralateral lung, resulting in a so-called bilateral left or right lung. Developmen-



**Fig. 50.3** Supernumerary right upper lobe bronchus arising from trachea shown at bronchography.

tal abnormalities of the heart, great vessels, liver, spleen and gut frequently coexist [38].

### **Bronchial atresia**

This rare condition has been reviewed by Meng and colleagues [39]. It probably arises as a result of a developmental interruption of normal bronchial continuity in which a length of bronchus, usually the apicoposterior segmental bronchus of the left upper lobe [40], becomes sealed off from the larger proximal airways to which it may remain connected by thin, uncanalized, fibrous, vestigial strands. This sealed-off or atretic bronchus becomes distended by bronchial secretions, resulting in the formation of a cystic space or mucocoele. Some degree of collateral ventilation to lung subtended by the atresia is maintained via the inter-alveolar pores of Kohn, although normal postnatal alveolar development to this part of the lung is retarded, with a reduced alveolar count. The pattern of bronchial branching distal to the atretic segment, having developed antenatally, remains intact [41]. Abnormalities of the vascular supply of the affected lungs have been recorded and may be causally related to bronchial atresia, as may a described association with pectus excavatum [42].

The majority of patients are asymptomatic and the diagnosis of bronchial atresia is made in young adult life following a chest radiograph that has been requested for some other reason. Less than one-third of patients present with symptoms due to lower respiratory tract infection. The chest radiograph shows the mucocoele as a coin lesion and part of the lung distal to it appears hyperlucent as a result of collateral air trapping. Bronchography showed non-filling of the affected bronchus, and the surrounding bronchi may appear to be displaced by the peripheral zone of hyperlucency [5]. CT allows the diagnosis to be made with some confidence [43]. Although the risk of infection in untreated bronchial atresia is estimated to be low, in most reported cases the diagnosis has been made following surgical excision of the atretic segment by lobectomy or segmentectomy [39].

### **Bronchogenic cysts (syn. bronchial cysts)**

Bronchogenic cysts arise as a result of abnormal budding of the tracheobronchial tree during the course of its development between the 26th day and 16th week of intrauterine life [1,44], in which a tracheal or bronchial bud becomes detached from its parent, thereafter developing separately to produce a cystic structure. Bronchogenic cysts are more common in males and apparently in Yemenite Jews [45,46]. They may be classified according to their situation as either central (syn. mediastinal) or peripheral (syn. intraparenchymal, intralobar). Central bronchogenic cysts presumably arise earlier in the devel-

opmental process, detaching themselves from major airways and occupying a position alongside the trachea, at the level of the carina or close to a main or lobar bronchus, or juxtaposed to the oesophagus [47,48]. If the developmental anomaly arises at a later stage, then the cyst or cysts are situated towards the periphery of the lung. In several reported series the peripheral situation is at least as common as the central one [49–52], and two-thirds of peripheral cysts occur in the lower lobes [36,52]. Bronchogenic cysts are usually single but are occasionally multiple and may sometimes arise in both lungs [36,52]; unusually they may occur in ectopic situations in relation to the pericardium [53], diaphragm [54], vertebral column [55] and skin [56].

### **Pathological features**

Bronchogenic cysts vary in size and may reach 10 cm in diameter [48,52]. Their walls may be thin but increase in thickness following infection. They are usually lined by ciliated respiratory epithelium and contain smooth muscle, elastic tissue, cartilaginous trabeculations and mucous glands. The presence of cartilage in their walls serves to distinguish them from cysts of different origin. A fistulous communication with an adjacent airway may be present, and in these circumstances the cyst may be filled with air. A ball-valve mechanism may cause it to enlarge and present in infancy or exceedingly rarely in young adult life by causing displacement of normal lung [57]. Intact and uninfected cysts contain clear fluid. The presence of infection tends to destroy the characteristic histological features so that it may become extremely difficult to distinguish between a chronically infected bronchogenic cyst and an acquired lung abscess [58]. Complication by development of rhabdomyosarcoma has been described [59].

### **Clinical features**

Bronchogenic cysts are frequently asymptomatic and may come to light as an abnormal shadow on a chest radiograph that has been requested for some unrelated reason. When symptoms do occur, they result from either a mass effect on adjacent structures or more frequently infection. Pressure on the trachea or a proximal bronchus may produce dyspnoea, cough and stridor, and on the heart may cause dysrhythmias. Oesophageal compression may result in dysphagia. Repeated lower respiratory tract infection or atelectasis may be caused by bronchial compression. Should the contents of the cyst become infected, it may enlarge and rupture into either the mediastinum or an adjacent airway, resulting in a cough productive of mucopurulent material or haemoptysis.

### Radiographic features

The diagnosis is suspected following the radiographic finding of a well-circumscribed, rounded, homogeneous opacity situated either in the mediastinum close to a major airway or in the lung periphery (Fig. 50.4). If a fistulous communication is present, an air–fluid level may be visible and rarely it may mimic a large emphysematous bulla. The presence of calcification in the wall of the cyst is a variable and uncertain feature. If the cyst is centrally situated, a barium swallow may demonstrate oesophageal compression.

### Treatment

Elective surgical resection of the lesion is generally advised because it is often impossible to make a firm diagnosis preoperatively, and a neoplastic condition cannot be excluded with certainty. Furthermore, there is a tendency for bronchogenic cysts to undergo serious or even lethal complications [60–62]. Only with small asymptomatic cysts or in patients in whom surgery is contraindicated is there a case for their being left *in situ*, and then only after needle aspiration [63].

### Congenital adenomatoid malformation of the lung

This condition is synonymous with congenital cystic adenomatoid malformation of the lung and in older literature was probably called congenital bronchiectasis or pulmonary cystic disease [8]. It may involve either a part or the whole of a lobe or rarely an entire lung. The affected lobe or lung derives its blood supply from the pulmonary circulation and comprises a firm and airless mass of disorganized pulmonary tissue that lacks a properly defined bronchial system but contains an excess of air passages resembling terminal bronchioles and often includes mucous cysts of varying sizes [64]. Occasionally, the congenital adenomatoid malformation may consist of a separate mass connected by an extra bronchus to the normal bronchial tree, in which case it can be regarded as a form of accessory lung. Stocker and colleagues [65] described 38 cases that they classified into three types.

Type I, characterized by single or multiple large cysts, was the most common form, accounting for 50% and carrying a good prognosis.

Type II, consisting of multiple small cysts of less than 1 cm in diameter, accounted for 40% of cases and carried a poor prognosis.

Type III carried a very poor prognosis and consisted of a solid airless mass of tissue.

It has been suggested that adenomatoid malformation of the lung results from a developmental failure of the

proximal bronchial system, arising from the epithelial laryngotracheal bud, to unite in a normal manner with mesodermally derived distal alveolated tissue [58]. To this extent it may be regarded as a developmental anomaly of both the tracheobronchial tree and the lung parenchyma.

About 50% of cases are born prematurely and 25% are stillborn [8]. Many of those born alive die within a few hours, often with anasarca caused by vena caval compression due to the space-occupying effect of the abnormal tissue mass. Infection of the cysts commonly occurs if the infant survives beyond the neonatal period, although the onset of symptoms may be delayed for 2 or 3 years [66]. The condition may be complicated by pneumothorax that occurs as a result of air trapping in the cystic spaces [67]. The condition may now be diagnosed antenatally by ultrasound examination, and in some cases treatment by surgical resection of the affected parts of the lung is practicable [68].

### Anomalies involving the lung parenchyma

#### Agenesis and hypoplasia of the lung

Inconsistencies in the use of the terms ‘agenesis’ and ‘hypoplasia’ may be found in the literature [8,36]. In this book the term ‘agenesis’ is taken to mean absence or almost complete absence of growth in the lung [58], while the term ‘hypoplasia’ indicates underdevelopment but not non-development of the lung. Thus the hypoplastic lung contains a normal number of lobes but is diminished in size, with fewer bronchial branchings and reduced numbers of alveoli.

Complete bilateral agenesis of the lungs is extremely rare [69]. Needless to say, it is incompatible with life. Unilateral agenesis of the lung is much less rare and may be present to varying degrees of severity [8,70]. The left lung is affected more frequently than the right and the majority of cases exhibit other congenital abnormalities, one of the most common being patent ductus arteriosus [71–73]. In the most common form of unilateral agenesis there is a rudimentary bronchus but complete absence of lung tissue. In a second form there is a total absence of both the lung and bronchial system, and in a third, the least common, there is a rudimentary bronchial system attached to a reduced amount of alveolated tissue, this form being more properly regarded as an example of lung hypoplasia.

In many patients the aetiology is unknown. However, conditions that decrease intrathoracic space, especially congenital diaphragmatic herniae, may cause unilateral lung hypoplasia [74–76] and this may also be associated with ipsilateral congenital vascular anomalies [77]. Bilateral pulmonary hypoplasia is associated with the presence



**Fig. 50.4** Posteroanterior (a) and lateral (b) chest radiographs of a 24-year-old man with large right-sided bronchogenic cyst.

of oligohydramnios caused variously by renal tract disorders or by amniotic fluid leak [78,79]. An important cause is premature rupture of the membranes, and impaired lung development is detectable antenatally by ultrasonographic measurement of chest wall diameter [75,80,81]. It has also been shown that maternal treatment with angiotensin-converting enzyme inhibitors during pregnancy may be associated with lung hypoplasia [82].

#### Clinical features and diagnosis

Agenesis or hypoplasia of the lung is frequently associated with major extrapulmonary developmental abnormalities, and when this is the case death frequently occurs in infancy. When the anomaly is confined to a lung or part of it, prolonged survival may be possible but is likely to be accompanied by recurrent episodes of lower respiratory tract infection. This may result from imperfect drainage of lung secretions or from the spillover of pooled secretions from a blind bronchial stump into initially normal lung tissue [83].

The chest radiograph in agenesis or hypoplasia of the lung shows a hemithorax of diminished volume with crowded ribs, elevated hemidiaphragm and mediastinal displacement to the affected side. The contralateral lung tends to overinflate and may expand across

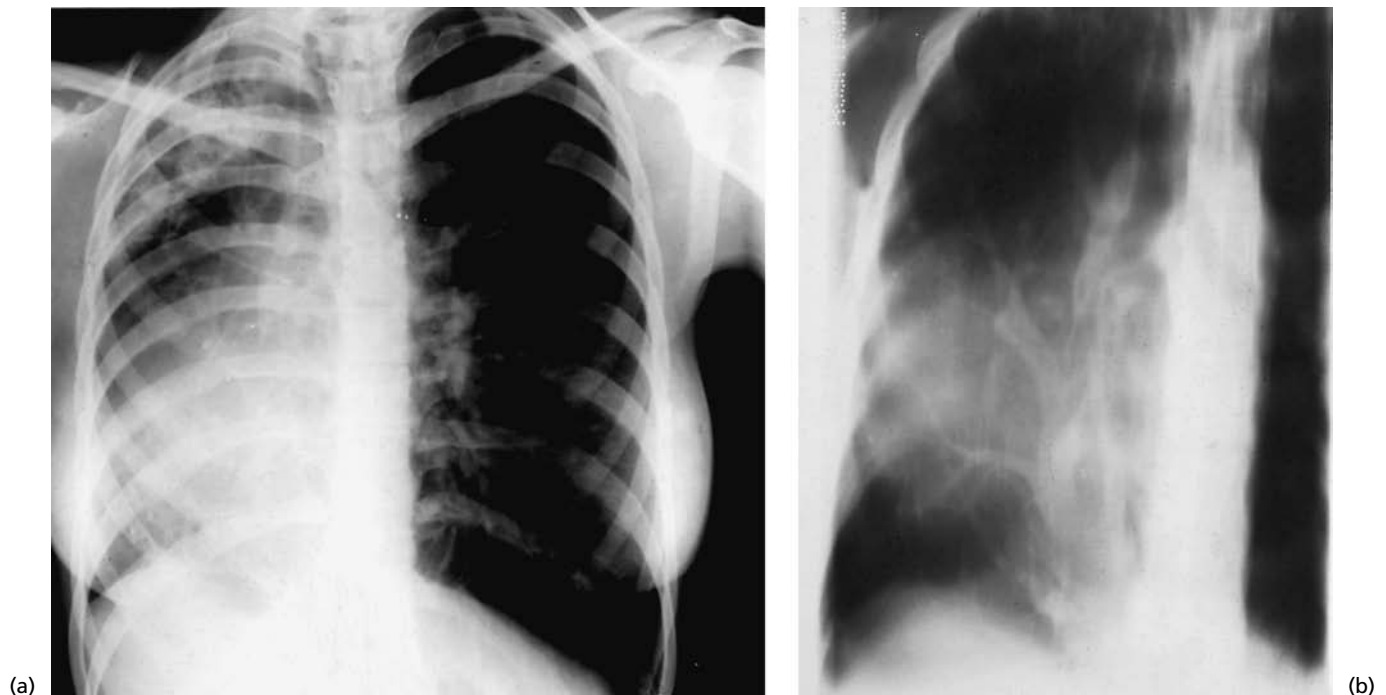
the midline [84] (Fig. 50.5). These appearances resemble atelectasis, and bronchoscopy, CT and occasionally pulmonary angiography may be required to make the distinction.

#### Congenital abnormalities of lobulation

Whereas complete agenesis of a lobe of the lung is rare [85], congenital anomalies of lobulation are much more common and one of those most frequently encountered is the so-called azygos lobe. An azygos lobe is really the medial portion of a bifurcated right upper lobe and in humans may be regarded as an anatomical variation, although students of comparative anatomy are aware that it is said to be a constant feature in the porpoise. It is formed during lung development if the apex of the right lung, as it enlarges, encounters the azygos vein as this vessel arches over the root of the right lung to join the superior vena cava. Whereas in normal circumstances the entire right upper lobe lies lateral to the azygos vein, in the case of this anomaly the right upper lobe assumes a bifid configuration so that a portion of lung lies on either side of the venous arch formed by the azygos vein [86]. The invagination that the azygos vein produces in the right upper lobe is in effect a supernumerary fissure and is bounded on each side by a layer of visceral and parietal pleura (Fig. 50.6). This fissure shows characteristically on chest radiographs as a thin outwardly convex line ending in a small triangular shadow at its lower end (Fig. 50.7).

The bronchial anatomy remains intact and the presence

**Fig. 50.5** (a) Posteroanterior chest film showing a hypoplastic right lung. (b) Tomogram of same patient showing anomalous veins draining a hypoplastic lung.





of an azygos lobe carries no morbidity. It is important only in that its features, which are present in about 0.25% of chest radiographs, require correct interpretation. A similar anomaly may very rarely occur in the left upper lobe [87].

### Lung sequestration

This term covers a spectrum of related developmental pulmonary anomalies generally characterized by the forma-

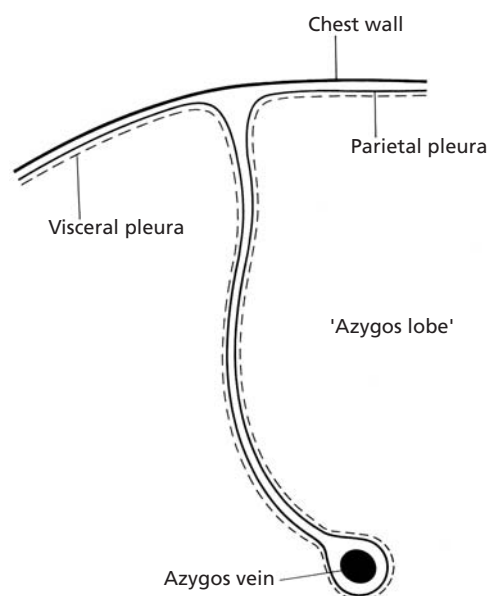


Fig. 50.6 Pleural infolding of an azygos lobe.

tion of an island of abnormal unventilated lung tissue that has no normal communication with the bronchial system and derives its arterial supply from the systemic rather than the pulmonary circulation.

Two principal types are defined for clinical convenience, namely intralobar and extralobar sequestration [88], although numerous variants have been described and much overlap may occur between these types [58,89]. The abnormal lung tissue in intralobar sequestration, which is the more common of the two types, is contained within the substance of normal lung tissue that completely surrounds it. In the rarer extralobar form the abnormal lung tissue, although lying close to normal lung, is situated outside the pleural coverings of the lung and is indeed invested by its own separate pleural membranes (Fig. 50.8). Since the latter form is entirely disconnected from normal lung, some authors refer to an extralobar sequestration as an 'accessory lung without a bronchial connection' [8,58]. The gender incidence is said to be equal for intralobar sequestration, while the extralobar form occurs four times more commonly in males than females [91]. Both forms occur more commonly in the left hemithorax; however, whereas the intralobar variety occurs on this side in 60% of cases, in the extralobar variety over 90% are left-sided [8,58,71,92]. The reasons for this left-sided propensity are unclear but may be connected with the observation that in normal development the primitive pleuroperitoneal canal closes on the left side later than on the right. Furthermore the absence of hepatic tissue on the left provides additional space in which abnormal tissue may develop. An ipsilateral diaphragmatic defect is

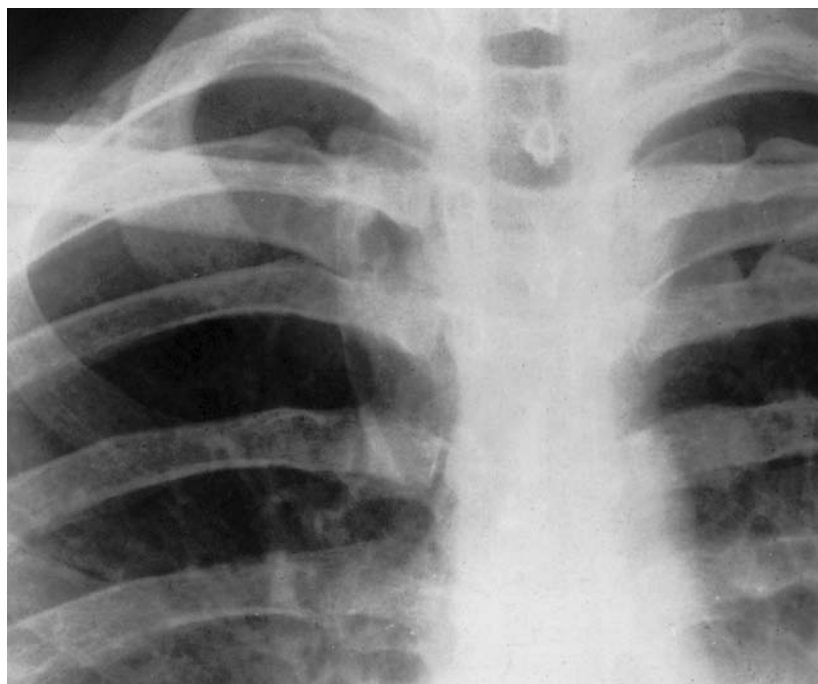


Fig. 50.7 Normal chest film showing typical appearance of an azygos lobe in the right upper zone medially.

common in extralobar sequestration, occurring in 60% of cases, but is rare in intralobar forms [8].

The posterior basal segment of either lower lobe is the most common site for intralobar sequestration. An upper lobe may be involved but this is rare [8,93]. Very occasionally an entire lung may be sequestered [94,95]. The majority of extralobar sequestrations are sandwiched between

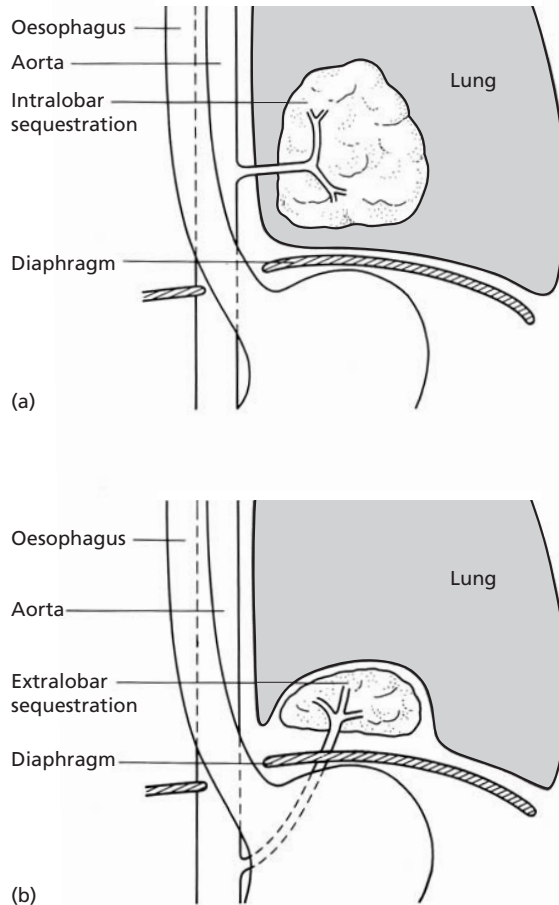
the left lower lobe and the diaphragm but may also occur below the diaphragm, within the diaphragmatic substance itself, within the mediastinum or even as far cephalad as the neck [58,96].

The various ways in which sequestered lung may receive its vascular supply have been reviewed by Thilenius and colleagues [97]. Both intralobar and extralobar sequestrations usually receive their arterial supply from the descending aorta or one of its branches, either above or below the diaphragm. Subdiaphragmatic supply is reportedly more common in extralobar sequestration [98], in which case the vessel passes through the aortic or oesophageal hiatus or through a separate diaphragmatic defect. Arteries that supply the intralobar variety tend to be disproportionately large with respect to the volume of tissue supplied [58]; in both the intralobar and extralobar types the supplying arteries may be multiple. The veins draining intralobar sequestrations usually empty into the pulmonary venous circulation, whereas it is more usual for extralobar sequestrations to be drained by the azygos system of veins. Considerable shunts may sometimes result, so that the patient may present in early life with heart failure [99,100].

About half of all patients with extralobar sequestration have other congenital abnormalities of sufficient severity to bring them to medical attention, so that the sequestration is diagnosed in the first year of life in up to 60% of patients. On the other hand, widespread congenital abnormalities in intralobar sequestration are rare [8,58,71] so that the diagnosis is seldom made in neonatal life and, in over 50% of cases, not before the age of 20. Table 50.1 compares some of the features of intralobar and extralobar sequestration.

### Aetiology

Pulmonary sequestration comprises a variety of congenital anomalies for which there is no hereditary basis, and none of the many theories of causation is entirely acceptable unless it has sufficient flexibility to explain the



**Fig. 50.8** Intralobar (a) and extralobar (b) sequestration. (After Gerle *et al.* [90].)

**Table 50.1** Points of comparison between intralobar and extralobar pulmonary sequestration.

Feature	Intralobar	Extralobar
Frequency	More common	Less common
Sex incidence (male : female)	1 : 1	4 : 1
Most common site	Within posterior basal segment	Between lower lobe and diaphragm
Side of thorax	c.60% left	c.90% left
Arterial supply	c.70% thoracic aorta	c.45% thoracic aorta
Venous drainage	Usually pulmonary veins	Often systemic veins
Diagnosed in neonates	Rarely	Commonly
Other congenital defects	Uncommon	Frequent

development of both intralobar and extralobar sequestration as well as more complex variants [58,89,101–103]. Occasional reports of the occurrence of both intralobar and extralobar sequestration in the same patient provide some evidence in support of a unitary theory [104,105]. One such proposition is that pulmonary sequestration develops as a result of the formation of an accessory lung bud distal to the normal laryngotracheal bud on the ventral aspect of the primitive foregut [103]. As this anomalous bronchial tissue grows, it becomes invested by primitive respiratory mesenchyme. The amount of mesenchyme determines the size of the sequestration and results in the development of its respiratory bronchioles and alveolar tissue [106]. The original foregut connection may involute and disappear, possibly as a result of outgrowth of its blood supply, although occasionally a foregut communication persists, particularly in the case of extralobar forms. Those accessory buds that arise in close proximity to the laryngotracheal bud may become incorporated into it during its development to become intralobar sequestrations, whereas those that arise from the foregut more distally either from the oesophagus or from the proximal part of the stomach escape envelopment and become extralobar sequestrations [102]. Each type of sequestration usually retains its primitive systemic arterial supply; venous drainage may be either into the pulmonary system if the sequestration developed in close proximity to the normal laryngotracheal bud, or to the systemic system if it arose more distally [100].

### Pathology

Intralobar pulmonary sequestration appears macroscopically as a well-circumscribed reddish-grey area that may be clearly differentiated from healthy lung but which is intimately related to it, being usually situated within the substance of the posterior basal segment of either lower lobe. An extralobar sequestration is separated from normal lung and the surface is shiny and homogeneous, being covered by its own pleural investment. Both forms typically receive a systemic arterial supply and although this is usually derived from the aorta, the vessels tend to have the elastic structure of a pulmonary artery rather than the muscular structure found in a normal aortic branch. Histologically both intralobar and extralobar sequestrations typically contain dilated ciliated bronchi together with focal development of alveolated tissue. Bronchial dilatation by retained secretions and oedema may result in the formation of cysts visible to the naked eye. The usual histological features may be lost in cases where the sequestration has become infected.

### Clinical features

Those sequestrations diagnosed in the first year of life are

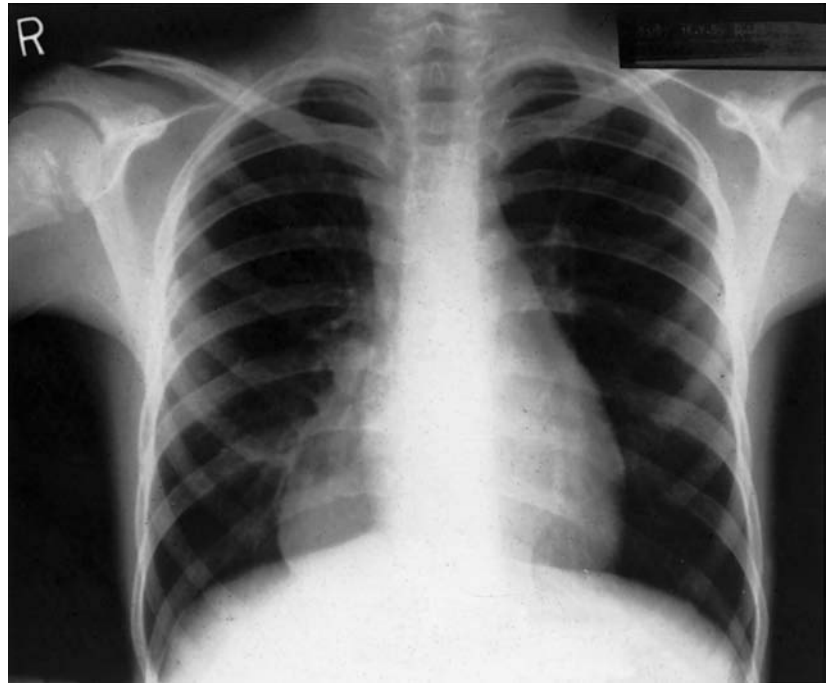
frequently brought to light in the course of the investigation of multiple congenital abnormalities and are usually extralobar in type. Some of those that escape detection in this manner are found in adult life in asymptomatic individuals following a routine chest radiograph. Others may present with non-specific symptoms of lower respiratory tract infection or with recurrent pneumonic episodes, characterized by cough, sputum production and occasionally haemoptysis, which may be massive. These complications may arise because there is a tendency for a sequestered segment to become distended by mucous secretions which, in the absence of a foregut communication, are unable to drain away so that surrounding normal lung tissue becomes compressed and liable to infection. Once infection is established in adjacent lung, a fistula between the sequestered segment and surrounding lung may develop and the infection tends to persist as a result of inadequate drainage.

Extralobar sequestrations may be less liable to infection as they are entirely separate from the normal lung [105]. Signs of pneumonic consolidation may be present but features of pleurisy and pleural effusion are said to be unusual [92]. Finger clubbing has been described, as have associated bony deformities of the ribs and chest wall.

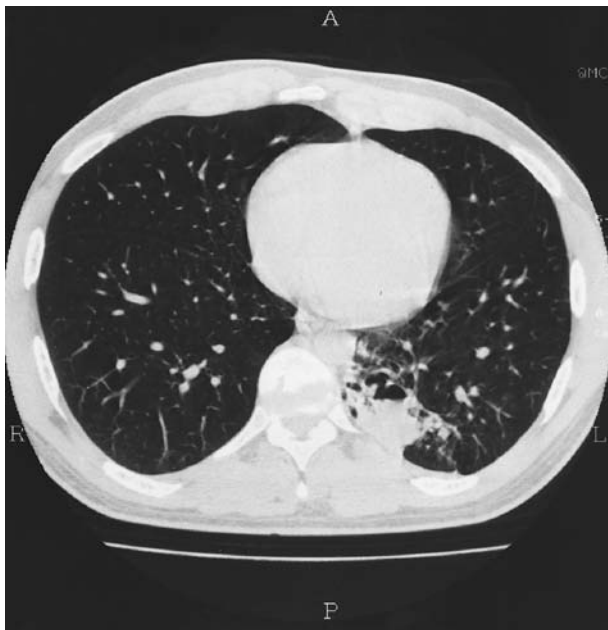
### Radiology and treatment

The radiographic features are variable. The diagnosis of intralobar sequestration should be suspected in the presence of a persistent opacity situated in either of the posterior basal segments (Fig. 50.9). The non-aerated tissue contained in the sequestration may produce a homogeneous shadow, the margins of which are not always well defined but which may have the appearance of a solitary pulmonary nodule. Cystic change may be visible radiographically and the 'cysts' may contain air–fluid levels, implying the presence of either a fistulous bronchial communication resulting from infection or some degree of collateral ventilation occurring at alveolar level (Fig. 50.10). Extralobar sequestration is less easily seen and may produce a small opacity contiguous with the left hemidiaphragmatic shadow. Both types of sequestration occasionally have persistent foregut connections and these are sometimes demonstrable by barium swallow [102,107].

Bronchography showed non-opacification of the sequestration, which was seen to be surrounded by displaced but normally ramifying bronchial branches. The diagnosis is now confirmed by CT and if necessary by retrograde thoracic aortography, which demonstrates one or more feeding arteries that usually arise from the descending aorta just above or below the diaphragm (see Fig. 1.2). These investigations are desirable because by identifying aberrant arteries they exclude other possibilities such as pneumonia, bronchiectasis, lung abscess and tumour, and also forewarn the thoracic surgeon of the existence and



**Fig. 50.9** Sequestered segment in right lower lobe posterior to right cardiac border.



**Fig. 50.10** CT scan of man showing extralobar sequestration posteriorly in the left lung. Note cavitation with fluid level following infection.

distribution of the vessels that require identification and ligation at thoracotomy.

Resection of a symptomatic pulmonary sequestration is indicated. Any infection that might be present is first treated with appropriate antibiotics. Intralobar sequestrations usually require segmental resection or lobectomy

[100]. Extralobar sequestration may be resected without disturbing normal lung. Disastrous bleeding may occur as a result of failure to identify properly the aberrant vascular supply [100] but has also been described as a complication of unresected sequestration [108].

### Anomalies of the pulmonary vasculature

The embryology of the pulmonary vasculature is relevant to the description of the developmental anomalies that follows (see Chapter 1). The intrapulmonary vasculature is derived from the mesenchymal investment of the primitive lung bud. The pulmonary vascular plexus so formed receives its initial arterial supply from paired segmental arteries arising from the aorta. Later the vascular plexus is joined by ramifications of the pulmonary arteries that are themselves derived from the sixth branchial arch. Once this connection is established, and as the aorta migrates caudally, the segmental aortic arteries normally involute and are lost, being replaced by the bronchial arteries that grow out of the aorta at what ultimately will be thoracic level.

The venous side of the pulmonary vascular plexus at first drains into the primitive anterior and posterior cardinal veins, although this route is later replaced when the pulmonary veins from each lung grow out to fuse with a single large pulmonary vein that in turn develops from the sinus venosus. Ultimately this structure is completely absorbed into the atrium to such an extent that the four pulmonary veins normally enter the left atrium separately.

The pulmonary vasculature is well developed by the 16th week of intrauterine life but clearly growth continues *in utero*, as does vascular remodelling at a microscopic level. Disturbances of this remodelling may result in the excessive muscularization of the intra-acinar arteries found in the condition referred to as persistent pulmonary hypertension of the newborn [5,109]. One such case has been described following maternal aspirin ingestion during pregnancy, and it was postulated that pulmonary hypertension in this patient arose as a consequence of premature closure of the ductus arteriosus that had in turn resulted from the prostaglandin-inhibiting effects of this drug [110].

### **Absent pulmonary artery trunk**

The pulmonary artery trunk may be completely absent as a result of agenesis of the primitive sixth branchial arch or of developmental failure of the septum that normally divides the truncus arteriosus into aorta and pulmonary artery trunk. A left-to-right shunt exists in such cases, the lungs being supplied by bronchial or other aberrant systemic vessels; prolonged survival is impossible unless major corrective surgery proves feasible [58,111].

### **Absent unilateral pulmonary artery**

Absence of one or other main pulmonary artery is rare and is a consequence of the failure of either the left or right side of the primitive sixth branchial arch to develop in the embryo. No connection exists between the main pulmonary artery trunk and the lung parenchymal vasculature on the affected side, which receives its blood supply systemically, most frequently from enlarged bronchial vessels but occasionally from aberrant arteries that usually arise from the descending aorta or less frequently from the ascending aorta, the arch, the left innominate artery, the left subclavian artery, their immediate branches or from a persistent right-sided ductus arteriosus.

The left and right pulmonary arteries are affected with equal frequency [112,113] but the right-sided lesion is more common in adult life because absence of the left pulmonary artery is strongly associated with congenital heart disease and therefore with increased early mortality [114]. In one series, 40% of cases of absent left pulmonary artery also had Fallot's tetralogy (ventricular septal defect, pulmonary outflow tract obstruction, overriding aorta and right ventricular hypertrophy) [113]. Absence of the right pulmonary artery carries no strong association with congenital heart disease and hence the tendency for patients with this anomaly to survive. The lung that receives the abnormal blood supply is frequently hypoplastic and may contain cystic and bronchiectatic changes [58]; 20% of patients with a right-sided absent pulmonary artery

have been found to have pulmonary hypertension [115]. Whereas patients who present in infancy usually do so as a result of associated cardiac disease, adults with unilateral absence of a pulmonary artery may be asymptomatic, the diagnosis being made following a chest radiograph requested for some other reason [36]. The affected lung receives its blood supply from systemic vessels and occasionally patients present with haemoptysis. The chest radiograph shows a small hilar shadow and a small hyperlucent lung on the involved side. The diagnosis may be confirmed and differentiated from Macleod's syndrome by a perfusion lung scan or pulmonary angiogram, both of which show complete lack of perfusion on the affected side. Treatment is not usually possible, although reconstructive anastomotic surgery and recanalization procedures may be practicable in some cases [116]. Rarely pneumonectomy has been required to control haemoptysis, in which case thoracic aortography to demonstrate the collateral circulation is desirable [36].

### **Pulmonary artery stenosis**

Postvalvular pulmonary artery stenosis (syn. pulmonary artery coarctation) is rare and may occur at any level from above the valve to the segmental arteries and beyond [117]. Centrally placed stenoses involving the pulmonary artery trunk or left or right main pulmonary artery branches are less common than multiple peripheral lesions, which are sometimes accompanied by pulmonary hypertension. Although pulmonary stenosis may occur in isolated form, this condition is more commonly detected in the course of the investigation of associated congenital heart disease. Postvalvular pulmonary artery stenosis has been described as part of the rubella syndrome [118] and in idiopathic hypercalcaemia. Chest radiography may show poststenotic dilatations that produce a beaded appearance contiguous with the lung vascular markings. Occasionally the poststenotic dilatations may reach aneurysmal proportions and may rupture causing haemoptysis. The diagnosis is confirmed by pulmonary angiography.

Large centrally placed lesions may be amenable to corrective surgery but this carries the risk of massive intrapulmonary bleeding due to the rupture of more distally placed pulmonary vessels as these are frequently hypoplastic [58].

### **Anomalous origin of the left pulmonary artery**

The failure of the pulmonary arterial plexus of the left lung and the left part of the sixth primitive branchial arch to connect in the normal way may result in the left pulmonary artery arising in anomalous fashion from the right pulmonary artery. In order to reach the left lung, this aberrant left pulmonary artery loops around the right main

bronchus like a sling and runs a peculiar course between the lower end of the trachea anteriorly and the oesophagus posteriorly, thereby crossing the midline to enter the left hilum [119] (Fig. 50.11). A condition known as 'sling' pulmonary artery syndrome may result, in which pressure from the aberrant left pulmonary artery may cause varying degrees of obstruction to the left main bronchus, trachea and oesophagus with consequent dyspnoea and dysphagia. Further tracheal obstruction may be produced in this developmental anomaly by an associated intrinsic tracheal defect, in which the pars membranacea is absent and the lumen of the trachea is completely encircled by so-called 'napkin-ring' cartilages [8]. The aberrant pulmonary sling vessel may be seen on a lateral chest radiograph as a rounded opacity between the air-filled trachea and oesophagus at the level of the carina. A barium swallow may provide supportive evidence and the diagnosis is confirmed by pulmonary angiography [115,120].

### Anomalous systemic pulmonary perfusion

Dysplastic lung tissue may sometimes receive a blood supply from systemic vessels other than the normal bronchial arteries, as has been described in pulmonary sequestration above. Other examples of abnormal systemic arterial supply may be found in the absence of sequestration and where the lung tissue supplied is apparently normal [121,122]. Such arteries usually arise from the descending thoracic aorta but may also originate from the ascending aorta, the arch, the innominate, subclavian, internal mammary and intercostal arteries or below the diaphragm from the abdominal aorta or the coeliac artery [115] (Fig. 50.11). These vessels usually have the characteristic elastic structure of a pulmonary artery, rather than the

muscular form of an aortic branch, and may communicate with the pulmonary circulation or drain systemically, creating a left-to-right shunt. The patient is frequently asymptomatic but may come to medical attention through recurrent haemoptysis. A systolic or a continuous bruit with systolic accentuation may be heard over the involved area of the chest. The chest radiograph may be normal or show increased irregular vascular markings in the vicinity of the anomalous vessels. Pulmonary angiography shows no abnormality, while aortography is diagnostic. Surgical ligation or clipping of anomalous vessels, therapeutic embolism or even resection of lung may occasionally be indicated to control haemoptysis. These anomalies may be classified as a rare form of pulmonary arteriovenous malformation (see below).

### Anomalous pulmonary venous drainage

Anomalous venous drainage of a lung arises as a result of persistent communications between the embryonic system of cardinal veins and the pulmonary venous plexus. These communications develop into aberrant pulmonary veins that drain systemically, usually into the inferior vena cava, rather than returning oxygenated blood into the left atrium in the manner of normal pulmonary veins. This anomalous drainage, which is usually partial rather than total, creates a left-to-right shunt and as with other developmental abnormalities of the lungs may be associated with congenital heart disease, the extent of which may govern the prognosis [123,124].

### Scimitar syndrome

The scimitar syndrome is synonymous with congenital pulmonary venolobar syndrome and vena cava bronchovascular syndrome [123–125]. The most consistent feature of the syndrome is drainage of part of the right lung by an anomalous scimitar-shaped pulmonary vein that passes through the lung running parallel to, but separate from, the mediastinal structures before joining the inferior vena cava, usually below the diaphragm. Other variable features that may be present include:

- 1 an anomalous systemic arterial supply to the territory drained by the scimitar vein, taking the form of multiple small arteries arising from the descending aorta, often below the diaphragm and entering the base of the right lung, the right main pulmonary artery being frequently small or even absent;
- 2 hypoplasia of the right lung itself, which is small and contains fewer airways that may show bronchial isomerism [125];
- 3 cardiac dextroposition, which is a consequence of the small right lung;
- 4 diaphragmatic abnormalities in which the right hemidiaphragm may have an accessory leaf, being fused

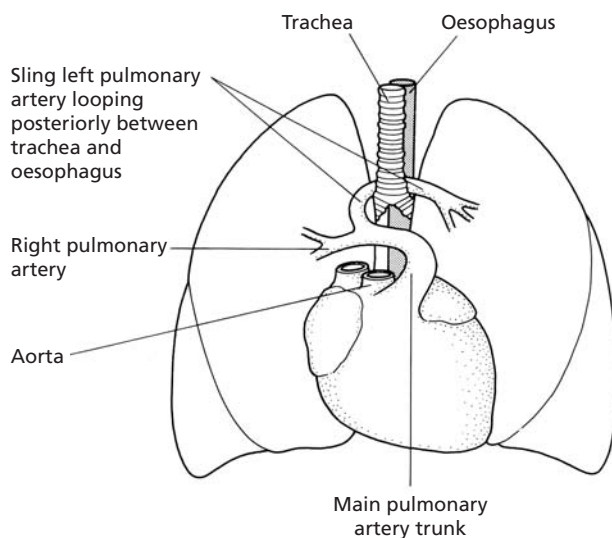


Fig. 50.11 'Sling' left pulmonary artery. (After Kale *et al.* [120].)

anteriorly but separated posteriorly and containing lung between its layers [126,127].

The scimitar syndrome may occur familiarly with an autosomal dominant pattern of inheritance [128]. The left-to-right shunt in these patients is usually of insufficient magnitude to produce ill-effects and the condition is most frequently diagnosed in adult life in asymptomatic subjects following a routine chest radiograph [124]. The chest radiograph shows a characteristic curvilinear vascular density in the right lower lung (from which the syndrome derives its name), with features of ipsilateral loss of lung volume as evidenced by mediastinal shift to the right and an elevated diaphragm (see Fig. 50.5). The abnormalities may be demonstrated in detail by CT and pulmonary angiography, although plain radiographs are usually adequate for diagnostic purposes and surgical intervention is in any case rarely necessary [126,129,130].

### Other variant syndromes

Further examples of anomalous pulmonary venous drainage that have been described include the following.

- 1 Drainage of the right lung into the superior vena cava, azygos vein or right innominate vein.
- 2 Drainage of the left lung into a left-sided superior vena cava or vertical vein, representing a persistence of the embryonic left anterior cardinal vein. This vessel may drain in a cephalic direction to join the left innominate vein or caudally to join the coronary sinus.
- 3 Drainage of the pulmonary veins into the coronary sinus attached to the right atrium.
- 4 Drainage of a common single pulmonary vein into the right atrium by way of an additional atrium-like chamber, an anomaly referred to as a cor triatriatum deformity [58,131].

### Pulmonary arteriovenous malformations and telangiectasia (see also Chapter 42)

Several terms used synonymously with pulmonary arteriovenous malformation are found in the literature, including pulmonary arteriovenous fistula, pulmonary arteriovenous aneurysm, pulmonary angioma, pulmonary haemangioma and pulmonary cavernous angioma.

### Definition and pathology

These lesions, although sometimes categorized as tumours, contain no neoplastic cells and are in fact developmental anomalies in which there are persistent vascular communications between arteries and veins within the lung that effectively bypass parts of the normal pulmonary capillary bed. Arteriovenous malformations are rare, approximately three per year having been recorded

at a major North American centre of referral over a 20-year period [132]. Le Roux [133] reported less than one case per year in a European thoracic surgical centre compared with approximately 300 cases of bronchial carcinoma and 13 bronchial adenomas seen in the same period. The majority of arteriovenous malformations probably originate during the development of the primitive pulmonary vascular plexus, when an anastomotic vessel arises which presents a significantly lower resistance to flow than that provided by the surrounding pulmonary vascular bed [58] (Fig. 50.12). Physical principles dictate that arterial blood is diverted through this passage of least resistance, and with increasing flow there is a gradual dilatation and enlargement both of the anastomotic vessel and of the arteries and the tributaries that feed it. Those veins draining the fistulous communication also distend and become varicose. The ultimate size of the lesion depends upon haemodynamic factors and ranges from the very small to a large labyrinthine mass of dilated interconnecting thin-walled vascular spaces of lobar proportions [135].

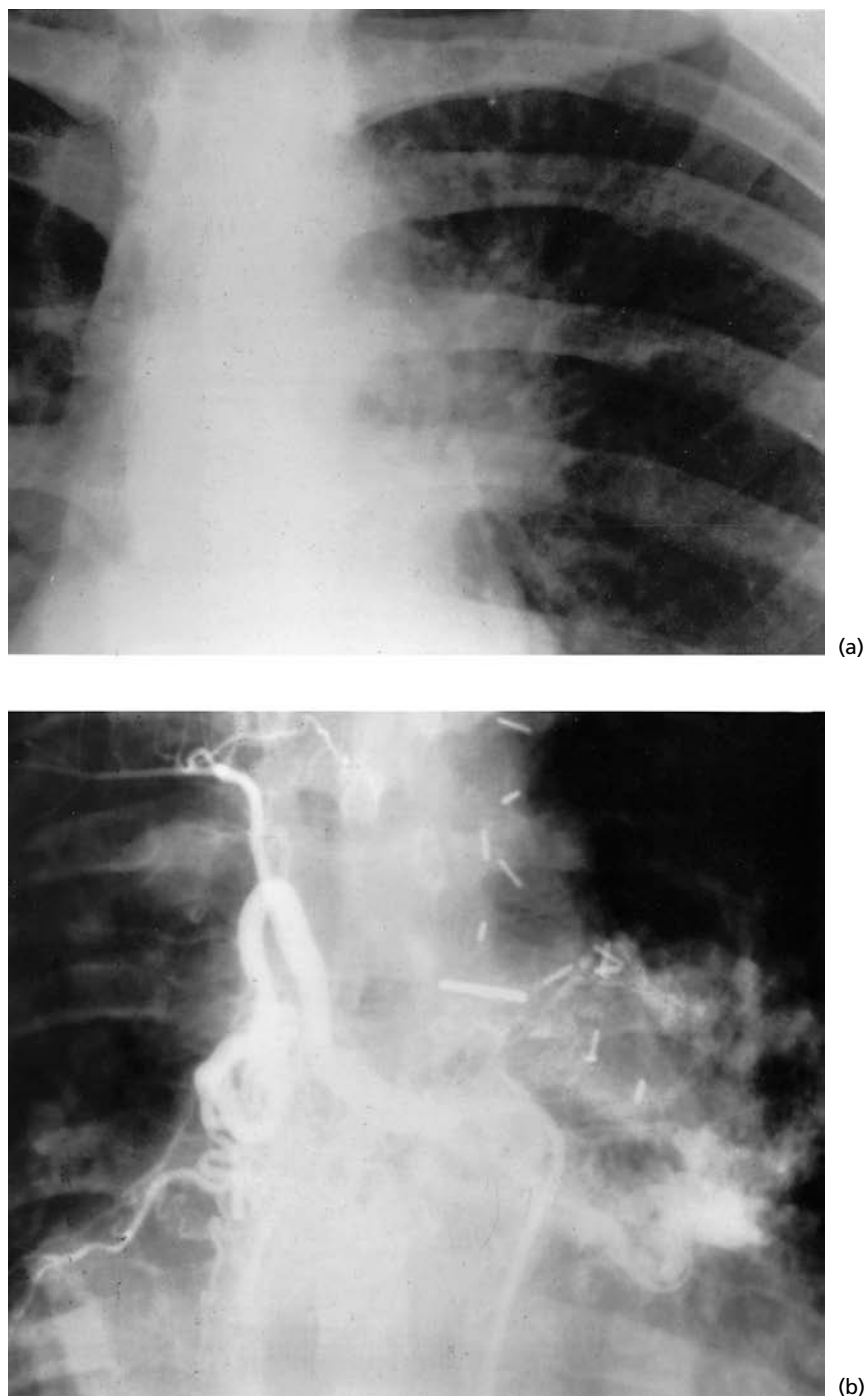
About 95% of arteriovenous malformations derive their blood supply from branches of the pulmonary artery and drain into the pulmonary venous circulation [132]. In the few remaining cases, the supplying vessels originate systemically from the aorta and innominate, subclavian, internal mammary, bronchial and intercostal arteries and drainage may be via systemic or pulmonary veins [136].

Pulmonary telangiectasis results if there is a fistulous communication between a small peripheral arteriole and venule. If large numbers of these defects are present and if they are diffusely distributed, then the condition may be referred to as pulmonary telangiectasia [137,138].

There is a close association between pulmonary arteriovenous malformations and hereditary haemorrhagic telangiectasia (Osler-Rendu-Weber syndrome), an autosomal dominant condition present in 50–60% of cases [132,139,140]. Conversely, only 5–15% of patients with hereditary haemorrhagic telangiectasia develop pulmonary arteriovenous malformations [141]. It has been shown that a gene located on chromosome 9q3 is strongly associated with the presence of the two conditions, whereas those subjects with Osler-Rendu-Weber disease without pulmonary telangiectasia do not have this abnormal gene [142–144].

Arteriovenous malformations are slightly more common in women than men [108,115]. The majority occur as single lesions, multiple malformations being found in 20–30% of cases, occurring more frequently in patients with hereditary haemorrhagic telangiectasia [108,109]. Approximately 10% of lesions occur bilaterally [132,133]. Arteriovenous malformations are usually closely related to the visceral pleura and 70% occur in the lower lobes [132]. Associated vascular anomalies have been recorded in other organs [140].



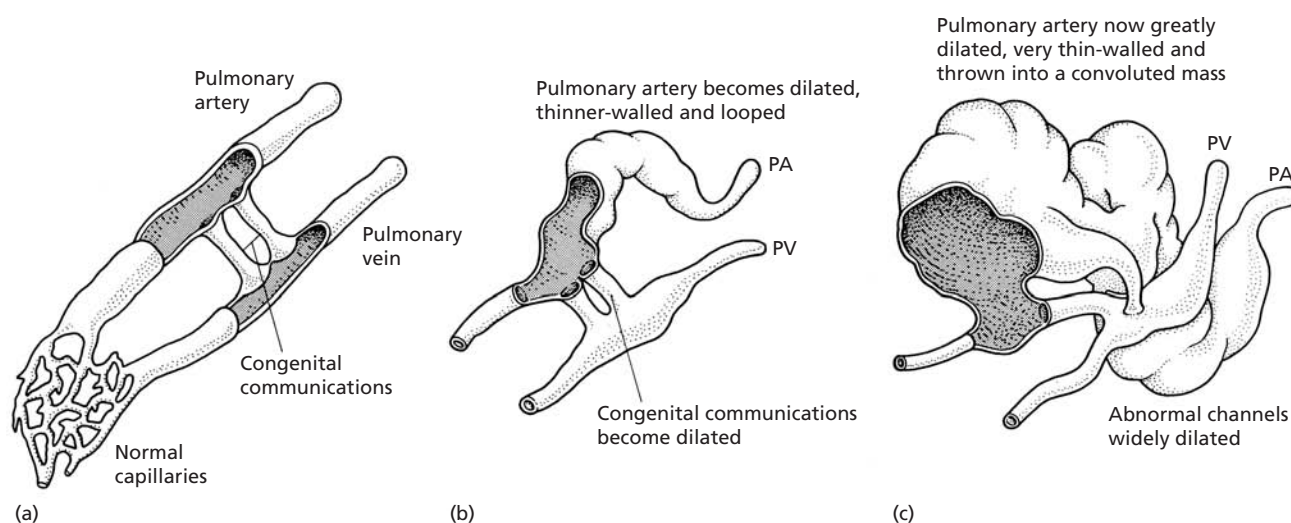


**Fig. 50.12** (a) Chest film shows abnormal vascularity in left upper zone. (b) Retrograde aortic catheter shows the aberrant artery supplying lung directly from the aorta.

### Clinical features

It is unusual for discrete arteriovenous malformations to be diagnosed before the third decade of life; hereditary haemorrhagic telangiectasia also usually manifests itself at puberty or later. In a series of 101 cases of all types of pulmonary arteriovenous malformation, the mean age at diagnosis was 40 years [132,145]. However, occasionally the condition is detected in infancy, especially in patients

with hereditary telangiectasia, and in some such cases treatment becomes necessary [146,147]. More than half of all patients have no symptoms referable to the malformations at the time of diagnosis, which is frequently made following a routine chest radiograph or during the investigation of hereditary haemorrhagic telangiectasia. This condition is characterized by the presence of small, raised, red telangiectatic lesions of 2–3 mm diameter that blanch on pressure and are found on the skin and mucosal



**Fig. 50.13** (a–c) Evolution of a convoluted vascular malformation from congenital precapillary arteriovenous malformations. (After Cope [134].)

surfaces, particularly about the face, lips, mouth and nasopharynx (Fig. 50.13). The mucosal lesions tend to bleed and the patient may present with epistaxis, an acute gastrointestinal bleed or symptoms of anaemia as a consequence of occult bleeding into the gut.

The respiratory symptom most commonly present at the time of diagnosis is dyspnoea, haemoptysis being less frequent [132,148]. A bruit is audible in over half of all patients with arteriovenous malformations [132,149]. This is typically heard over the site of the lesion and is systolic or continuous with systolic and inspiratory accentuation. Cyanosis may be present as a result of right-to-left shunting and, when this is present, finger clubbing is a frequent accompaniment [132,150]. Symptoms are unlikely to occur in the case of single discrete lesions provided that the radiographic diameter of the malformation is less than 2 cm. The frequency of symptoms need not be greater in the presence of multiple lesions with the exception of the numerous tiny lesions found in the syndrome of pulmonary telangiectasia, in which symptoms and signs are usually evident from childhood [137,138].

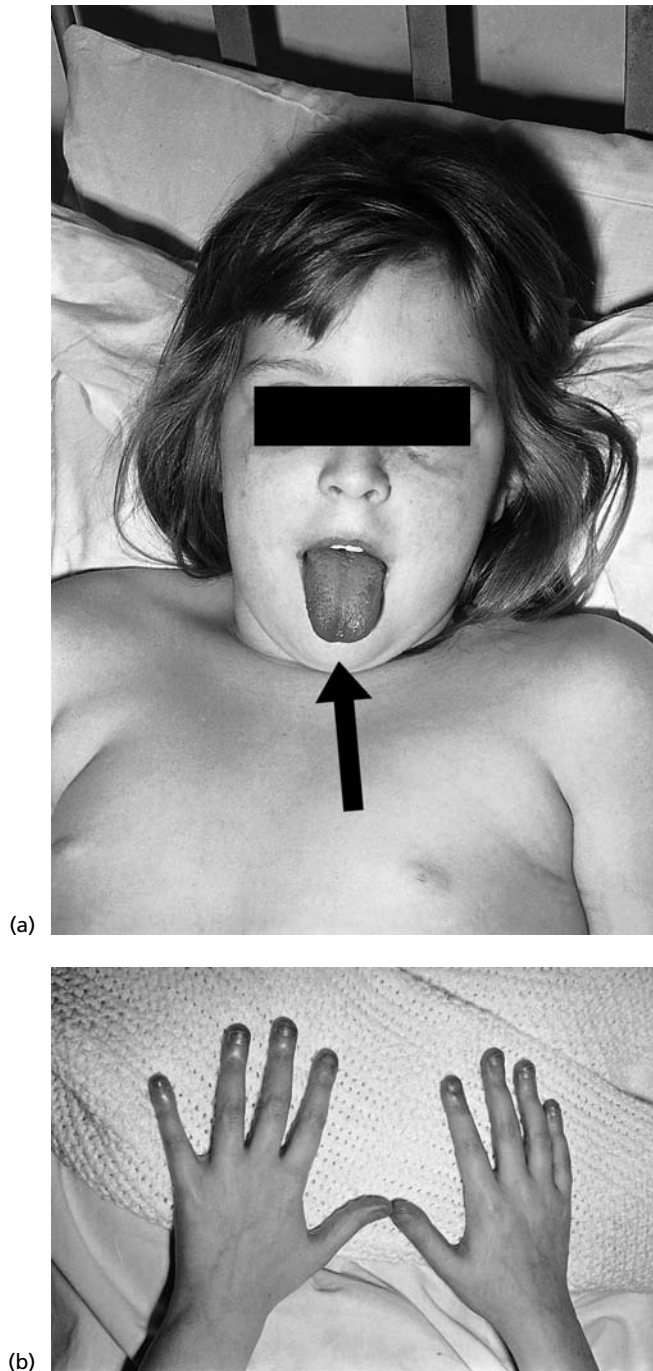
### Complications

The most common complication is haemorrhage, either into the bronchial tree producing haemoptysis or rarely into the pleural cavity producing a haemothorax [151–155]. Exceptionally pneumothorax may occur. Transient cerebral ischaemic attacks or cerebral infarction may be produced by a combination of systemic arterial

hypoxaemia and secondary polycythaemia, while in some series as many as 50% of patients have had episodes suggestive of paradoxical embolization [132,156,157]. Less frequently, cerebrovascular accidents may result from the rupture of an associated intracranial arteriovenous malformation or from an embolus arising within a pulmonary arteriovenous malformation or passing through it in paradoxical fashion [157]. Bacterial endangitis may occur with a pulmonary arteriovenous malformation, giving rise to metastatic abscesses in the brain or at other sites [156]. Cerebral abscesses may also occur if infected material passes straight through an arteriovenous malformation rather than being filtered by the pulmonary capillaries.

### Radiographic features

Arteriovenous malformations may be seen on the chest radiograph as one or more rounded lobulated or tortuous opacities, frequently occupying the periphery of the lower lung fields [133]. Feeding or draining vessels that link the malformation with the hilum are sometimes visible on either plain films or tomograms [158]. CT is a useful method for identification and delineation of lesions [159]. Vascular calcification is uncommon [145]. Serial radiographs may show gradual enlargement of the malformations with the passage of time. The shadows are often well defined and the radiograph may be misinterpreted as indicating metastatic tumour [145]. The radiographic size of the discrete lesion may be shown to vary according to intrathoracic pressure, increasing in size during a Müller manoeuvre and becoming smaller with a Valsalva manoeuvre [160]. Bilateral pulmonary angiography confirms the diagnosis in all but a few cases [158] (Fig. 50.14). This investigation, together with CT, should always be undertaken if surgical treatment is being



**Fig. 50.14** (a) Facial appearance of 10-year-old girl, cyanosed from birth, with Osler–Rendu–Weber syndrome showing cyanosed lips and an angioma on her tongue (arrowed). (b) Finger clubbing in the same patient.

considered since they may demonstrate small lesions not detectable on plain radiographs. In the few malformations that derive their arterial supply from systemic vessels, aortography is required in order to demonstrate them adequately.

The radiographic appearance of pulmonary telangiectasia differs in that the salient feature is diffuse nodularity,

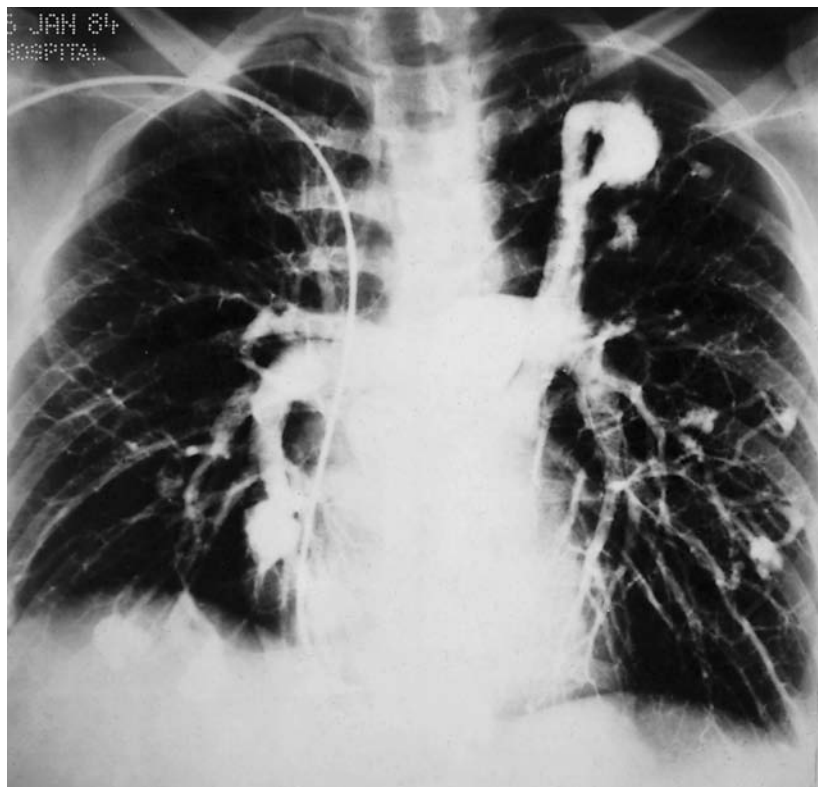
particularly in the lower zones, which may be mistaken for pulmonary fibrosis and which may increase as time passes. As the vascular lesions in pulmonary telangiectasia are small, they are not usually demonstrable by pulmonary angiography.

#### Functional abnormalities

The majority of pulmonary arteriovenous malformations produce a right-to-left shunt, an exception being those lesions with a systemic arterial supply. If the shunt is of sufficient size, arterial hypoxaemia results. However, this is usually mild and is associated with a normal or reduced  $PCO_2$ . In such cases,  $SAO_2$  is reduced and is not entirely correctable by the administration of pure oxygen. The size of the intrapulmonary shunt, expressed as a percentage of cardiac output, may be obtained from measurements of mixed venous and arterial oxygen content while the patient is breathing 100% oxygen for 20 min [161]. Dye dilution curves are of little value in the quantification of shunt in pulmonary arteriovenous malformations because the fistulae are so close to capillary level that two separate peaks of dye are not seen at the arterial sampling site [145]. The former technique may also be inaccurate in the case of pulmonary telangiectasia, in which the proximity of the abnormal vessels to the alveoli and their small size (relative to larger discrete arteriovenous malformations) permits them to take up significant quantities of oxygen when this is being breathed in pure form. An alternative method of determining shunt has been developed in order to overcome this difficulty, by means of radioactively labelled albumin macroaggregates injected into a peripheral vein. Normally almost all of these particles would be arrested in the pulmonary capillaries, but in pulmonary telangiectasia a significant quantity pass straight through the telangiectatic vessels. Since the proportion of cardiac output normally received by the cranial and renal circulations is known, the size of the shunt may be estimated by counting radioactivity over the lungs, brain and kidneys [137,162].

Secondary polycythaemia was present in 23% of a combined series of 101 patients with arteriovenous malformation, anaemia due to hereditary haemorrhagic telangiectasia being present in 19% [132,145]. Right heart and pulmonary artery pressures were recorded in 22 patients in this series and the values obtained were normal in all cases. However, pulmonary hypertension, the mechanism of which is uncertain, has been reported in a few cases [163].

Measurements of diffusing capacity using carbon monoxide ( $DLCO$ ) require correction for haemoglobin level if polycythaemia or anaemia is present [164].  $DLCO$  may be reduced in pulmonary telangiectasia, presumably as a result of a diminished pulmonary capillary blood volume [136].



**Fig. 50.15** Pulmonary arteriogram in patient with multiple arteriovenous malformations.

### Treatment

The more widespread availability of embolization techniques and studies of their success rates and complications has led to a reappraisal of management of arteriovenous malformations, and it is now generally agreed that active treatment is desirable for lesions with feeding vessels greater than 3mm in diameter [165–168]. Indeed, the relatively high rate of complications in untreated malformations is regarded by some as a reason for screening of relatives of patients with hereditary haemorrhagic telangiectasia in order to detect and treat asymptomatic lung lesions. Surgical treatment should be considered following full evaluation of a solitary pulmonary arteriovenous malformation. Discrete peripheral arteriovenous malformations may be removed by local resection with ligation of the afferent and efferent vessels. Deeper and more extensive lesions may be removed by wedge resection, segmental

resection or lobectomy with the general aim of conserving as much lung tissue as possible [145,160]. When the arteriovenous malformations are multiple or bilateral, selective treatment is indicated and embolization or occlusion techniques, using balloons or steel coils, have been used with success. The occluding devices are lodged in a distal part of the feeding vessels. These methods have become the treatment of choice in patients with multiple or bilateral arteriovenous malformations in order to avoid the need for extensive or repeated surgery [165–168]. Complications occur in around 10% of embolizations, including systemic displacement of the embolus and puncture of the myocardium. Nevertheless, these forms of therapy result in increased  $Pao_2$  and improved exercise tolerance, and recanalization is relatively infrequent.

Finally, in some cases of multiple lesions and telangiectasia with cyanosis, lung transplantation becomes an option [169].

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# SOME LESS COMMON PULMONARY DISEASES

ANTHONY SEATON

## Alveolar haemorrhage

Intrapulmonary bleeding occurs in many lung disorders. In general, two patterns are discernible: bleeding from the main conducting airways, as in carcinoma, may be distributed to peripheral areas of the lung but most of the bleeding becomes evident as haemoptysis; in contrast, when bleeding occurs distal to the mucociliary transport system, much or even all of the blood may remain in the lung. This form of alveolar haemorrhage may cause haemoptysis but is also associated with breathlessness, anaemia, hypoxaemia and diffuse pulmonary shadowing.

## Causes

The common causes of alveolar haemorrhage are shown in Table 51.1. Goodpasture's syndrome consists of alveolar haemorrhage/haemoptysis and nephritis [1], and is now further classified into four main conditions: antiglomerular basement membrane antibody disease [2–7], the vasculitides and collagen vascular disorders (although not all cases are associated with nephritis) [8–18], idiopathic rapidly progressive glomerulonephritis [4,12,19,20], and D-penicillamine-induced disease [21,22].

Alveolar haemorrhage may also result from chemical insults such as exposure to trimellitic anhydride [23] and as a consequence of lymphangiography [24], and has been described with azathioprine sensitivity [25] and following exposure to hard metal (tungsten carbide) [26]. Finally, idiopathic pulmonary haemosiderosis is a syndrome of alveolar haemorrhage of unknown cause without involvement of other organ systems. In most series of Goodpasture's syndrome, the vasculitides account for 40–60% of cases of alveolar haemorrhage, idiopathic rapidly progressive glomerulonephritis for 15–30% and antibasement membrane antibody disease for 20–40% [4,7,12]. This section is principally concerned with antibasement membrane antibody disease as a cause of Goodpasture's syndrome and with idiopathic pulmonary haemosiderosis. The other causes of Goodpasture's syn-

drome and alveolar haemorrhage are discussed in the chapters indicated in Table 51.1.

## Antiglomerular basement membrane antibody disease

### Definition

This disease is characterized by alveolar haemorrhage and glomerulonephritis with linear deposition of IgG on the basement membranes of glomeruli and alveoli. Circulating antibodies to glomerular basement membrane can be detected in the blood [3,5–7].

### Aetiology and prevalence

Between 1980 and 1984, 71 patients with this condition were reported in the British Isles [6], although this is certainly an underestimate, and the disease is now thought to occur in rather fewer than 1 per million of the population annually [6]. The peak incidence is seen between 20 and 30 years of age with a 4:1 male predominance. A second peak is seen in middle age where women in their sixties may present with glomerulonephritis alone [6].

The precipitating factor for the disease is unknown, although some cases have followed exposure to hydrocarbon vapour [27] and study of workers exposed to petroleum mineral oils have shown an excess of antibasement membrane antibodies [28]. In other cases, including the original description by Goodpasture, the illness has been preceded by a viral infection. The distinguishing feature of the disease is the presence of circulating antibody to glomerular basement membranes, with linear deposition of this antibody on alveolar and glomerular basement membranes [29]. The antigen to which the antibody is directed is located in the C-terminal domain of type IV collagen from glomerular and alveolar basement membrane and has a molecular mass of 26 000 kDa [30–33]. It has been shown that the antigen is the non-collagenous part of the  $\alpha_3$  chain of type IV collagen, expressed by a gene in the

**Table 51.1** Causes of alveolar haemorrhage and references to the literature.

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<i>Goodpasture's syndrome (alveolar haemorrhage plus nephritis)</i>
Antibasement membrane antibody disease [2–7]
Vasculitides and collagen vascular diseases (Chapters 40 & 53)
Systemic lupus erythematosus [8–10]
Wegener's granulomatosis [4,11]
Non-specific systemic necrotizing vasculitis [4,12]
Rheumatoid arthritis [13,14]
Progressive systemic sclerosis [15]
Mixed connective tissue disease [16]
Polyarteritis nodosa [13]
Behçet's disease [17]
Essential mixed cryoglobulinaemia [18]
Tumour-related vasculitis [12]
Endocarditis-related vasculitis [12]
Idiopathic rapidly progressive glomerulonephritis [4,12,19,20]
D-Penicillamine induced [21,22]
<i>Chemical related</i>
Trimellitic anhydride [23]
Lymphangiography [24]
<i>Idiopathic pulmonary haemosiderosis</i>

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q35–37 region of chromosome 2 [34,35]. The pathogenesis is believed to involve a cytotoxic type II hypersensitivity reaction consequent on antibody binding to this antigen. Certainly the disease can be passively transferred to monkeys by administration of human anti-glomerular basement membrane antibody and the severity of the disease is proportional to the titre of circulating antibodies [36]. Savage and colleagues [6] reported a peak incidence of the disease in spring and early summer, which might be consistent with a viral trigger factor. Genetic factors would also appear to have some importance; cases have been reported in identical twin sisters living together and in two brothers who lived apart [37,38]. In addition, there is a strong association with HLA-DR2, which is present in 60–70% of cases [39–41]. It is tempting to speculate that, in those genetically predisposed, infection with a virus that shares a similar antigen to the Goodpasture antigen may precipitate disease. Such an association with influenza A2 virus infection has been described [42].

It thus seems likely that pulmonary haemorrhage occurs as a result of damage to type IV collagen in alveolar basement membrane and that, particularly in the genetically predisposed, this may occur as a consequence of a number of trigger factors, which may include viral infection and inhaled or ingested toxic substances. Type IV collagen is important in protecting the pulmonary capillaries from physical stress, and when weakened allows leakage of blood [43]. Other factors may damage collagen in the lung, perhaps explaining why cigarette smokers are at greater risk of Goodpasture's syndrome [44]. In most cases the renal lesion is presumably a consequence of the anti-

collagen IV antibodies also attacking the collagen of the glomerular basement membrane.

### Pathology

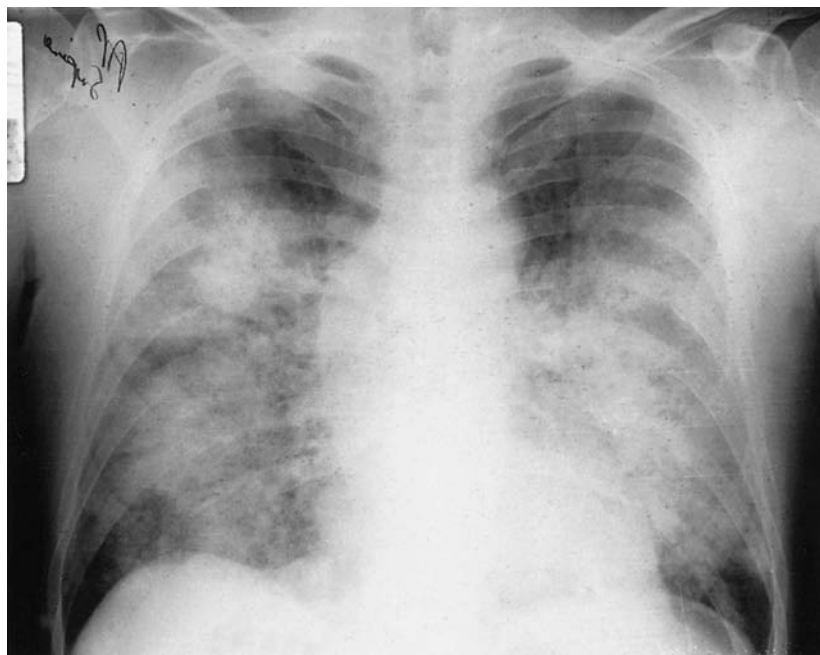
Renal biopsy shows a diffuse crescentic or focal glomerulonephritis or even, rarely, normal glomeruli [2,45]. Linear deposits of IgG can be detected on the glomerular basement membrane using immunofluorescence techniques. Occasionally, immunofluorescent stains for IgA, IgM, the C3 component of complement and fibrinogen are positive [46]. Similar techniques can be applied to lung tissue obtained by open, needle or transbronchial biopsy in order to demonstrate linear deposition of IgG on alveolar basement membranes [47,48]. Light microscopy of lung biopsies shows active intra-alveolar haemorrhage with collections of haemosiderin-laden macrophages [46].

### Functional abnormality

Where measured, a restrictive pattern of lung volumes is usually found. The diffusing capacity for carbon monoxide ( $DLCO$ ) is increased during episodes of haemorrhage as a result of sequestration of blood within the alveoli. The single-breath diffusion coefficient for carbon monoxide ( $Kco$ ) is considered abnormal if raised by more than 30% and serial measurements are of considerable value in monitoring the progress of alveolar haemorrhage [49–52]. Although  $Kco$  frequently parallels the extent of airspace shadowing on the chest radiograph, it may also increase in the presence of a persistently normal film or alternatively precede the development of shadowing by up to 48 h [53].

### Clinical and radiological features

There is often a preceding upper respiratory tract infection [2,3,5,6,12,54–58]. Haemoptysis is found in 80–90% of presentations and is more common in smokers. In one series of 51 patients, 100% of smokers with this disease developed pulmonary haemorrhage while only 20% of non-smokers did so [44]. Cough, dyspnoea, weakness and fatigue are common complaints. Fever and chills may occur. Pallor is common and hypertension is found in a minority of cases. Auscultation of the chest frequently reveals inspiratory crepitations. The chest radiograph is abnormal in over 80% of cases and most commonly shows diffuse bilateral patchy consolidation in the mid and lower zones with relative sparing of the apices and costophrenic angles (Fig. 51.1). Air bronchograms may be seen. Urinalysis is abnormal in over 90% of patients, with microscopic haematuria, proteinuria, granular casts and occasionally frank haematuria. An iron-deficiency anaemia is usual and uraemia is found in over 70% of cases. Examination of sputum or bronchoalveolar washings reveals the presence of blood



**Fig. 51.1** Radiograph of patient acutely dyspnoeic with Goodpasture's syndrome showing extensive bilateral consolidation and air bronchograms.

and/or haemosiderin-containing alveolar macrophages. Occasionally renal involvement without pulmonary haemorrhage or pulmonary involvement without obvious renal disease may occur [3,6,45].

### Differential diagnosis

The differential diagnosis includes the disorders listed in Table 51.1. Drug or chemical-related disease is readily identified by taking a history. The vasculitides and collagen vascular diseases frequently have other systemic manifestations (see Chapters 40 & 53) that assist in diagnosis. Idiopathic rapidly progressive glomerulonephritis is diagnosed when a renal biopsy shows crescentic glomerulonephritis without arteritis or linear immunofluorescence in the absence of any other features of a multisystem disorder. Nevertheless, it is managed in the same way as the vasculitides. It has been suggested that it is a variant of Wegener's disease, with antineutrophil cytoplasmic antibodies [59]. The definitive diagnosis of antiglomerular basement membrane disease is made by demonstrating linear immunofluorescence (usually to IgG) on the glomerular basement membrane (less commonly the alveolar basement membrane) and by detecting an elevated titre of antiglomerular basement membrane antibodies in the serum using radioimmunoassay or enzyme-linked immunosorbent assay [60].

### Treatment and progress

The condition often presents to the chest physician as rapidly increasing haemoptysis with progressive renal failure, although there is frequently a history of previous

smaller haemoptyses. While spontaneous remission may occur, the course is usually progressive and fatal unless treated [61–63]. The renal manifestations require treatment with high-dose prednisolone (60 mg daily reducing to 20 mg over 4 weeks) and cyclophosphamide (2–3 mg/kg daily). As the patient responds, the cyclophosphamide may be stopped after about 2–3 months and the prednisolone tailed off and stopped within about 6 months.

The addition of plasmapheresis to immunosuppression has improved the speed of response and effectiveness of the above regimen and in general a good response can be expected if the patient is not already oliguric at the time of presentation [64]. Usually this is associated with resolution of the pulmonary haemorrhage within a few days and recovery of renal function. The plasma exchange is usually continued for about 2 weeks until the antibasement membrane antibodies are reduced to baseline levels. There has been one report of successful treatment of a patient unresponsive to plasmapheresis by immunoadsorption of IgG to staphylococcal protein A [65]. In patients with severe renal failure, dialysis may be necessary and ultimately transplantation if recovery does not occur. In this case, the operation should be delayed until antiglomerular basement membrane antibodies have fallen to low levels [3]. In exceptional cases bilateral nephrectomy has been necessary to control alveolar haemorrhage when all else has failed [3,66].

Relapse of disease may occur during treatment, when it is more often due to an intercurrent infection than to a rise in antibody titres [67]. Once successfully treated, recurrence is rare but has been reported, on one occasion following exposure to hydrocarbon solvents [68–70]. Lung

function often shows permanently reduced gas transfer [71] and sometimes there is a slow decline in renal function. If relapse does occur, it is likely to respond to the same regimen as described above.

### **Idiopathic pulmonary haemosiderosis**

Idiopathic pulmonary haemosiderosis is a condition of uncertain cause characterized by recurrent episodes of alveolar haemorrhage, haemoptysis and secondary iron-deficiency anaemia. Most cases begin in childhood but some start in adult life. The disease is often fatal though apparently complete recovery can occur.

### **Aetiology and prevalence**

This is a rare disease but in 1962 Soergel and Sommers [72] were able to review 132 cases from the literature and from personal experience. Most were aged 1–7 years at onset but about 15% were aged 16 or over when symptoms began. The sex distribution was equal in childhood but in adult life the disease was twice as common in men. The disease is not familial and from the number of different associations recorded in the literature it seems likely that its aetiology is multifactorial.

The accompanying iron-deficiency anaemia is certainly due to loss of iron into the lung through haemorrhage, as has been shown by iron turnover studies, although the cause of the haemorrhage is uncertain [73]. Epidemiological observations in northern Greece have shown an excess of cases in poor rural areas where toxic insecticides were often applied to cereals stored within or close to the dwelling place [74]. A reduction in case numbers was seen when these conditions were improved, possibly implicating insecticides in the pathogenesis.

Immunological causes are fashionable and might be supported by the presence of eosinophilia in one-eighth of cases, the aggregation of mast cells in the lung, an increase in plasma cells in the reticuloendothelial system and the presence of cold agglutinins in some cases [75,76]. Immunological diseases that have been associated with pulmonary haemosiderosis include rheumatoid arthritis, autoimmune haemolytic anaemia, dermatitis herpetiformis, thyrotoxicosis and coeliac disease [77–82]. In addition, children and adults have been described with idiopathic pulmonary haemosiderosis secondary to gluten enteropathy and cows' milk allergy who responded clinically to withdrawal of gluten and cows' milk respectively [75,83–85]. Nevertheless, the aetiology in the majority of cases remains unknown.

### **Pathology**

Histologically, there is degeneration, shedding and hyperplasia of alveolar epithelial cells with marked localized

alveolar capillary dilatation [72]. Haemosiderin-containing macrophages are plentiful in the alveolar spaces and interstitium [86,87]. Depending on the chronicity of the condition there may be varying degrees of interstitial fibrosis, degeneration of the alveolar, interstitial and vascular elastic fibres, dilatation and moderate subendothelial sclerosis of pulmonary arteries and veins, and slight muscular hypertrophy of the bronchial arteries. These changes are secondary to the recurrent bleeding [72]. Electron microscopic examination has shown widespread capillary endothelial and basement membrane damage [88,89]. Deposits of protein, in one case characterized as IgA, have occasionally been observed on the alveolar basement membrane [79,88].

### **Functional abnormality**

In acute incidents of alveolar haemorrhage *Kco* is elevated, values of greater than 130% predicted being considered abnormal [49,50]. In chronic cases, where interstitial fibrosis has developed, a restrictive pattern of lung volumes and reduced *DLco* is usual, although a pattern of airways obstruction is also seen in some patients [82,87].

### **Clinical and radiological features**

The intensity and duration of the pulmonary haemorrhages determine the clinical course, which may be very variable [72,79,86,90,91]. Commonly, continuous mild intrapulmonary bleeding results in a chronic non-productive cough with tiredness, pallor and failure to thrive in children. The sputum may be intermittently blood-stained or the child may vomit swallowed blood. An iron-deficiency anaemia is usual and the faecal occult blood test may be positive. A minority of patients may have generalized lymphadenopathy or hepatosplenomegaly. The chest radiograph may show transient blotchy shadows. With a severe bleed, cough and haemoptysis worsen and dyspnoea, chest pain or tightness and pyrexia may develop. The anaemia worsens and the chest radiograph is likely to show more extensive, bilateral, patchy shadows particularly in the middle and lower zones. Crepitations may be audible in the chest.

Bleeding episodes continue for years and eventually chronic dyspnoea becomes a feature in addition to the anaemia. Finger clubbing develops in 25%. The chest film may show reticulonodular infiltrates, fine stippling or a ground-glass appearance in the perihilar or lower lung zones due to pulmonary fibrosis. The apices and costophrenic angles are often spared. Hilar lymphadenopathy is occasionally seen. Cor pulmonale secondary to pulmonary fibrosis and hypoxaemia develop in a minority [92]. Massive pulmonary haemorrhage may occur at any time and most patients die in a severe bleeding episode.

### Investigations

Haemosiderin-laden macrophages are found in sputum or bronchial washings. A hypochromic microcytic anaemia is usual and a minority of blood films show an eosinophilia [72]. Idiopathic pulmonary haemosiderosis is a diagnosis of exclusion and no evidence of other organ involvement is found, although confusion with Goodpasture's syndrome before renal disease presents may lead to diagnostic problems. Diagnosis depends on excluding other causes of pulmonary haemorrhage, especially those such as Wegener's syndrome, Goodpasture's disease and microscopic polyarteritis that may require immunosuppressive treatment.

### Treatment

Patients with cows' milk allergy or gluten enteropathy have responded to withdrawal of the offending substance [83–85]; unfortunately, these patients are a small minority. Iron-deficiency anaemia responds to replacement therapy and occasionally blood transfusion is required during severe bleeding episodes. Corticosteroid and immunosuppressive drugs do not appear to affect the long-term prognosis but either may be of value during acute episodes of alveolar haemorrhage, as in Goodpasture's syndrome [93]. Anecdotal reports of therapeutic success with assorted agents such as sodium cromoglycate (cromoglycate) [76] and budesonide [94] abound. However, the disease may remit spontaneously and these reports should be viewed with caution.

### Prognosis

The course of the disease is very variable. Although it is often fatal, a number of patients appear to recover and remain symptom-free for long periods. Soergel and Sommers [72] found that 20 of 68 patients were dead after an average duration of disease of 3.3 years; 17 still had active disease after an average duration of 5.5 years; 12 had relatively inactive disease but still with chronic symptoms, such as exertional dyspnoea and anaemia, after an average duration of 5.4 years; and 19 were apparently completely free of the disease and symptoms after an average duration of 4.5 years. These authors contrast a 28-year-old woman who died after an illness of only 9 days and a boy aged 6 years at onset who died of cor pulmonale 20 years later.

## Pulmonary alveolar proteinosis

First described in 1958 by Rosen and colleagues [95], pulmonary alveolar proteinosis is a rare disease of unknown origin characterized by progressive dyspnoea, febrile episodes and a cough that is usually unproductive. The

radiological appearances are often similar to those of pulmonary oedema. Histologically, the alveoli contain a granular eosinophilic material strongly positive to periodic acid–Schiff (PAS) stain.

### Aetiology

The disease is three times as common in men as in women and usually occurs in young adults, although it has been described in the neonatal period, in children and in old age [96,97]. Primary alveolar proteinosis is characterized by uniform immunoperoxidase staining of the specific surfactant apoprotein in alveoli [98,99]. Two surfactant proteins, Sp-A and Sp-D, have been described in alveolar fluid from such patients [100,101]. Secondary alveolar proteinosis, which is found in association with immunosuppression due to haematological malignancy [102–106], myeloma [107], hypogammaglobulinaemia [108] or, more recently, human immunodeficiency virus (HIV) infection [109,110], shows only focal immunoperoxidase staining of the specific apoprotein [98]. Congenital alveolar proteinosis was first described in four siblings [111] and appears to be associated with an inherited deficiency of Sp-B [112]. The syndrome has also been described in children with a recessive amino acid transport disease, lysinuric protein intolerance [113]. Opportunistic infections, especially *Nocardia*, *Aspergillus*, *Mycobacterium* and *Cryptococcus* spp., are common in secondary alveolar proteinosis but rare in the primary condition [105,114]. Exposure to aluminium or silica dust has been associated with alveolar proteinosis and the condition can be produced in experimental animals by inhalation of large doses of finely divided mineral dust [106,115].

Pulmonary alveolar proteinosis is believed to be due to a failure of reprocessing of surfactant by type II alveolar cells, with resultant accumulation of phospholipid and glycoprotein-rich material in the alveolar spaces [116]. Electron microscopy of the alveolar material shows myelin-like multilamellated structures, which represent phospholipid bilayers separated from each other by amorphous proteinaceous material [117]. The glycoprotein has been isolated and characterized and appears to be a monomeric and dimeric form of the surfactant glycoprotein found in normal alveolar lining fluid [118,119]. Macrophage numbers are diminished in bronchoalveolar lavage fluid from patients with alveolar proteinosis and the cells may be increased in size [120,121]. The macrophages also have diminished phagocytic capacity, with decreased phagolysosome fusion [121,122]. These phagocytic defects can be induced in mouse peritoneal or human macrophages on exposure to cell-free fractions of the alveolar material, suggesting that the macrophage defect is secondary and not primary [121,122]. Leukotriene (LT)C<sub>4</sub>-like substances and LTB<sub>4</sub> have been found in significant quantities in alveolar proteinosis

lavage fluid, although the source and their contribution to the pathogenesis of the disease are not clear [123].

### Pathology

Macroscopically, the lungs contain firm, grey-white, nodular or diffuse masses, which microscopically consist of alveoli, bronchioles and bronchi stuffed with eosinophilic granular material staining with PAS (Fig. 51.2). Bronchial and alveolar walls may be infiltrated by lymphocytes. The alveoli are often lined by flattened epithelial cells and occasional foamy mononuclear cells containing lipoid. In frozen sections, long, thin, birefringent crystals may be present. A few cases may have some interstitial fibrosis.

### Functional abnormality

The extent of the abnormality depends on the amount of lung involved. A restrictive pattern of lung volumes with reduced *DLCO* is usual and hypoxaemia, which may be extreme, occurs. The ratio of forced expiratory volume in 1 s to forced vital capacity is usually normal.

### Clinical features

The usual presentation is with progressive dyspnoea on exertion with or without a dry unproductive cough [116,120,124,125]. Weight loss, chest pain and fever may also occur. The initial presentation is often wrongly diagnosed as pneumonia, sarcoidosis, allergic alveolitis or tuberculosis; in one series the median interval between onset of symptoms and diagnosis was 2 years, with a range of 6 weeks to 6 years [124]. Fine inspiratory crackles may be audible in the chest and finger clubbing develops in a minority.

### Radiology

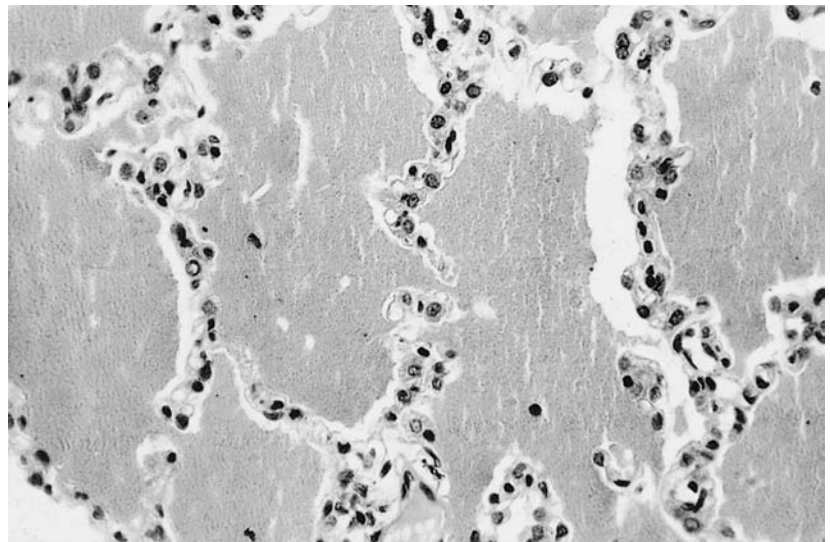
The chest film most often shows diffuse perihilar shadows resembling pulmonary oedema (Fig. 51.3). Peripheral nodular and lobar consolidation may also occur [126,127]. There may be numerous cyst-like translucencies possibly due to pneumatoceles from bronchial obstruction. Occasionally, shifting densities may suggest pulmonary eosinophilia. Changes in the radiological appearances are not always related to changes in the patient's symptoms, and clinical improvement may coincide with radiological deterioration and vice versa. Sometimes the initial radiographic appearances may suggest interstitial fibrosis [128,129]. In children, the radiographic appearance may differ from the classical adult picture; reticulonodular and miliary nodular patterns have been recorded as well as focal consolidation [97].

### Investigations

Sputum or bronchial washings contain PAS-positive, alcian blue-negative staining material. Lamellar bodies may be seen on electron microscopy [130]. Serum lactate dehydrogenase levels may be elevated [131].

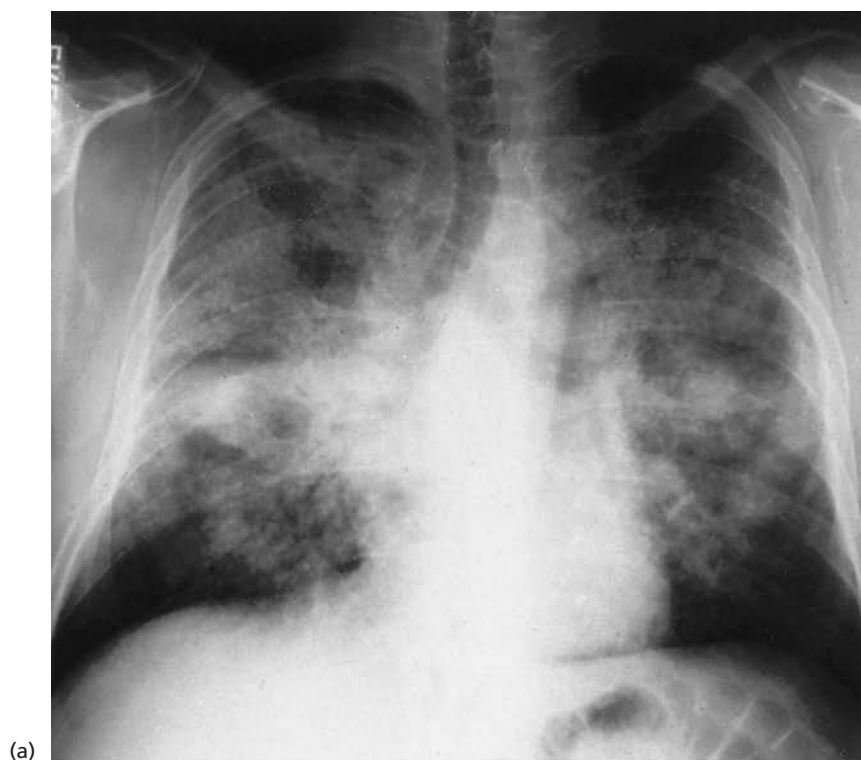
### Treatment

A number of patients with this condition (25% in one series [120]) improve spontaneously and do not require treatment. Spontaneous remission for 18 years has been reported [132]. However, the majority require treatment for progressive symptomatology and deteriorating pulmonary function. The treatment of choice is unilateral lung lavage while the contralateral lung is isolated and ventilated by using a double-lumen endobronchial tube [116,124,133]. The lavage lung is filled with saline buffered

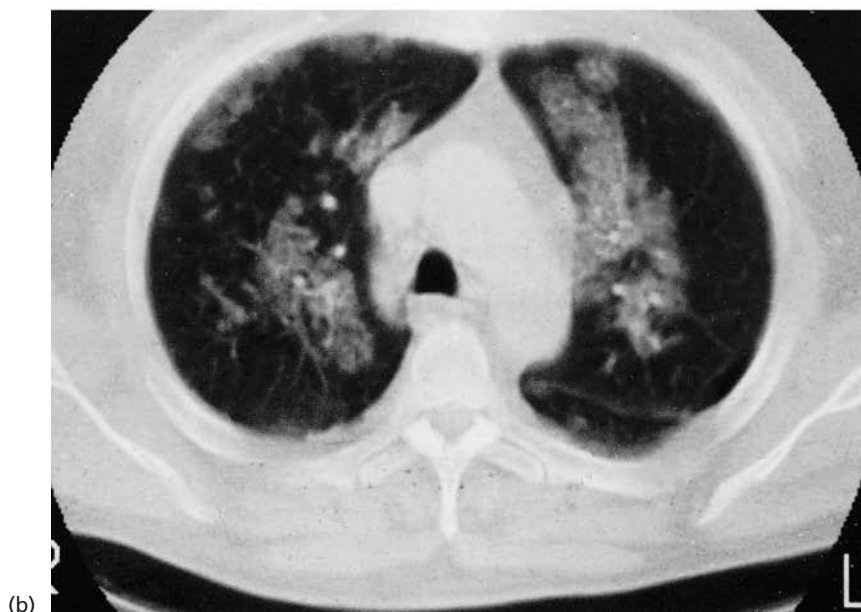


**Fig. 51.2** Open lung biopsy from patient with alveolar proteinosis showing typical granular exudate, strongly eosinophilic (and also PAS-positive) (haematoxylin & eosin  $\times 300$ ).





(a)



(b)

**Fig. 51.3** (a) Radiograph of a patient with alveolar proteinosis showing diffuse patchy shadows, more dense round the hila. (b) CT of another patient with alveolar proteinosis shows the patchy distribution of alveolar filling. (Courtesy of Dr N. LeRoy Lapp.)

to pH7.4 at a temperature of 37°C and volumes of 500–1000 mL are washed in and out until a total of 40–50 L has been exchanged or the effluent has become clear. At the conclusion of the procedure, vigorous suction and manual ventilation are followed by a short period of assisted ventilation. The second lung can be lavaged at a later date. Not surprisingly, chest radiographs taken during the lavage procedure show worsening of the pulmonary shadowing; within a few hours the chest film may

have deteriorated further or improved but thereafter there is a gradual improvement at 1 week and marked to moderate improvement at 6 weeks [134]. Lavage may need to be repeated at intervals, the frequency varying between individual patients. Lavage via the fiberoptic bronchoscope is less satisfactory than the above but has been successfully employed to treat the right middle and upper lobes in a patient with only one lung [135].

In patients who are too hypoxic to undergo lung lavage,



various forms of support, including hyperbaric oxygen [136], use of a membrane oxygenator [137] and partial cardiopulmonary bypass [138], have been employed to maintain  $P_{aO_2}$  during the procedure. In one patient who refused bronchopulmonary lavage a satisfactory response was obtained to treatment with ambroxol, a surfactant activator [139].

### Prognosis

The prognosis of primary alveolar proteinosis in adults has been much improved by bronchopulmonary lavage, which helps in 80% of those who require it although it may have to be repeated at intervals to maintain this improvement [120]. Death is more likely to occur in children and in those with secondary alveolar proteinosis, where opportunistic infection and the underlying disease are the main causes.

## Amyloidosis

Amyloidosis is usually secondary to one of the well-recognized causes, although primary amyloidosis of unknown cause may occur. Amyloid consists of protein that shows a characteristic fibrillar pattern on electron microscopy. The amyloid in primary amyloidosis (AL) is formed from the light chains or part of the light chains of immunoglobulin [140]. In secondary amyloidosis the protein differs from that found in primary amyloidosis and is designated AA. Additional amyloid types such as AEt, found with endocrine neoplasms and which is related to calcitonin, have also been described [140]. Both primary and secondary amyloidosis may be generalized or localized to the lung. A convenient classification is shown in Table 51.2.

In generalized amyloidosis, whether primary or secondary, amyloid infiltrates are commonly found in alveolar septa and pulmonary arteries though these lesions seldom give rise to important symptoms, which are more commonly due to amyloid infiltration at other sites, particularly the heart.

Localized primary or secondary amyloidosis may affect the tracheobronchial tree or the pulmonary parenchyma. The most common form of tracheobronchial involvement is with multifocal submucosal plaques, often with diffuse infiltration of the entire airway wall leading to stenosis [141–144] (Fig. 51.4). The less common form of tracheobronchial involvement is with single or multiple amyloid tumour-like masses that are sometimes discovered incidentally at bronchoscopy. Parenchymal involvement is most frequently in the form of single or multiple nodules of 1–15 cm in diameter [145–150] with or without hilar or mediastinal node involvement [151–154]. One case of an isolated mediastinal amyloid mass has been reported [155]. Diffuse alveolar septal involvement with amyloid

**Table 51.2** Classification of lower respiratory tract amyloidosis.

<i>Generalized (systemic) amyloidosis*</i>	
Primary	
Secondary	
<i>Localized amyloidosis*</i>	
Primary	
Tracheobronchial	
Multifocal submucosal plaques	
Tumour-like mass	
Pulmonary	
Nodular: multiple (parenchymal) or solitary	
Diffuse alveolar septal	
Secondary	
Tracheobronchial	
Multifocal submucosal plaques	
Tumour-like mass	
Pulmonary	
Nodular: multiple (parenchymal) or solitary	
Diffuse alveolar septal.	

\* Including hilar lymph node involvement.

[156] is probably more common than is reported, although only 4 of 157 cases reviewed by Thomson and Citron [141] were in this category.

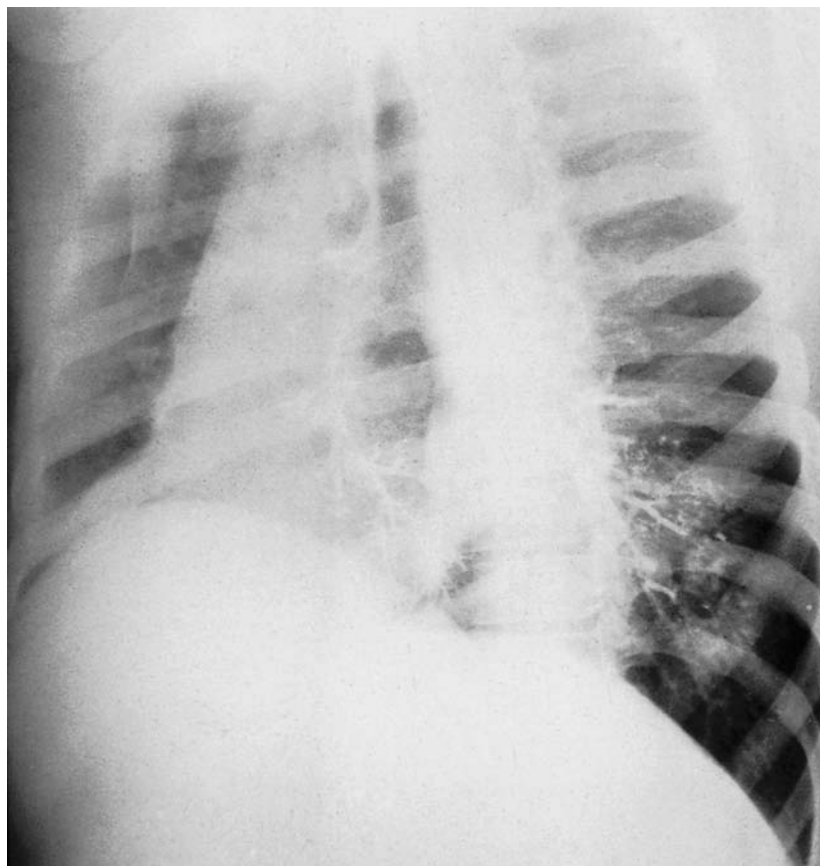
### Clinical and radiological features

Patients with tracheobronchial involvement are usually in their fifties, on average 10 years younger than those with pulmonary parenchymal involvement [142]. Tracheobronchial lesions come to notice by causing symptoms of obstruction, such as cough, wheeze and dyspnoea, which may be slowly progressive over the years. Parenchymal lesions are often detected on routine radiography when they are usually thought to be carcinoma or, if multiple, metastases [157]. The diagnosis of airway lesions can be established by endoscopic biopsy; pulmonary lesions can also be diagnosed by transbronchial biopsy [158], although this may not be without risk [159]. In secondary cases there is evidence of the primary cause. In some cases this causes diagnostic difficulties, for example when it is confused with rheumatoid, Sjögren's or ankylosing spondylitis lung or the lung disease associated with inflammatory bowel disease [160–163].

Rarely amyloidosis can cause respiratory failure by infiltration of the diaphragm or other respiratory muscles [164,165]. Sleep apnoea due to amyloid macroglossia has also been reported [166].

### Functional abnormality

With extensive nodular or diffuse disease of the pulmonary parenchyma, a restrictive pattern of lung volumes with reduced gas transfer may be seen.



**Fig. 51.4** Left anterior oblique bronchogram of patient with diffuse tracheobronchial amyloidosis showing multiple areas of airway narrowing.

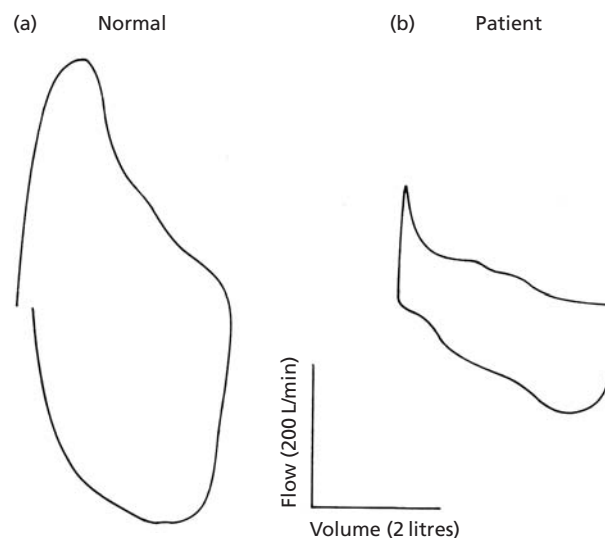
Tracheobronchial involvement may result in an obstructive pattern of lung volumes and sometimes the typical findings of large airway obstruction on flow–volume loops (Fig. 51.5).

#### Treatment

The only possible treatment is surgical. Isolated pulmonary nodules are usually removed (and cured) under suspicion of carcinoma. No treatment is available for multiple pulmonary nodules. Tracheobronchial amyloid may be successfully controlled by endoscopic removal or by laser photoresection [167]. Untreated lesions progress slowly over the years and long survivals have been documented [153]. One patient with primary tracheobronchial amyloidosis treated personally for over 10 years responded clinically to the combination of prednisolone and melphalan. The melphalan was subsequently discontinued but deterioration in symptoms and lung function always followed attempts to stop the steroids.

#### Tracheopathia and bronchopathia osteoplastica

The term ‘tracheopathia osteoplastica’ was first used by Aschoff [168], although Wilks in 1857 [169] was the first to



**Fig. 51.5** Flow–volume loops of (a) normal subject and (b) patient with tracheobronchial amyloid, which shows the severe inspiratory and expiratory obstruction.

report the presence of large numbers of bony plates protruding into the lumen of the larynx, trachea and bronchi of a 38-year-old man dying of pulmonary tuberculosis. The term ‘tracheobronchopathia osteoplastica’ has been

coined to embrace all the possible sites of the disease process [170].

### **Prevalence, aetiology and pathology**

Some 245 cases had been reported in the world literature up to 1974, mostly in middle-aged and elderly men but occasionally in women [171]. Since then there have been regular isolated case reports. The bony or cartilaginous bosses or plaques arise over the cartilages and are continuous with the perichondrium. Histologically, the lesions are of bone, cartilage or calcified acellular protein matrix. The mucosa overlying the protrusions is usually intact and histologically normal, although squamous metaplasia has been reported [171–173]. The lesions may be localized or diffuse and are usually only diagnosed at autopsy, although occasionally they may be diagnosed because they cause bronchial obstruction. While the aetiology is unknown, it has been suggested that metaplastic changes occur in elastic tissue with conversion to elastic cartilage that may then ossify [174]. A simpler explanation is that the protrusions simply represent exostoses and ecchondroses from tracheal cartilage rings [175]. Finally, it has been suggested that the condition may be a late development in tracheobronchial amyloidosis [176].

### **Clinical features**

Most cases have only been diagnosed at autopsy in patients dying of other diseases, although a few have been diagnosed by the characteristic bronchoscopic appearances [177]. Recurrent pneumonia may occur distal to obstruction and lead to a bronchoscopic diagnosis [178]. Minor symptoms may include cough, dry throat, voice change, dyspnoea and haemoptysis. The complaint of haemoptysis frequently leads to diagnosis at bronchoscopy [177].

### **Radiology**

Bronchial obstruction may cause collapse and pneumonia. The condition cannot be recognized on routine radiography, although tomography of the trachea or main bronchi may reveal the characteristic projecting nodules [177,179].

### **Treatment**

Treatment is only necessary for complications such as infection or collapse. If the collapsed lung is not severely damaged, endoscopic removal or sleeve resection of the blocked bronchus might be justified. When the larynx is affected, laser treatment has been used to remove protrusions [180].

## **Alveolar microlithiasis**

Pulmonary alveolar microlithiasis is a disease that is often familial and characterized by a radiographic appearance of very fine, sand-like mottling uniformly distributed through both lungs. This mottling represents an extensive intra-alveolar deposit of calcium-containing bodies. Despite extensive radiographic changes, symptoms at the time of discovery are often minimal or absent, but later there is gradual progression to respiratory failure and cor pulmonale.

### **Aetiology**

The cause of the disease is quite unknown. It may occur at any age between infancy and 80 years but the majority are diagnosed between the ages of 30 and 50 years. The sex distribution is equal. A familial incidence, particularly in siblings, is common, leading to the suggestion that a local defect of calcium metabolism may be responsible [181]. A report from Turkey indicates that the condition seems to be more frequent than would be expected on the basis of reports from elsewhere in the world, 52 cases having been described over 30 years; several of these were also familial [182].

### **Pathology**

The lungs are solid and may sink in water [181], and throughout there are sand-like grains diffusely distributed but maximal at the bases. At necropsy, a saw may be required to cut the lung. Microscopically, there are 'onion-skin' bodies, resembling corpora amylacea, in 30–80% of alveoli and these bodies are usually densely calcified. There may or may not be interstitial fibrosis and inflammatory cell infiltration. Emphysematous blebs may be found at the apices or anterior margins of the lungs. There are usually no changes in other organs, although deposits in the lumbar sympathetic chain and probably in the testes have been reported in one patient [183].

### **Clinical and radiological features**

These patients are often discovered by routine radiography at an asymptomatic stage when they may have no complaints despite dramatic changes on the chest film. Over a period of years there is progression of disease, with the development of increasing dyspnoea, cough and, later still, cyanosis, polycythaemia and cor pulmonale. Haemoptysis occasionally occurs [184] and clubbing may be seen [185]. The patient may occasionally cough up calcified bodies. Recurrent pneumothoraces may occur [186]. There are often no physical signs in the chest even when the radiograph is grossly abnormal. Later there may be inspiratory crepitations and, ultimately, the signs of cor

pulmonale. Death usually results from respiratory or cardiac failure.

### Functional abnormality

Respiratory function tests are often normal or near normal even with extensive radiographic changes. However, with progression of disease, a restrictive pattern of lung volumes develops and impairment of gas transfer with disturbed ventilation-perfusion ratios have been reported [185,187].

### Treatment and prognosis

Therapeutic bronchoalveolar lavage has been shown to be ineffective in one case [185], and it is apparent that in progressive cases the only management course may be lung transplantation. This has been carried out successfully in at least one patient, a 32-year-old man who developed severe pulmonary hypertension [188]. Prior to this extreme measure, there is one report of nasal continuous positive pressure ventilatory support being used to improve gas exchange in a patient with respiratory failure [189].

The disease is probably slowly progressive, although occasionally it appears to arrest. One reported patient was followed for 22 years from diagnosis to death [185].

## Idiopathic pulmonary hilar fibrosis

Chronic idiopathic pulmonary hilar fibrosis is a fibrosing condition restricted to the pulmonary hila that appears to have many similarities to idiopathic mediastinal fibrosis and retroperitoneal fibrosis [190–192]. The aetiology is unknown.

### Pathology

Hilar fibrosis has been classified into two types depending on the relative involvement of the pulmonary artery or vein [190]. In type I disease, the pulmonary artery is narrowed or occluded by the fibrotic hilar mass, with the resultant development of exuberant bronchopulmonary anastomoses. Loss of lung volume is seen on the affected side and pleural thickening occurs due to repeated chest infections and the development of collateral vessels between the lung and chest wall. Narrowing of one of the main bronchi by the fibrotic process is often seen. In type II disease, the main pulmonary veins are occluded by fibrous tissue, with resultant pulmonary capillary hypertension in the affected lung. Loss of lung volume, pleural thickening and narrowing of main bronchi due to the fibrotic process are again seen. The fibrous tissue may extend through the bronchial cartilage. Histologically, the fibrous mass is composed of relatively acellular fibrous

tissue comprising intertwining collagen fibres. The interstices contain a few fibroblasts and lymphocytes with more plasma cells and occasional foci of polymorphonuclear leucocytes. Various degrees of hyalinization, calcification and ossification may be present.

### Clinical and radiological features

Patients commonly present in young adult life with repeated haemoptyses and dyspnoea and there may be clinical signs of pulmonary hypertension. Radiographically, there may be pleural thickening and diminution of the size of the affected lung, and segmental narrowing of one or more major bronchi may be demonstrated at bronchoscopy or with bronchography (Fig. 51.6). The pulmonary artery shadow may be diminished in type I disease and pulmonary angiography shows absent or diminished pulmonary blood flow. In type II disease, an ill-defined hilar shadow may be seen with radiographic evidence of pulmonary venous distension.

### Treatment and prognosis

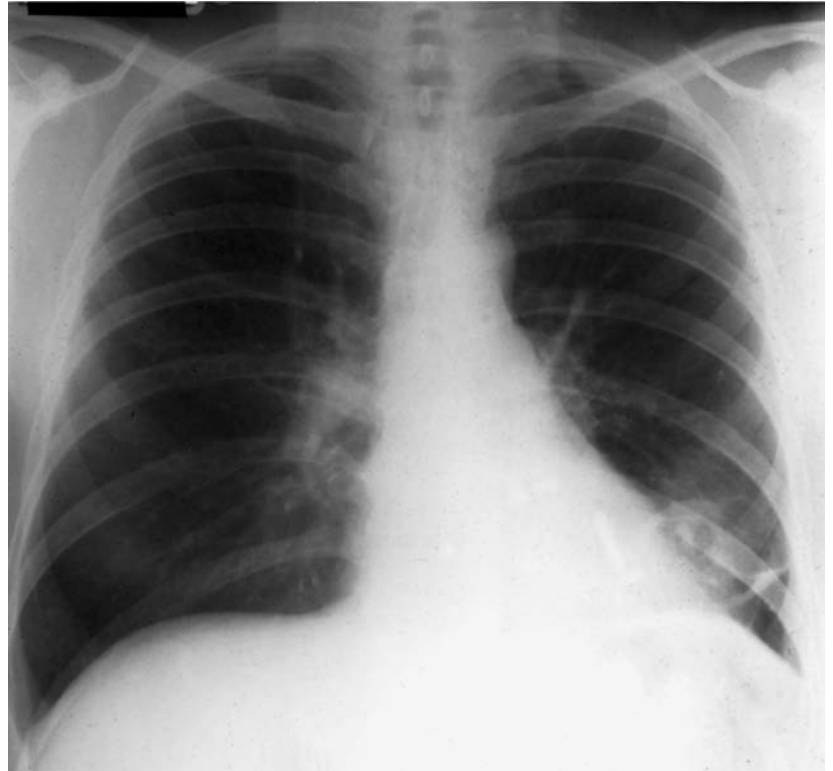
No form of medical treatment is available. Most patients are subjected to thoracotomy, and resection of the 'tumour' and affected lung is carried out in the belief that the process is malignant. Treatment by simple ligation of bronchial arteries on the affected side also appears to have been effective in one case [190]. Where the condition is unilateral the prognosis, given surgical intervention, appears to be relatively good [190]. Bilateral hilar fibrosis has a poor prognosis when bilateral pulmonary venous obstruction occurs [193,194].

## Pulmonary hyalinizing granuloma

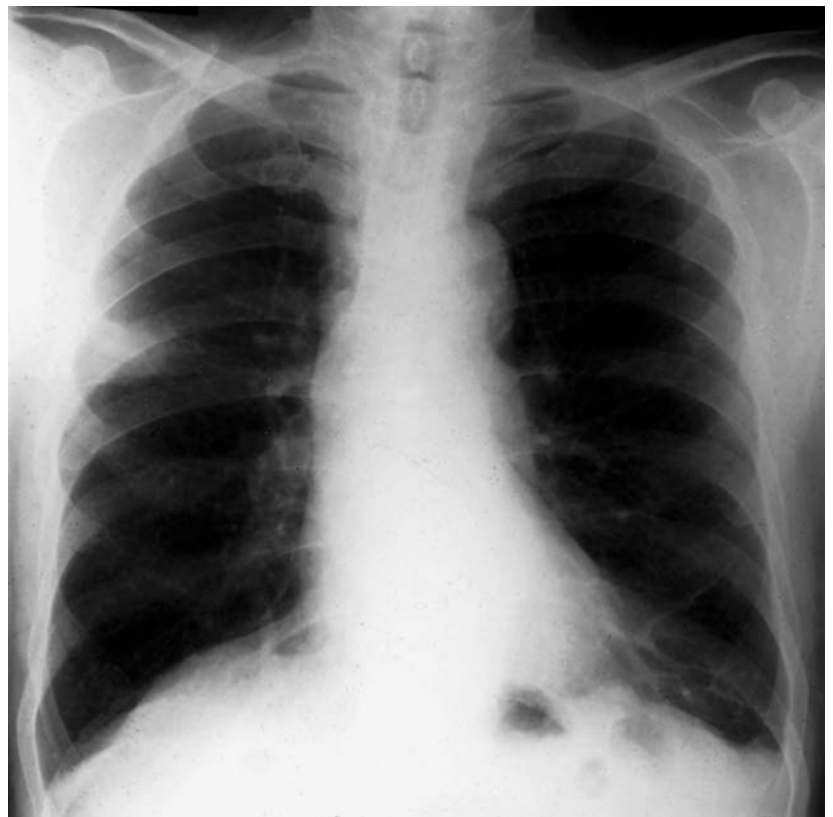
Pulmonary hyalinizing granuloma is a condition of unknown aetiology, usually diagnosed by pathological examination of nodules resected following their discovery on routine chest radiography.

### Pathology

Macroscopically, the waxy white lesions are found in the pulmonary parenchyma or just below the pleural surface [195]. Microscopically, they are seen to be composed of homogeneous pink hyaline lamellae surrounded by plasma cells, lymphocytes and histiocytes, which may also be found locally in a perivascular distribution. Occasional eosinophils and foci of ischaemic necrosis may be seen and foreign body giant cells may be present at the periphery of the lesion. In many of the 20 patients reported by Engleman and colleagues [195] the hyaline material stained with Congo red and had the characteristics of amyloid.



**Fig. 51.6** Chest film of patient with left-sided idiopathic hilar fibrosis who presented with left lower lobe bronchial obstruction and secondary lung abscesses in posterior basal segment.



**Fig. 51.7** Peripheral lesion in right mid zone that on excision proved to be a hyalinizing granuloma.

## Clinical and radiological features

The average age of patients reported by Engleman and colleagues [195] was 45 years, with a range of 27–66 years. The majority were asymptomatic or had only mild symptoms, including cough, haemoptysis, fever, fatigue and pleuritic chest pain. The abnormality was commonly detected on routine chest radiography, which usually showed multiple, frequently bilateral, nodules with no predilection for any particular lung zone. Single lesions also occur (Fig. 51.7). The lesions were usually well defined and round, although irregular ill-defined nodules and cavitation were also seen. Calcification was not present. Lesions tended to grow very slowly, in one case with a doubling time of 2.5 years. The behaviour of the lesions was reminiscent of nodular pulmonary amyloid.

## Treatment and prognosis

Isolated lesions are often resected as suspected carcinomas with resultant cure. No treatment is available for multiple lesions but the prognosis appears to be good, with no significant impact on longevity [195]. Four patients have been reported as developing sclerosing mediastinitis and two retroperitoneal fibrosis [195,196], an association that must be considered signifi-

cant even though the aetiology of all these conditions is unknown.

## Castleman's disease

Two subtypes of the very rare Castleman's disease, angiofollicular hyperplasia, have been described [197,198]. The more common presents as a mediastinal or hilar lymph node mass, usually asymptomatic or with cough or wheeze due to local compression. Occasionally there are febrile symptoms and a raised erythrocyte sedimentation rate. Biopsy at mediastinoscopy shows follicles of pericapillary lymphocytes, with proliferation of the plump and eosinophilic capillary endothelial cells. Patients with this condition generally do not seem to show a progressive illness and symptoms may be relieved by removal of the nodes.

A more aggressive variant, with prominent plasma cell infiltration, may be associated with other systemic manifestations, including generalized lymph node enlargement, hepatosplenomegaly, paraproteinaemia and skin rash. It may require treatment with corticosteroids and sometimes chemotherapy as for lymphoma, though it is thought not to be truly neoplastic but associated with overproduction of interleukin 6. There seems to be some evidence of an association with HIV infection and Kaposi's sarcoma.

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# RESPIRATORY INFECTION IN THE IMMUNOSUPPRESSED

R. ANDREW SEATON, JULIAN M. HOPKIN AND DOUGLAS SEATON

Respiratory infection in the immunosuppressed has become a major clinical issue with the advance of human immunodeficiency virus (HIV) and with progress in transplant and oncology programmes. Defence of the lungs against infection is complex, comprising laryngeal and cough reflexes, the mucociliary escalator, the scavenging macrophages of the alveolar spaces, a range of innate immune factors (e.g. mannose-binding protein, surfactant proteins A and D) and acquired T-cell immunoglobulin immunity.

Defects in these defences are various and can produce characteristic syndromes of infection. The first part of this chapter focuses on the general principles of respiratory infection complicating severe deficiency of acquired immunity, most commonly seen among patients on cancer chemotherapy and organ transplantation programmes, in those with AIDS and in those receiving immunosuppressive agents for inflammatory disorders, for example vasculitis. Among these patients, pneumonia is a leading cause of disease and death. The second part of the chapter deals specifically with an important opportunistic lung infection, *Pneumocystis carinii* pneumonia (PCP). Actinomycotic and fungal pneumonias are covered in Chapter 21, tuberculosis and opportunistic mycobacterial disease in Chapters 17–20 and bacterial and viral pneumonias in Chapter 13. Diseases that may mimic infection in the immunosuppressed are dealt with elsewhere: radiation pneumonitis in Chapter 13, cytotoxic and other drug-induced lung disease in Chapters 9 and 55, and lymphomas and Kaposi's sarcoma in Chapter 42. The minimally invasive procedures used in diagnosing lung disease in immunosuppressed patients are described in Chapter 8.

Pulmonary complications in the immunosuppressed may be due to infection with pathogenic organisms and opportunistic organisms of medium to low pathogenicity (Table 52.1) or to various non-infective complications (Table 52.2). These often have overlapping clinical and radiographic features, and pose diagnostic and therapeutic difficulties. Establishing a diagnosis, often by invasive

investigation, allows the use of specific and effective treatment, with the minimum of side-effects. This significantly improves survival [1].

An effective diagnostic approach requires knowledge of the potential pulmonary complications, a thorough approach to clinical assessment and a strategy for further investigation.

## Patterns of pulmonary complication

The type of immune disruption provides useful clues to the likely causes of infection (Table 52.1). However, the immunosuppression can be mixed in type in any patient and may vary with the stage of the underlying disease and treatment.

### Cancer chemotherapy programmes

Patients receiving vigorous cytotoxic chemotherapy for leukaemia and lymphoma have a high risk of fatal respiratory infection that threatens their survival, despite control of the malignancy.

Profound neutropenia during the early phases of treatment and consequent Gram-negative pneumonia is a special risk; fungal pneumonia (see Chapter 21), particularly that caused by *Aspergillus fumigatus*, is also possible if the neutropenia is severe and prolonged. Later in the course of the illness, T-lymphocyte immune deficiency develops and with it the special risk of PCP; before the introduction of specific chemoprophylaxis, this produced an attack rate of 18% annually in the childhood leukaemia population.

Non-infectious complications are various and include diffuse pneumonitis as a reaction to cytotoxic agents and the rare leucagglutinin reaction of the lung, in which diffuse radiographic change and hypoxaemia may follow white cell transfusion.

**Table 52.1** Opportunistic respiratory infection in the immunosuppressed.

Defect	Infections
Neutropenia, e.g. treated leukaemia	Bacteria: Gram-negatives, <i>Staphylococcus aureus</i> Fungi: <i>Aspergillus fumigatus</i> , <i>Mucor</i> spp.
Immunoglobulin deficiency, e.g. multiple myeloma, inherited defects	Encapsulated bacteria: <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>
T-lymphocyte deficiency e.g. AIDS organ transplant recipients, treated malignancy	Fungi: <i>Pneumocystis carinii</i> , <i>Cryptococcus neoformans</i> Cytomegalovirus Mycobacteria: tuberculous and atypical Bacteria including <i>Legionella pneumophila</i> , <i>Nocardia asteroides</i>

**Table 52.2** Non-infectious complications in the immunosuppressed.

Pulmonary oedema
Pulmonary haemorrhage
Pulmonary embolism
Tumour (solid tumour, lymphoma/leukaemia, Kaposi's sarcoma)
Drug-induced pneumonitis
Radiation pneumonitis
Alveolar proteinosis
Leucagglutinin reaction

## Organ transplantation

### Renal

Bacterial pneumonias, particularly due to Gram-negative organisms including *Legionella* spp., may occur at any stage after transplantation [2,3]. Mycobacterial disease, especially tuberculosis, is a high risk for individuals with a past history of tuberculosis or likely exposure due to their country of origin. The disease often takes a rapid and disseminated pulmonary form.

Cytomegalovirus (CMV) pneumonia usually presents as a diffuse pneumonitis of mild to moderate severity at 4–6 weeks after transplantation. The most severe form occurs in patients with negative serology for CMV who receive a CMV-positive donor kidney [4].

Fungal infections are significant, particularly *P. carinii*; without chemoprophylaxis the attack rate for *Pneumocystis* in most centres is 10–12% annually [3]. The disease occurs typically from the onset of the second to the sixth month after transplantation, when immunosuppression is at its greatest, and presents with a rapidly progressive diffuse pneumonitis that is fatal unless specific treatment is initiated quickly. Other fungal pneumonias can be caused by *A. fumigatus*, *Mucor*, *Fusarium* and *Trichosporon* spp. and, in some parts of the world, by *Coccidioides* and *Histoplasma*.

Non-infectious complications are frequent and include pulmonary oedema (the result of impaired renal salt and

water excretion, cardiac dysfunction or fluid overload) and thromboembolism. Recurrence in the lung of the original renal-destroying disease may occur, as in Wegener's granulomatosis or Goodpasture's syndrome.

### Liver

The infective risks are similar to those for renal transplantation. Non-infectious complications include postoperative collapse and effusion, particularly at the right base, and also postoperative adult respiratory distress syndrome (ARDS).

### Heart/lung

The infective complications are similar to those listed for renal transplantation but there are also risks of disease due to *Nocardia asteroides* and the protozoan *Toxoplasma gondii*, both of which may be transmitted with the donor heart.

Non-infectious complications include collapse of the left lower lobe and paralysis of the left diaphragm, often due to cold injury of the phrenic nerve. Pulmonary oedema, due to heart failure or ARDS (post-pump syndrome), is not rare. A common late complication after lung transplantation is the development of obliterative bronchiolitis as a manifestation of organ rejection.

### Bone marrow transplantation

Profound neutropenia makes Gram-negative pneumonia a special risk [5]. CMV pneumonia, occurring at 6–12 weeks, is especially common; it is often progressive in this patient group and carries a high mortality despite initiation of treatment.

Non-infectious complications include early pulmonary oedema due to large-volume donations of intravenous fluid or to the cardiotoxicity of cytotoxic drugs. Common and important is an often fatal interstitial pneumonitis likely to be due to the direct pulmonary toxicity of the preparative irradiation and methotrexate therapy.

## AIDS

The current AIDS pandemic has had a major impact on respiratory medicine. The many pulmonary manifestations of HIV infection are discussed later in this chapter.

## Hypogammaglobulinaemia

Hypogammaglobulinaemia may be due to a variety of congenital and acquired causes and may be global or confined to subclass deficiency of IgA or IgG. Pulmonary complications can take the form of recurring bronchial infection, the development of bronchiectasis or bacterial pneumonias due to encapsulated *Streptococcus pneumoniae* or *Haemophilus influenzae*. Pneumococcal disease is especially common in the marked hypogammaglobulinaemia that accompanies multiple myeloma.

## Clinical features of lung disease

Thorough clinical and radiographic review is essential, and needs to take account of the various potential infectious and non-infectious pulmonary problems and the clues that arise from the history, examination, review of fluid charts, drug schedules and chest radiology. In many instances, the respiratory illness may simply be an episode of acute bronchitis; cough and purulent sputum follow a coryzal illness and there is little constitutional disturbance and no clinical or radiographic signs of pulmonary consolidation. The more important clinical problem is the patient with breathlessness or radiographic consolidation accompanied by fever, for whom the differential diagnosis is broad and includes non-infectious disease. Fever itself, particularly when it is high and associated with chills, suggests infection though some non-infectious conditions such as drug reactions may also cause this.

The patient's background provides useful pointers in the differential diagnosis. Gram-negative sepsis and fungal disease are particular risks in the profound neutropenia seen in the early vigorous treatment of leukaemias and lymphomas, while PCP is a possibility at a later stage; CMV complicates organ transplantation usually at about 2 months and may be severe and fatal in bone marrow transplantation, whereas it is relatively milder after renal transplantation. Geographical factors may be relevant: infection with fungal disease such as coccidioidomycosis or histoplasmosis occurs in the Americas, while disseminated strongyloidiasis is seen in patients particularly from the West Indies and Far East. Tuberculosis may be reactivated in patients from developing countries but especially the Indian subcontinent and South-East Asia. The disease may disseminate and progress more rapidly in the immunosuppressed.

Physical examination needs to be comprehensive and should include a search for tumour or bleeding at extra-

pulmonary sites. Skin disease may be present in graft-versus-host disease and cutaneous lesions may provide diagnostic clues of systemic vasculitis. Signs of intracerebral infection are a principal feature of cryptococcal disease and may complicate aspergillar and nocardial infections. Arthropathy and biochemical evidence of hepatitis occur frequently in CMV disease. Haemoptysis may be part of an infective syndrome but raises the possibility of pulmonary embolism or haemorrhage. Pleurisy with pleural pain and pleural rub is neither a feature of infection with *Pneumocystis* nor of cardiogenic pulmonary oedema or alveolar haemorrhage. In PCP, fever and breathlessness may precede definite radiographic changes; absence of auscultatory physical signs in the chest is characteristic.

## Radiology and lung sampling

The plain chest radiograph usually provides definitive evidence of the presence, extent, distribution and character of pulmonary consolidation, and the presence or absence of other features including those of cardiac failure (cardiomegaly, pulmonary venous congestion and Kerley B lines) or pleural disease. The lateral chest radiograph is valuable in localizing lesions for further investigation by bronchoscopy. Focal radiographic abnormalities are more likely to be infective than non-infective and are also more likely to be due to bacterial than opportunistic organisms. A retrospective review of the aetiology of episodes of pulmonary infiltration in 139 patients with leukaemia showed that in those with focal radiographic abnormalities, 74% of infiltrates were infective and, of these, 87% were bacterial and only 13% opportunistic [6]. On the other hand, 65% of diffuse infiltrates were non-infective but of the remaining 45% that were infective, the great majority (93%) were opportunistic.

CT may provide more detailed information, including anatomical information for targeting of sampling procedures. However, there are few microbe-specific radiographic changes, for instance the radiographic features of *Pneumocystis*, mycobacterial and CMV infection can be very similar. However, confluent segmental or lobar consolidation accompanying an acute clinical illness (<48 h) strongly suggests bacterial pneumonia.

Sputum, if expectorated, provides a valuable sample for preliminary microbiological assessment by Gram staining and culture. Sputum may be induced by the inhalation of nebulized hypertonic (2.7%) saline [7]; such samples have proved useful in the diagnosis of PCP (see below) in AIDS subjects, although precautions are needed to protect other patients from the dissemination of microorganisms in this process.

Blood cultures should be taken in all patients in whom sepsis is a possibility and may give a positive yield in up to one-third of such cases [8], although it is probable that

appropriate antimicrobial therapy has been initiated on empirical grounds in advance of the result.

Open lung biopsy (see Chapter 8) provides the best sample of pulmonary tissue but may precipitate the need for assisted ventilation or be complicated by pneumothorax or wound sepsis. Percutaneous lung biopsy or fine-needle aspiration (see Chapter 8) carries risks of bleeding or pneumothorax (proportional to the calibre of the needle) but is very useful in sampling peripheral nodules. Fibreoptic bronchoscopy (see Chapter 8), with bronchoalveolar lavage (BAL) and with or without transbronchial biopsy, is now widely used for investigating pneumonitis in the immunosuppressed and can produce diagnostic rates of 50–80% [9–12]. BAL provides a good specimen for microbiological assessment using staining, monoclonal antibodies and DNA probes, and culture; cytological examination of the fluid may diagnose pulmonary haemorrhage and malignant infiltrates. BAL rarely produces bleeding or pneumothorax. It does not provide definitive information on drug-induced lung disease or other non-infective alveolitis, which need biopsy of tissue for histology.

In all these samplings, the application of molecular techniques such as DNA amplification is improving the rapidity and sensitivity of screening for organisms such as *P. carinii* and *Mycobacterium tuberculosis* [13,14].

## Practical approach to diagnosis

Episodes of bronchitis are typified by prominent cough producing purulent sputum but no clinical or radiographic evidence of consolidation. After sputum has been obtained for study, these episodes should be treated with an antibiotic effective against the likely pathogens, *H. influenzae* and *Strep. pneumoniae*. There are  $\beta$ -lactamase-producing strains of *H. influenzae* (20% of isolates in the UK currently), although treatment with oral co-amoxiclav or doxycycline is usually effective.

A pneumonia of abrupt onset and progress, with accompanying segmental or lobar radiographic shadowing, strongly suggests bacterial infection. Antibiotic treatment should be started promptly after swift and simple microbiological investigation based on blood, urine, natural or induced sputum and, if available, pleural fluid samplings. A regimen that provides broad antibacterial activity, i.e. covering *Strep. pneumoniae*, *H. influenzae*, *Staphylococcus aureus* and many Gram-negative organisms, should be given intravenously. One suitable combination is an antipseudomonal penicillin with a  $\beta$ -lactamase inhibitor and gentamicin. The possibility of infection by *Legionella* spp. (see Chapter 13) should be considered and may be covered with a macrolide [15].

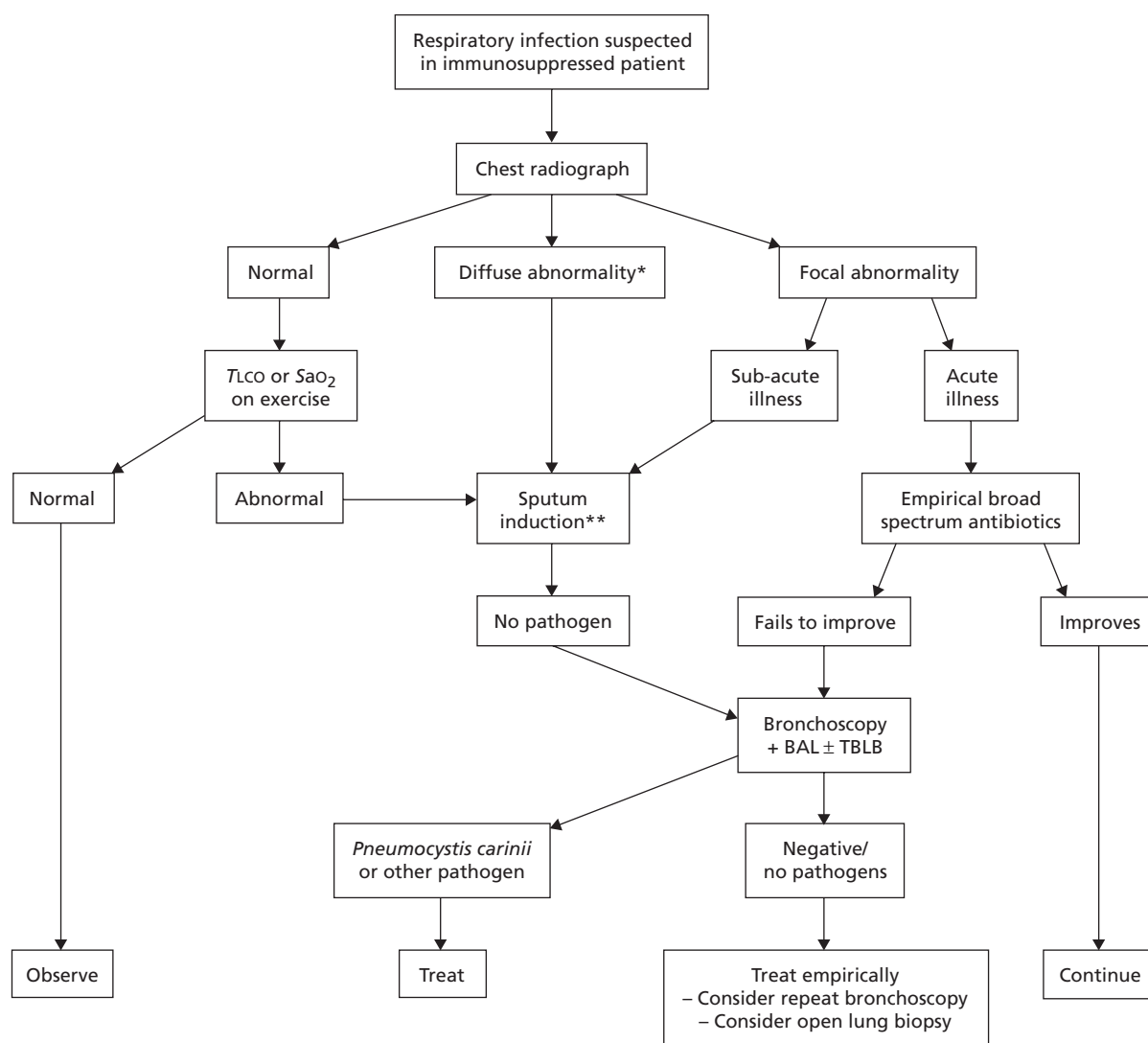
When the pace of the illness is less acute or when the chest radiograph shows more diffuse or scattered change, the differential diagnosis enlarges. First, sputum or

induced sputum should be examined by microscopy using both Gram stain and appropriate techniques for *P. carinii* (see below) and mycobacteria; the sample should also be cultured. If this does not provide a prompt diagnosis, a decision needs to be made about further diagnostic techniques. Percutaneous fine-needle aspiration for cytology and microbiology is most applicable in the case of peripherally placed nodules. For infiltrative or pneumonic radiographic changes when infection is primarily suspected, fibreoptic bronchoscopy with BAL is appropriate. If there is suspicion of autoimmune or drug-induced alveolitis, transbronchial lung biopsies can also be taken at bronchoscopy (see Chapter 8). The procedure can be completed in 15 min and be performed in hypoxaemic patients using local anaesthesia with concurrent oxygen supplementation. Chest radiographs allow localization of the pneumonia and the accurate direction of the flexible bronchoscope to a bronchus subtending the site. In diffuse disease, the middle lobe may be chosen and the bronchoscope is impacted firmly there. Three or four 50-mL aliquots of sterile saline are instilled singly and 30–60% of the fluid recovered by suction into a trap. Some of this sample is centrifuged and slides made from the deposit for diagnostic microscopy. The remainder is used for culture. Semi-quantitative techniques improve accuracy in diagnosing bacterial disease. The use of monoclonal antibodies facilitates the counting of CMV-‘positive’ alveolar macrophages. Immunofluorescent staining with conjugated *P. carinii* monoclonal antibodies also demonstrates brightly stained cysts and is a very useful microbiological search technique. Grocott–Gomori methenamine silver staining of BAL fluid for *P. carinii* has been shown on correlative postmortem studies to have sensitivity and specificity approaching 100%. Mycobacteria are more efficiently screened using fluorescent microscopy with auramine stains rather than by the Ziehl–Nielsen method. Giemsa stains are used to assess haemorrhage or malignant infiltration. *Legionella* may be identified in secretions by direct immunofluorescent antibody testing. Many of these foregoing results should be available within 4 h and simple cultures within 36 h.

If the procedure provides no diagnosis in a patient who is in a declining state, then open lung biopsy offers definitive sampling. Open lung biopsy is the only technique that gives totally reliable information on alveolitis of non-infective origin. Pulmonary capillary wedge pressure measurements, pulmonary angiography and ventilation–perfusion lung scanning may be required to establish the diagnosis of pulmonary oedema or embolism. A diagnostic algorithm is presented in Fig. 52.1.

## Treatment

With the exception of acute-onset lobar pneumonia, antimicrobial therapy is best started when a specific diag-



**Fig. 52.1** Algorithm for the management of an immunosuppressed patient in whom respiratory infection is suspected. \*, If suspicion of *Pneumocystis* pneumonia is high, start treatment at this point. \*\*, If mycobacterial or *Pneumocystis* pneumonia is suspected and patient is unable to expectorate. BAL, bronchoalveolar lavage; TBLB, transbronchial lung biopsies.

nosis has been made. In PCP, the first-line treatment is still high-dose co-trimoxazole or pentamidine [16] as described later in this chapter. In the AIDS population, the rate of side-effects of these agents is high and reactions that include fever, rash and renal impairment often demand change of therapy to the alternative agent or to other agents, including trimetrexate-folate or dapsone-trimethoprim, in order to allow the necessary 3 weeks of treatment to be completed. There is little evidence that changing regimens because of failure of the pneumonia to respond is useful, although there are data supporting the

coadministration of corticosteroids particularly in AIDS (see below).

Despite the severity of the disease, recovery is frequently seen in aspergillar pneumonia treated vigorously with amphotericin [17,18]; the side-effects of this agent may be limited by formulation of the drug with liposomes or lipid emulsion (see Chapter 9).

The standard chemotherapeutic regimens should be used for tuberculosis, though increasing rates of drug resistance to agents that include isoniazid and rifampicin are being documented in cities in the USA [19].

CMV pneumonia is most effectively treated with the guanine analogue ganciclovir (see Chapter 9); the addition of intravenous immunoglobulin should be considered in severe disease [20,21].

Often the severe hypoxaemia accompanying many of these pneumonias may demand a period of mechanical ventilation, high concentrations of inspired oxygen and the use of positive end-expiratory pressure. Previously, the outlook for AIDS patients with disease of such severity



was grim so in appropriate circumstances humane terminal care was often more appropriate for this group [22]. In recent years, with the advent of highly active antiretroviral therapy, patients can attain sustained good health even after such a life-threatening illness.

In transplant patients and oncology patients still receiving immunosuppressive chemotherapy, there may be need to taper the dosage of such agents to allow recovery from pneumonia. Neutropenic patients (including those with HIV infection) benefit from adjuvant treatment with granulocyte colony-stimulating factor.

## Prevention

Prevention of PCP depends upon chemoprophylaxis with either thrice-weekly oral co-trimoxazole or monthly inhaled pentamidine [16,23]. Such prophylaxis is a routine part of leukaemia chemotherapy in childhood, organ transplantation schedules and the management of AIDS patients, provided the agent can be tolerated (see below).

Chemoprophylaxis is also important in the prevention of tuberculosis. Daily oral isoniazid over 1 year can be used at the initiation of immunosuppressive chemotherapy, for example in the transplant group, if there is a past history of tuberculosis or if the patient is from a geographical location where the disease is prevalent. CMV disease is most severe in transplant patients who are seronegative and who receive seropositive blood products or transplant. Avoidance of a positive organ is advised if possible, although many centres now administer live attenuated CMV vaccine to CMV-seronegative potential transplant recipients since it offers protection against disease of moderate to high severity [24].

The risk of any opportunistic pneumonia is increased by the number and dosage of immunosuppressant agents. Clinicians and investigators should try to define the lowest dosages of such agents that achieve the goals of suppressing inflammatory vasculitis, maintaining an organ transplant or eradicating treatable tumour.

## HIV and AIDS

AIDS was first recognized in 1981 following clusters of PCP in young gay and drug-using men in California and New York [25,26]. Since that time pulmonary infections have accounted for much of the morbidity and mortality related to this infection. About 70% of patients with HIV infection experience a pulmonary complication during life [27], and additional pulmonary pathology (particularly pneumonia, tuberculosis and pulmonary embolism) is an often unexpected finding at autopsy [28]. Worldwide, it is estimated that 30.6 million patients are living with HIV and 90% of these are in developing countries [29]. The burden of HIV-related pulmonary disease in developing countries is therefore immense.

The nature of the pulmonary complications of HIV reflect level of immunodeficiency, socioeconomic status, lifestyle, country of residence and access to prophylactic and HIV disease-modifying therapies. For the fortunate few in developed countries, HIV disease-modifying drugs dramatically alter the natural history and hence pulmonary complications of the disease (see below). The great cost of antiretroviral therapy (estimated at \$US12 000 per person per annum) makes therapy unfeasible for those dependent on state healthcare in developing countries.

The three most important and common pulmonary complications of HIV are tuberculosis, PCP and bacterial pneumonia, these comprise greater than 90% of pulmonary complications worldwide. The incidence of PCP in developed countries has markedly declined since the introduction of effective prophylaxis with co-trimoxazole and HIV disease-modifying therapy. In developing countries, bacterial infections (including *M. tuberculosis* and *Strep. pneumoniae*) are of much greater importance, perhaps because these virulent infections occur at an earlier stage in the disease before the profound immunosuppression required for PCP.

Although most of the pulmonary complications of HIV infection are not unique to the disease, the variability and non-specificity of clinical and radiological findings in these patients frequently complicate their diagnosis.

## HIV and lung defences

HIV-infected patients with respiratory symptoms frequently have detectable HIV in BAL fluid, even in the absence of opportunistic infections or tumours [30]. The lung may become diseased via pro-monocytes infected in the bone marrow that subsequently migrate and then mature into alveolar macrophages. Alternatively, free virus may be transported to the lungs via the pulmonary circulation [31]. The nature of the deficiencies in pulmonary host defences to infection in patients infected with HIV is complex and largely extrapolated from studies of circulating immune cells. HIV infection is characterized by an acquired depletion of circulating CD4<sup>+</sup> lymphocytes whose primary role is in the regulation of cell-mediated immunity. CD4<sup>+</sup> lymphocytes recognize antigens presented by accessory cells, regulate the expansion and differentiation of antibodies (B lymphocytes) and regulate the development of macrophages and other cytotoxic cells. HIV is directly cytopathic to CD4<sup>+</sup> lymphocytes but also leads to qualitative defects in surviving cells, including functional defects in response to soluble mitogens, reduced recall proliferation to previously encountered antigens, defective interleukin 2 production and reduced production of interferon  $\gamma$  in response to antigen. Such defects in cell-mediated immunity lead to increased susceptibility to viral, fungal and protozoal infections.

Antibody production is also critically dependent on activation of B lymphocytes by CD4<sup>+</sup> lymphocytes, so humoral defects in immunity such as recurrent serious bacterial infections are common. Natural killer cells, which are important in host defence against infection and tumour surveillance, may be non-functional in HIV infection as they require signals from CD4<sup>+</sup> lymphocytes for optimal function. BAL fluid in patients with AIDS generally shows increased numbers of lymphocytes in comparison with HIV-negative patients; however, the numbers of CD4<sup>+</sup> cells are markedly reduced and CD8<sup>+</sup> lymphocytes (which are cytotoxic to HIV-infected cells) are increased. Non-specific interstitial pneumonitis (found in about half of asymptomatic HIV-infected adults) and lymphocytic interstitial pneumonitis (found in about half of HIV-infected children with pulmonary disease) are characterized by pulmonary infiltration with CD8<sup>+</sup> lymphocytes (see later). The conditions differ histologically but it is thought that they both occur as a result of an immunological response of CD8<sup>+</sup> cells to HIV-infected cells in the lungs.

In addition to the changes described in T-cell lymphocytes, there are also disturbances in the numbers and function of a wide variety of other cell types. In particular, alveolar macrophages (which express the CD4 receptor and are directly infected by HIV) show decreased chemotaxis, which may account for the reduced granulomatous reaction seen in mycobacterial disease. Defects in phagocytosis, intracellular killing and antigen presentation have also been described.

### Differential diagnosis in HIV-infected patients with pulmonary disease

The pulmonary complications of HIV infection can be broadly classified as infectious or non-infectious (Table 52.3). For the physician presented with an HIV-infected patient with respiratory symptoms, the clinical history can give important clues as to the nature of the pulmonary disease (Table 52.4). Respiratory symptoms and signs may be less rewarding in determining the aetiology of pulmonary involvement, although general physical examination is more helpful. Radiological signs are highly variable and may mask dual pathology (Table 52.5).

Formal staging of HIV infection is of some help in guiding a differential diagnosis and is also an important epidemiological tool. The Centers for Disease Control and Prevention in the USA published a revised classification system for HIV infection in 1993 (Table 52.6), which takes into account the CD4<sup>+</sup> lymphocyte count as well as the occurrence of opportunistic infections; this system is now widely adopted and more usefully reflects disease progression than previous definitions [32]. In developing countries, where radiological and laboratory facilities may be limited, these definitions can be adapted [33].

**Table 52.3** Infectious and non-infectious respiratory tract complications of patients with HIV infection.

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<i>Infectious</i>
Upper respiratory tract infections
Acute bronchitis
Acute sinusitis (viral, bacterial, fungal)
Bacterial pneumonia
<i>Streptococcus pneumoniae</i>
<i>Haemophilus influenzae</i>
<i>Staphylococcus aureus</i>
<i>Moraxella catarrhalis</i>
<i>Rhodococcus equi</i>
Fungal pneumonia
<i>Pneumocystis carinii</i>
<i>Cryptococcus neoformans</i>
<i>Histoplasma capsulatum</i>
<i>Aspergillus fumigatus</i>
<i>Coccidioides immitis</i>
<i>Mycobacterium tuberculosis</i>
<i>Mycobacterium avium-intracellulare</i>
Other mycobacteria
Protozoal infections
<i>Strongyloides stercoralis</i>
<i>Toxoplasma gondii</i>
<i>Cryptosporidium parvum</i>
Viral pneumonitis
Cytomegalovirus
Herpes simplex
Varicella zoster
<i>Non-infectious complications*</i>
Malignancies
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Hodgkin's lymphoma
Adenocarcinoma lung
Others
Lymphocytic interstitial pneumonitis
Non-specific interstitial pneumonitis
Bronchiolitis obliterans organizing pneumonia
Primary pulmonary hypertension
Pulmonary embolism

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\* Some 'non-infectious' complications are associated with infectious agents (see text).

### Patients with primary HIV infection

An acute seroconversion illness occurs in upwards of half of those infected with HIV within the first few weeks of exposure (sexual or parenteral). This is manifested by a mononucleosis-type syndrome, with fever, rash, myalgia, lymphadenopathy and sore throat. It may be associated with high circulating levels of virus and can lead to a precipitous but short-lived depression of cell-mediated immunity, manifested by a low CD4<sup>+</sup> lymphocyte count. At this time a minority of patients may develop PCP or bacterial pneumonia as well as a variety of neurological conditions and oesophageal candidiasis.

**Table 52.4** Clinical evaluation of a patient with HIV infection and respiratory disease.

Risk factor	Pulmonary disease
Nationality and travel history	Tuberculosis, endemic mycoses
Use of prophylaxis for PCP, MAI	Reduce risk of PCP, MAI and other bacteria
Past and present antiretroviral use and compliance	Reduces risk of opportunistic infections and Kaposi's sarcoma
Intravenous drug misuse	Bacterial infection, <i>Rhodococcus</i> , tuberculosis, pulmonary embolic and granulomatous disease
Sexuality	Kaposi's sarcoma, cytomegalovirus in gay men
Smoking history	Bacterial infection, <i>Legionella</i>
Social deprivation	Tuberculosis
Prior respiratory disease	Consider in differential diagnosis
Occupation	Exposure to airborne particles/agents Farms ( <i>Rhodococcus</i> )
Pets	Cats (toxoplasmosis) Pigeons (cryptococcosis)
Undercooked meat	Toxoplasmosis
CD4 <sup>+</sup> T-lymphocyte count*	
< 0.5 × 10 <sup>9</sup> /L	Tuberculosis in selected groups (above), bacterial infection
< 0.2 × 10 <sup>9</sup> /L	PCP
< 0.1 × 10 <sup>9</sup> /L	Kaposi's sarcoma, MAI, cytomegalovirus, non-Hodgkin's lymphoma
HIV RNA viral load > 30 000/mL	Increased risk of progression to opportunistic infections
Low neutrophil count	Aspergillosis, candidosis, Gram-negatives

\* These CD4<sup>+</sup> counts are offered as a guide only. Opportunistic infections may occur outwith these ranges.

PCP, *Pneumocystis carinii* pneumonia; MAI, *Mycobacterium avium-intracellulare*.

**Table 52.5** Chest radiograph findings in patients with HIV infection.

Chest radiograph	Diagnosis
Normal	No pulmonary disease Bronchitis <i>Pneumocystis carinii</i> pneumonia
Focal infiltrate(s) (may cavitate)	Bacterial pneumonia Tuberculosis and other mycobacteria <i>Pneumocystis carinii</i> pneumonia Cryptococcosis and other mycoses Adenocarcinoma Kaposi's sarcoma
Pleural effusion	Bacterial pneumonia Tuberculosis and other mycobacteria Kaposi's sarcoma Adenocarcinoma
Mediastinal adenopathy	Tuberculosis and other mycobacteria Non-Hodgkin's lymphoma Kaposi's sarcoma
Interstitial infiltrate (may have focal nodularity)	<i>Pneumocystis carinii</i> pneumonia Bacterial pneumonia Tuberculosis and other mycobacteria Lymphocytic interstitial pneumonitis Non-specific pneumonitis Cytomegalovirus pneumonitis

### Progressive immunosuppression

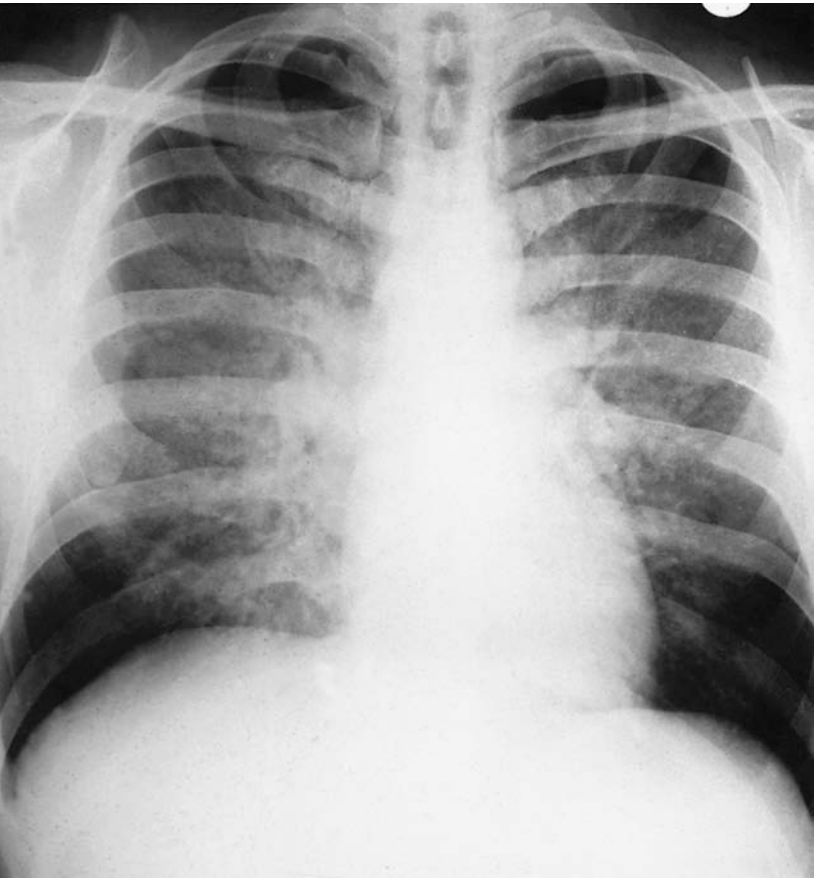
The spectrum of respiratory disease changes as immunodeficiency develops. In the patient with a normal CD4<sup>+</sup> lymphocyte count and undetectable or low HIV RNA in blood (<10 000 copies/mL), the risks of opportunistic infection are low. Lower respiratory tract infections are no more common than in the normal population at this early stage, although there is increased reporting of upper respiratory tract infections. This may simply reflect increased surveillance in the HIV-infected population. Intravenous drug misusers who are infected with HIV run the risk of endocarditis, septic pulmonary emboli and talc (magnesium trisilicate) embolism with subsequent granulomatous reactions [34].

As one might expect, more virulent organisms cause problems earlier in the natural history of HIV infection. Bacterial pathogens such as *Strep. pneumoniae* and *H. influenzae* are important at CD4<sup>+</sup> counts of less than 0.5 × 10<sup>9</sup>/L in both developing [35] and developed [36] worlds. In areas of endemicity, tuberculosis also occurs at relatively preserved CD4<sup>+</sup> counts and tends to dominate the burden of HIV-related ill-health [37,38]. Such high-virulence infections, when occurring early in the course of HIV infection, present in a similar fashion to disease

**Table 52.6** Revised classification system for HIV infection and expanded AIDS surveillance case definition for adolescents and adults, 1993.

CD4 <sup>+</sup> T-cell count	Clinical categories		
	A: asymptomatic, acute (primary) HIV or PGL	B: symptomatic, not A or C conditions	C: AIDS-indicator conditions*
1 $\geq 0.5 \times 10^9/L$	A1	B1	C1
2 $0.2\text{--}0.499 \times 10^9/L$	A2	B2	C2
3 $< 0.2 \times 10^9/L$ AIDS-indicator T-cell count	A3	B3	C3

\* AIDS-defining conditions are shown in Table 52.7.  
PGL, persistent generalized lymphadenopathy.  
Categories A3, B3 and C1–C3 are included in the AIDS case definition.



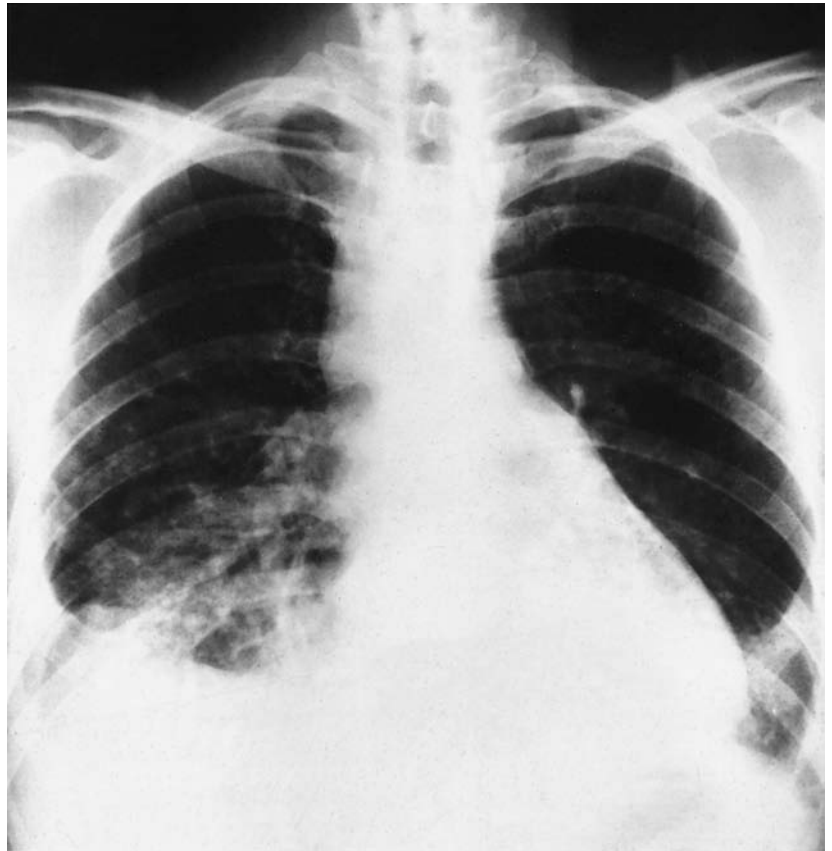
**Fig. 52.2** Miliary tuberculosis in young African woman with AIDS. (Courtesy of Dr Dwight McLeod.)

in immunocompetent HIV-negative patients. Tuberculosis presenting in advanced immunosuppression can be more cryptic and is more frequently extrapulmonary than in HIV-negative patients (Figs 52.2–52.4). Although PCP does occur in developing countries it is infrequently isolated (when facilities for its detection are available), presumably because it is a true opportunist and does not occur at the level of immunosuppression that predisposes patients to bacterial and tuberculous infections [39].

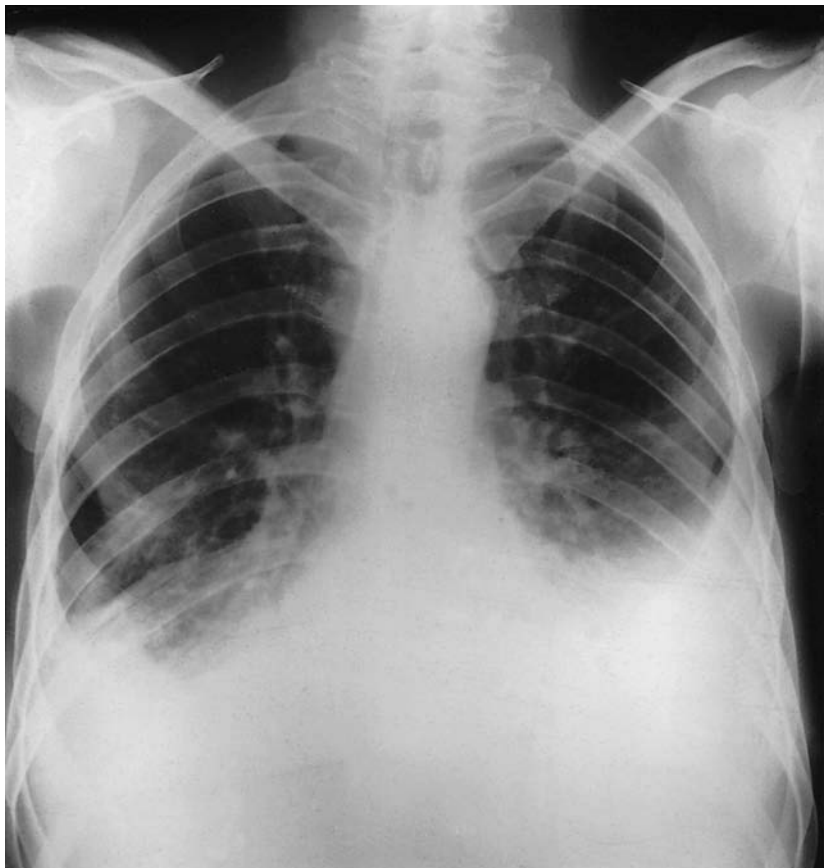
Opportunistic infections that occur later in HIV infection depend on the endemic infections of the patient's

country of past and present residence, for example cryptococcosis is rare in cold climates, tuberculosis is common in developing countries and deprived social groups, histoplasmosis is common in the Americas and toxoplasmosis is more common in Africa. Pulmonary complications may also be suggested by other systemic features of the disease (Table 52.7). Examples include characteristic skin and mucosal lesions in Kaposi's sarcoma, meningoencephalitis in cryptococcosis, cerebral mass lesions in toxoplasmosis, oral/pharyngeal thrush in patients with pulmonary candidiasis, and retinitis with CMV pneumonitis. In such

**Fig. 52.3** Atypical appearances of tuberculosis in AIDS patient. Chest film shows consolidation mainly in right lower zone, right pleural effusion, and hilar and paratracheal lymphadenopathy. (Courtesy of Dr Diana Buchanan.)



**Fig. 52.4** Bilateral pleural effusions in AIDS patient that proved to be tuberculous. (Courtesy of Dr Diana Buchanan.)



**Table 52.7** Conditions in the 1993 AIDS surveillance case definition.

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Bacterial infections, multiple or recurrent*†
Candidiasis, oesophageal or pulmonary†
Cervical cancer (invasive)
Cryptococcosis (disseminated or extrapulmonary)†
Coccidioidomycoses (extrapulmonary)†
Cryptosporidiosis (intestinal for > 1 month)†
Cytomegalovirus retinitis or disease (other than liver, spleen or nodes)†
Encephalopathy related to HIV
Herpes simplex (chronic ulcer(s), > 1 month duration, pulmonary, oesophageal)†
Histoplasmosis (disseminated or extrapulmonary)†
Isosporiasis (intestinal > 1 month)
Kaposi's sarcoma†
Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia†
Lymphoma (primary of brain, Burkitt's, immunoblastic)†
Mycobacterium avium-intracellulare or <i>M. kansasii</i> (disseminated or extrapulmonary)†
Tuberculosis†
Other species of mycobacteria (disseminated or extrapulmonary)†
<i>Pneumocystis carinii</i> pneumonia†
Recurrent pneumonia†
Progressive multifocal leucoencephalopathy
Recurrent <i>Salmonella</i> septicaemia
Cerebral toxoplasmosis†
Wasting syndrome due to HIV

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\* In children < 13 years.

† Conditions that may have a pulmonary component.

conditions the pulmonary manifestations may be of secondary importance. It should be remembered that it is common for patients with HIV infection to have concurrent infections or malignancy.

### Selected pulmonary conditions associated with HIV infection

The reader is referred to other sections of this book for detailed descriptions of pneumonia (Chapter 13), tuberculosis (Chapters 16–19), lung tumours (Chapters 41 & 42) and interstitial lung disease (Chapters 31, 40 & 51). PCP is described separately in this chapter. This section outlines some of the peculiarities of less well-known or well-recognized pulmonary complications and is not meant as an exhaustive description of pulmonary disease in HIV infection.

### Infectious complications

#### *Mycobacterium tuberculosis*

As mentioned above, tuberculosis presenting later in HIV infection may show atypical radiographic features. Infiltrates may be present in any part of the lung and node

enlargement is common, as is miliary dissemination. The presence of hilar and mediastinal node enlargement often provides the diagnostic clue.

#### *Mycobacterium avium-intracellulare*

Infection with this and other non-tuberculous mycobacteria usually occurs when the CD4<sup>+</sup> lymphocyte count is below  $0.1 \times 10^9/L$ . These organisms are ubiquitous in nature and may colonize the respiratory or gastrointestinal tracts. Up to 40% of patients with advanced HIV infection develop disseminated disease. Typically, patients present with fever, night sweats, weight loss, anaemia, diarrhoea and abnormal liver function tests. Pulmonary disease without dissemination is uncommon in patients with HIV infection, although cavitating lung infiltrates are well recognized [40]. A wide range of radiological appearances may be seen (Figs 52.5 & 52.6). Non-tuberculous mycobacteria in sputa must be differentiated from the morphologically similar *M. tuberculosis* since the atypicals are frequently colonizers of the respiratory tract. *M. avium-intracellulare* is resistant to first-line antituberculous therapy but like tuberculosis requires combination therapy with at least three active drugs. Prognosis is poor following the diagnosis of disseminated infection with *M. avium-intracellulare* and drug therapy is often poorly tolerated (see Chapter 20).

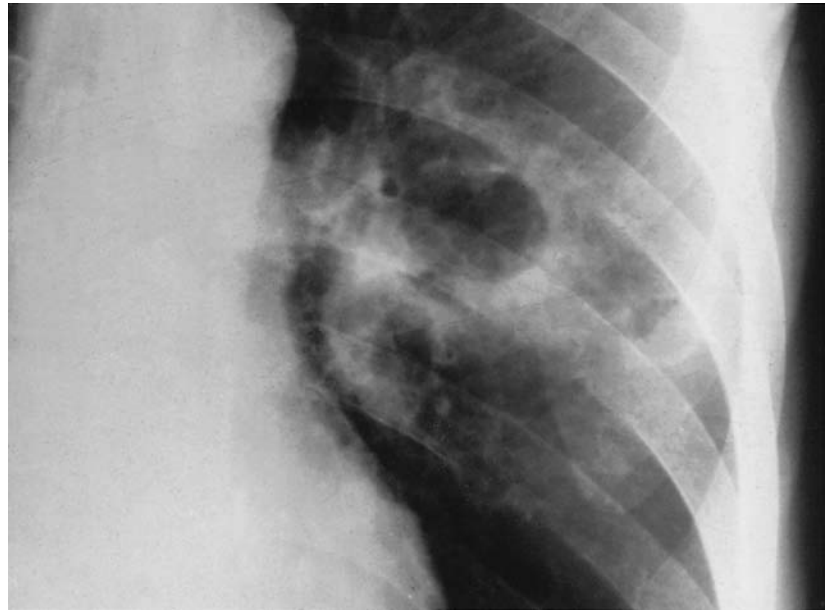
#### *Rhodococcus equi*

This facultative, intracellular, coccobacillary organism is a soil saprophyte and a common pulmonary pathogen of farm animals and occasional opportunist in humans. It is a well-described but infrequently recognized cause of acute or insidious pulmonary infections (often cavitating pneumonia), bacteraemia and disseminated disease in patients with advanced HIV infection (CD4<sup>+</sup> count  $< 0.1 \times 10^9/L$ ). When isolated, *R. equi* is often found with other pulmonary pathogens and, without careful consideration, may be dismissed as a diphtheroid. Infection is most frequently described in intravenous drug misusers and is often associated with exposure to farm animals [41]. Therapy for *R. equi* infection requires months of combination antimicrobial therapy because the organism persists and multiplies within macrophages. *In vitro* the organism is sensitive to ciprofloxacin, gentamicin, glycopeptides, erythromycin, rifampicin, tetracyclines and co-trimoxazole. Some patients who have responded poorly to antibiotics have been managed with surgical resection.

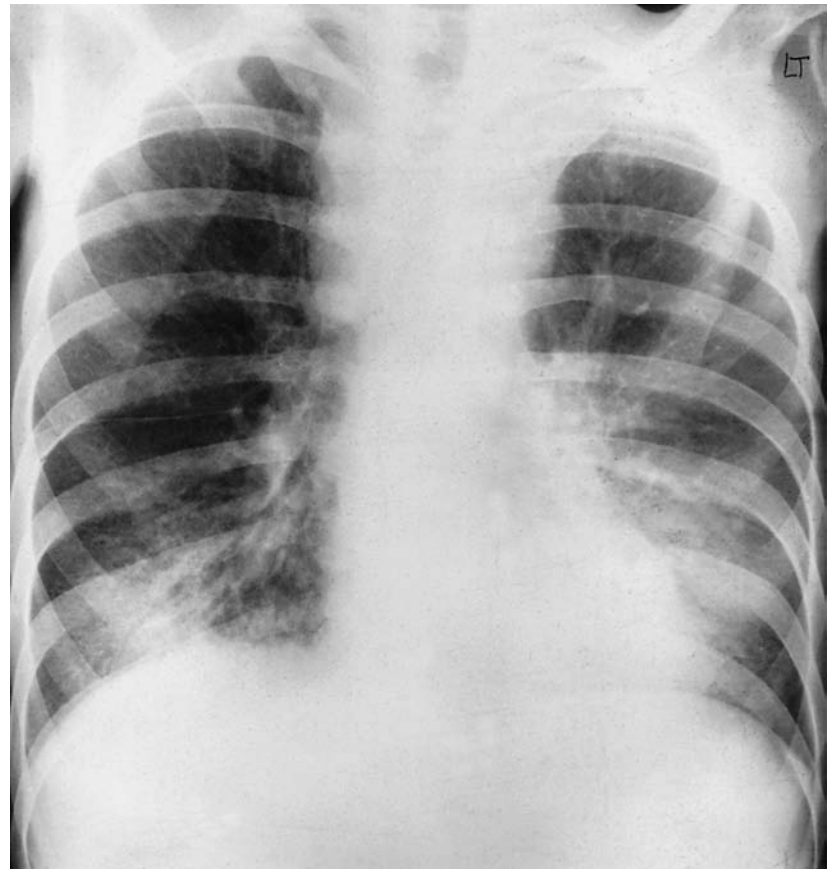
#### *Herpesvirus*

HIV infection is characterized by infections with the herpes group of viruses [42]. Complications are usually manifest in extrapulmonary sites. The most important of

**Fig. 52.5** Cavities in area of consolidation in left mid zone of patient with AIDS. Postmortem culture showed this to be due to *Mycobacterium avium-intracellulare*. (Courtesy of Dr Diana Buchanan.)



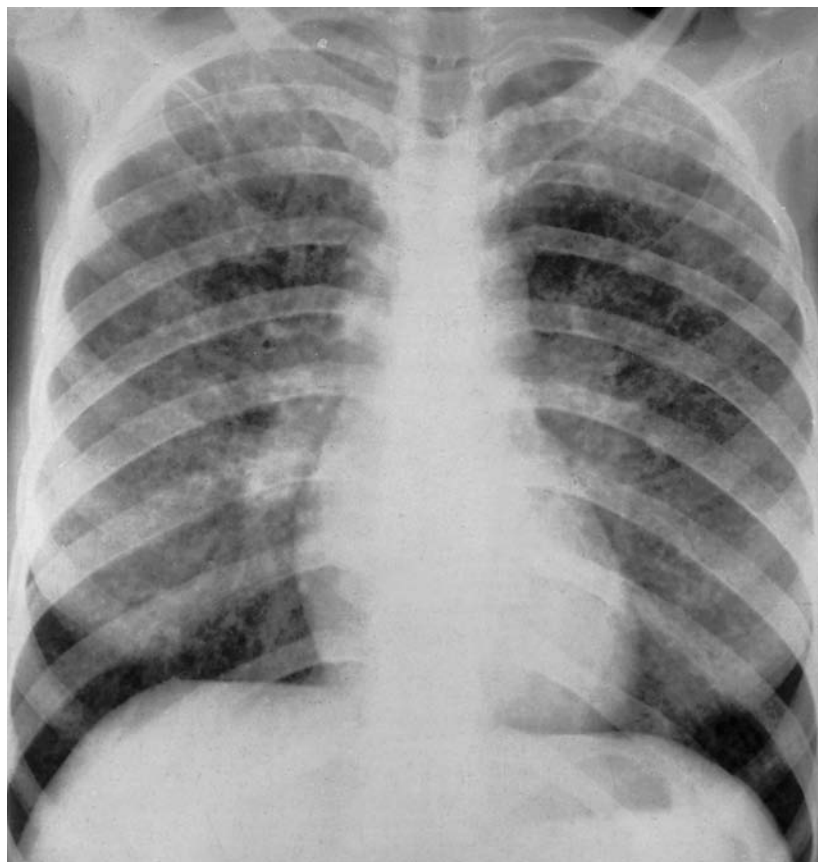
**Fig. 52.6** Bilateral lower zone consolidation and superior mediastinal node enlargement in patient who died of disseminated *Mycobacterium avium-intracellulare* infection. (Courtesy of Dr Diana Buchanan.)



the herpes group is CMV infection, which occurs in 100% of gay men with HIV infection and to a lesser extent in other risk groups. Disease usually occurs after significant immunosuppression ( $CD4^+$  count  $<0.1 \times 10^9/L$ ). The most common manifestation of CMV disease is retinitis,

although the lungs, adrenals, central nervous system, liver and colon may also be involved. Pneumonitis may be sub-clinical but occasionally causes respiratory failure. Most cases occur with other opportunistic pathogens like PCP, and it is often difficult to fully gauge the importance of





**Fig. 52.7** Diffuse bilateral shadowing in AIDS patient who failed to respond to treatment for *Pneumocystis* pneumonia; biopsy confirmed cytomegalovirus. (Courtesy of Dr Diana Buchanan.)

CMV in such situations (Fig. 52.7). Rapid fulminant disease, which characteristically occurs in patients following bone marrow transplantation, is unusual in HIV-infected patients. Diagnosis is via BAL or sputum induction, which reveals typical inclusion bodies in smears fixed with Giemsa or haematoxylin–eosin in 20–30% of cases. Sensitivity may be improved by using CMV-specific DNA probes or monoclonal antibodies. However, it should be remembered that CMV causes a subclinical infection of the salivary glands and so can be isolated in respiratory secretions in the absence of pneumonitis. Treatment with the nucleoside analogues ganciclovir, foscarnet or cidofovir should be considered in symptomatic patients if there is documented CMV pulmonary involvement in the absence of other pathogens. Alternatively, treatment should be considered in patients with other copathogens if they are deteriorating clinically despite optimal therapy for the other organisms.

Herpes simplex virus (HSV) and varicella zoster virus (VZV) pneumonitis have both been described in HIV infection but probably occur less commonly than CMV pneumonitis. VZV pneumonitis is a particularly severe complication of HIV infection in children and is usually accompanied by the vesicular rash. Shingles is not usually accompanied by pneumonitis in adults. The diagnosis of HSV by virus culture and histopathology may be compli-

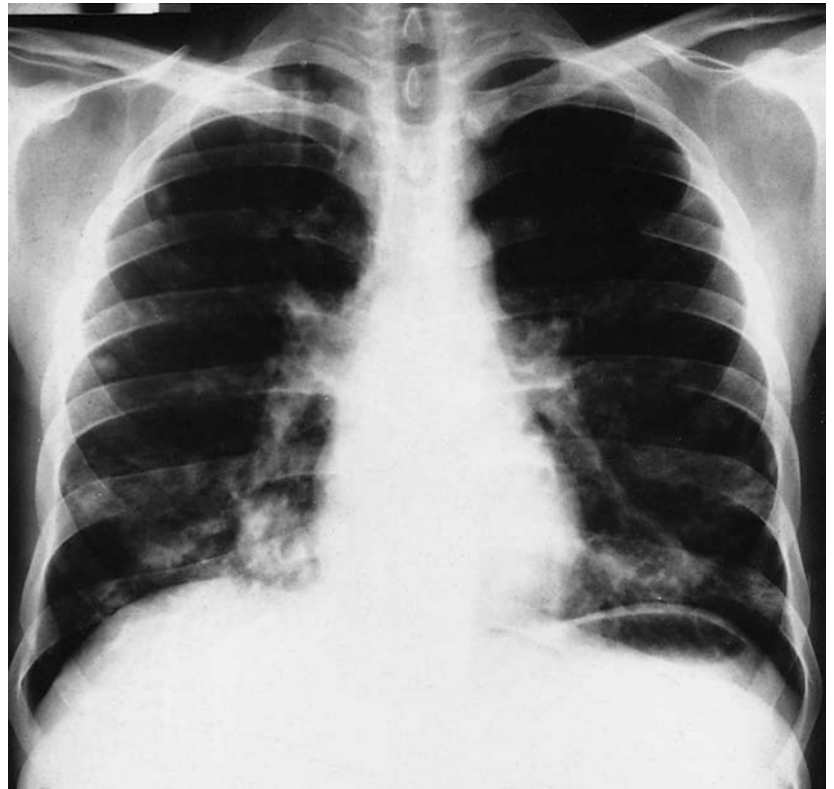
cated by virus shedding from cold sores. Treatment in both VZV and HSV is effective with intravenous aciclovir.

Kaposi's sarcoma is now believed to arise as a result of infection with a newly described virus, human herpes virus 8 [43]. Pulmonary involvement is usually accompanied by skin and mucosal lesions but has been described in isolation. The radiographic appearances are highly variable (Table 52.5, Figs 52.8 & 52.9) but endobronchial lesions, which are red or purple, are often present in parenchymal disease. The lesions are highly vascular so biopsy should be avoided (Fig. 52.10). The clinical course of pulmonary disease is also variable. Therapy with cytotoxic chemotherapy has been relatively unsuccessful and palliative radiotherapy is often required for bleeding or obstructing lesions. More recently, regression of pulmonary and cutaneous lesions has been demonstrated following highly active antiretroviral chemotherapy (see below) [44].

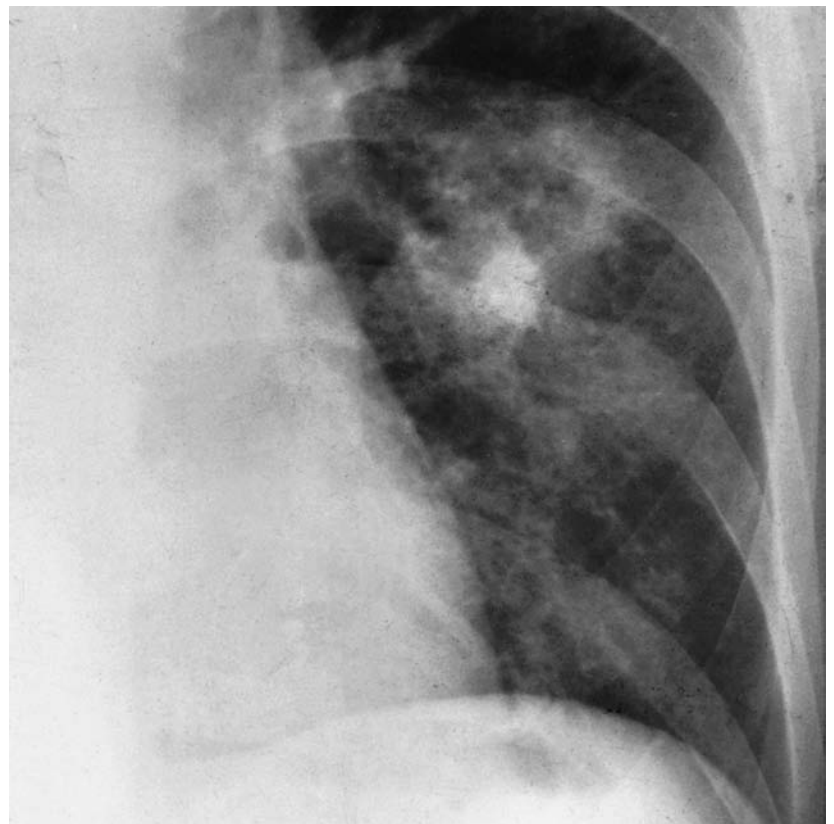
### Non-infectious complications

#### *Non-Hodgkin's lymphoma*

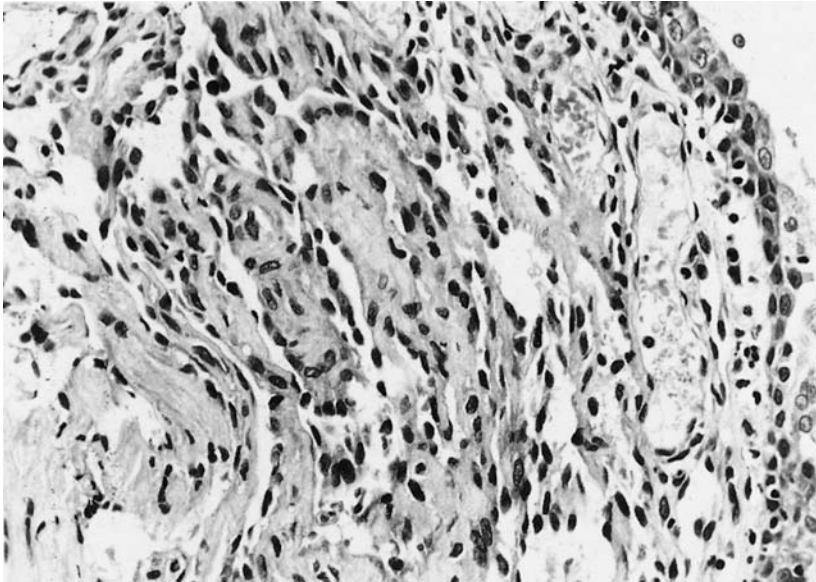
In some cases B-cell tumours are related to prior Epstein–Barr virus infection. Patients with HIV-related non-Hodgkin's lymphoma present with symptoms of



**Fig. 52.8** Chest film of AIDS patient showing multiple nodules of Kaposi's sarcoma. (Courtesy of Dr Diana Buchanan.)



**Fig. 52.9** Cavitating consolidation in left mid zone of AIDS patient with intrapulmonary Kaposi's sarcoma. (Courtesy of Dr Diana Buchanan.)



**Fig. 52.10** Kaposi's sarcoma of bronchus showing epithelium to right with underlying slit-like vascular spaces lined by prominent endothelial cells (haematoxylin & eosin  $\times 250$ ). (Courtesy of Dr Nick Francis.)

night sweats, fever and weight loss, usually when CD4<sup>+</sup> counts are less than  $0.1 \times 10^9/L$ . Disease is often extranodal and although patients may have an enlarging mass on a chest radiograph, many other radiographic signs may be present. Transbronchial biopsies are often not successful in obtaining diagnostic tissue, which usually requires more invasive measures. Prognosis following a diagnosis of non-Hodgkin's lymphoma is extremely poor.

#### *Interstitial pneumonitis*

This is a group of histologically well-defined pulmonary complications whose aetiology and clinical significance is currently uncertain [45–47]. Lymphocytic interstitial pneumonitis occurs frequently in children infected with HIV but is only occasionally seen in adults (usually Afro-Caribbeans). It is also associated with other autoimmune disorders such as Sjögren's syndrome and chronic active hepatitis. Lymphocytic interstitial pneumonitis is thought to occur as a result of an immunological reaction to HIV or Epstein-Barr virus within the lung and is classified as a lymphoproliferative disorder by some. Symptoms and signs are non-specific in HIV infection but patients usually develop progressive dyspnoea. Symptoms may resolve spontaneously or progress to respiratory failure. Diagnosis depends on histology and exclusion of opportunistic infections. Lung biopsy reveals firm grey nodules characterized by a lymphocytic infiltrate. Although granulomas are not present, the infiltrate can take on a follicular appearance with germinal centres. Antiretroviral therapy may help and corticosteroids have been used in patients without HIV infection.

Non-specific interstitial pneumonitis is well described in adults with HIV infection and is characterized by an interstitial inflammatory infiltrate with a predominance of

lymphocytes and plasma cells. In contrast to lymphocytic interstitial pneumonitis, a follicular pattern with germinal centres is not seen. The aetiology is not known but it may occur as a result of previous opportunistic infections or, like lymphocytic interstitial pneumonitis, as an immune response to HIV in the lung. There are no specific clinical features that distinguish non-specific interstitial pneumonitis from other more common pulmonary disorders, although symptoms are usually mild and the condition may resolve or stabilize spontaneously.

Bronchiolitis obliterans organizing pneumonia has been described in patients infected with HIV. Its mode of presentation is similar to the condition in HIV-negative patients and there is no evidence to suggest that it occurs more frequently in the HIV-infected population [48].

#### *Pulmonary hypertension*

Pulmonary hypertension is estimated to occur in 1 in 200 patients with HIV infection. It does not correlate with the stage of HIV infection or with the occurrence of opportunistic infections. Compared to patients with primary pulmonary hypertension, patients with HIV-related pulmonary hypertension are younger, less dyspnoeic and have lower peak pulmonary artery pressures. The pathological findings are usually of plexogenic pulmonary arteriopathy, although less frequently the thrombotic-fibrotic variant occurs. It is believed that HIV infection is the cause, perhaps through release of epidermal growth factors, induction of nitric oxide synthase and subsequent increased vessel tone and endothelial proliferation [49]. Secondary causes of pulmonary hypertension in patients with HIV include obstructive talc granulomas within small pulmonary arteries in intravenous drug users and pulmonary hypertension associated with chronic liver

disease and portal hypertension (e.g. induced by hepatitis C virus). In addition, pulmonary thromboembolic disease is often an unexpected finding in autopsies in patients with HIV infection.

### **Primary lung tumours**

Primary lung tumours are weakly associated with HIV infection. A recent large-scale survey of 98336 patients with HIV infection and a large cancer register in the USA estimated a relative risk of lung adenocarcinoma of 2.5 (95% confidence interval 1–5.1). Other tumours, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, brain tumours and seminomas, were unequivocally associated with HIV infection [50].

### **Prevention of HIV-related pulmonary disease**

The 1990s has seen an explosion in the development of new antiretroviral agents that have revolutionized the management of HIV infection. Initial pessimism following the poor success of monotherapy with the nucleoside analogue zidovudine [51] has been replaced with optimism as dual and triple drug regimens have shown at least short-term promise [52]. Highly active antiretroviral therapy is a combination of an HIV-protease inhibitor and two nucleoside reverse transcriptase inhibitors and is the standard care for many patients in developed countries. The nucleoside reverse transcriptase inhibitors (zidovudine, lamivudine, didanosine, zalcitabine, stavudine) are phosphorylated by thymidine kinase and then bind preferentially to retroviral reverse transcriptase. Proviral DNA formation is blocked because the drug is incorporated into the viral DNA with resultant 'misreading' and chain termination. The protease inhibitors inhibit post-translational processing of the polyprotein products of *gag* and *gag-pol* genes into the functional core proteins and viral enzymes, leading to release of immature non-infectious virus [53].

Outside clinical trials in countries where such therapy is freely available, AIDS-related mortality has dramatically declined [54]. In addition, the rate of progression to an AIDS diagnosis (particularly PCP) has been reduced [55]. Guidelines in HIV therapy are evolving as trial data emerge and experience with newer agents such as the non-nucleoside reverse transcriptase inhibitors improves [56].

Long-term compliance with complex drug regimens with large side-effect profiles may be difficult for many patients. The protease inhibitors are associated with a growing number of metabolic disturbances, including renal stones, diabetes mellitus, body fat redistribution and abnormalities in lipid metabolism [57]. In addition, cryptic mycobacterial and CMV infection may flare up during ini-

tiation of highly active antiretroviral therapy, presumably due to immune reconstitution. There is good evidence that viral resistance, leading to renewed risk of opportunistic infections, rapidly emerges with suboptimal therapy (potentially through non-compliance) and this has tempered enthusiasm for the long-term efficacy of current antiretroviral combinations. Guidelines for prophylaxis of opportunistic infections are still based on lowest measured CD4<sup>+</sup> count, symptoms and prior opportunistic infections [58]. However, recent evidence suggests that primary prophylaxis against PCP may be discontinued when there is virological and immunological response to HIV therapy. HIV RNA viral load tests are useful in guiding the initiation and monitoring of therapy, but their usefulness in guiding prophylaxis has not yet been fully evaluated.

Prophylaxis against PCP with co-trimoxazole (described later) is also effective prophylactic therapy for toxoplasmosis and gives some protection against bacterial pathogens. Primary prophylaxis against *M. avium-intracellulare* infection is usually initiated when the CD4<sup>+</sup> count is less than  $0.1 \times 10^9/L$ . Clarithromycin or azithromycin (in combination with rifabutin) not only protects against *M. avium-intracellulare* but also reduces the incidence of, and hospital admissions due to, other bacterial infections [59,60]. Currently, prophylaxis against community-acquired respiratory tract infection is not recommended except in unusual circumstances such as recurrent serious bacterial infections. However, pneumococcal vaccine is recommended, preferably when the CD4<sup>+</sup> count is greater than  $0.2 \times 10^9/L$  [58], and probably should be repeated at 5-yearly intervals. In the USA it is also recommended that patients are immunized against influenza annually [58], although there is little evidence to justify this.

Prophylaxis against tuberculosis with isoniazid (300 mg daily) in African HIV-infected patients has been shown to be efficacious in purified protein derivative (PPD)-positive patients [61] and probably is also indicated in high-risk PPD-negative patients as this may reflect anergy due to immunosuppression. In the USA, where bacille Calmette-Guérin (BCG) is not available, a positive PPD skin reaction or contact with a case of active tuberculosis is an indication for prophylaxis, assuming there is no evidence of active disease [58]. Primary prophylaxis against endemic mycoses depends on place of residence and relative risk. There is evidence in appropriate settings for the efficacy of fluconazole against cryptococcosis [62]. The risks of primary prophylaxis include the emergence of drug-resistant organisms (particularly *Candida* spp.).

### ***Pneumocystis carinii* pneumonia**

On the basis of various microbiological characteristics, *P. carinii* is classed as a eukaryote as are protozoa, algae and fungi. It used to be regarded as a protozoon on the basis of

its morphology, and this supposition was supported by the responsiveness of the pneumonia that it causes to antiprotozoal antibiotics. However, ultrastructural findings, DNA sequencing and other molecular data have now led taxonomists to classify it as an atypical fungus [63,64]. Such considerations have been of no practical consequence to clinicians who are well aware that, unlike fungi, *P. carinii* cannot be cultured on cell-free media nor is it susceptible to treatment with any antifungal agents that target the usual fungal pathway of sterol synthesis (see Chapter 9).

*P. carinii* exists extracellularly in the form of tiny unicellular trophozoites. These form cysts, each cyst containing up to eight sporozoites or 'intracystic bodies'. Once mature, the cyst ruptures and the released sporozoites complete the life cycle as new trophozoites.

*P. carinii* is not a recent discovery. The organism was first described over 80 years ago in guinea-pig and rat lung and was mistakenly thought to be trypanosomal by Carini, after whom it was later named [65]. Infection of the lungs of mammals by strains of *P. carinii* appears to be species specific, with no good evidence of transmission from animal to humans and no known animal reservoirs. It is of low pathogenicity and was first associated with pneumonia in malnourished and debilitated institutionalized children on the European mainland during the Second World War, subsequently being identified as a cause of pneumonia in premature infants in the 1950s [65,66]. By the 1970s *P. carinii* had become a fairly well-recognized but somewhat infrequently diagnosed opportunistic cause of pneumonia in immunocompromised patients, particularly those receiving chemotherapy for leukaemia and other forms of cancer [67]. Reports of outbreaks of PCP in 1981 in previously healthy homosexual men and intravenous drug abusers led to the recognition and description of AIDS [25,26]. The incidence of PCP increased dramatically in the early 1980s in parallel with the AIDS pandemic.

## Epidemiology

Although *P. carinii* only causes disease in susceptible individuals who are significantly immunocompromised, harmless infection by this organism appears to be common and antibodies to *P. carinii* have been found to develop in the majority of non-immunosuppressed persons before the age of 13 years [68,69]. This has led to the suggestion that PCP is caused by a reactivation of latent infection that occurs once the patient's resistance has become sufficiently impaired. Opposing this hypothesis have been the negative findings of absent *P. carinii* DNA when lung tissue from immunocompetent patients has been examined using sensitive DNA amplification polymerase chain reaction (PCR) techniques [70]. Although no environmental reservoir of human pathogenic *P. carinii* has been identified, the organism has never-

theless been detected in outdoor air samples [71]. Furthermore, cluster cases have been described in groups of immunodeficient patients, implying that case-to-case transmission may occur [72], and *P. carinii* DNA has also been detected in air filters serving the rooms of units in which patients with PCP have been managed, supporting the hypothesis of airborne transmission [73]. The chance of such transmission is evidently low, so that it is not general practice to isolate patients with PCP. It seems probable that (i) the population in general encounters environmental *P. carinii* [71] and develops immunity against it [68,69], (ii) patients whose cell-mediated immunity becomes sufficiently impaired are susceptible to reinfection and colonization with the subsequent development of PCP [74,75] and (iii) airborne spread of the organism may occur between susceptible individuals who come into close contact with one another [72]. The reported incidence of PCP in sub-Saharan Africa in patients with HIV infection has been much lower than found in Europe and North America, probably as a result of earlier deaths from bacterial infection including tuberculosis, which is much more prevalent in the countries of these regions [76].

## Susceptibility

PCP occurs almost exclusively in the immunocompromised host. The chief characteristic of conditions that predispose to PCP is impaired cell-mediated immunity, as may be found in patients with HIV infection, those receiving chemotherapy for haematological and solid malignant lesions, those receiving immunosuppressive drugs following organ transplantation or for other inflammatory conditions, and premature infants and those suffering from protein malnutrition and primary immunodeficiency disorders. Highly unusual cases have been reported in elderly adults without apparent predisposing causes [77], although it is possible to speculate that these patients may have had subtle immune defects that went undetected. Although cell-mediated immunity is the primary defence against *P. carinii*, it is possible that defects of humoral immunity may play a role since PCP has exceptionally occurred in patients in whom only B-cell defects have been detectable [78].

HIV-seropositive patients are at greatest risk of PCP, although this risk has been substantially reduced by chemoprophylaxis. Without chemoprophylaxis, PCP was the AIDS-defining diagnosis in about 47% of HIV-seropositive patients in Europe and North America, this figure having fallen progressively to about 15% following the gradual uptake of chemoprophylaxis [79–82]. Despite this reduced incidence, PCP remains the most common opportunistic lung infection in HIV-infected patients in the western world; in one North American cohort, 28% of patients developed PCP at some point in their illness

despite chemoprophylaxis, this intervention delaying the onset of the first AIDS-defining illness by 6–12 months, by which time the CD4<sup>+</sup> count was lower [79]. The risk of developing PCP in HIV-infected patients correlates with the number of circulating CD4<sup>+</sup> lymphocytes, patients with counts of less than  $0.2 \times 10^9/L$  being at considerably greater risk than those with counts above this level [83,84]. It is also recognized that there may be a transient but quite profound fall in the CD4<sup>+</sup> count in patients at the initial or 'primary' stage of their infection, at which time they are in the process of seroconversion, and that this early fall may also result in PCP [85].

Patients receiving chemotherapy for malignant disease are at risk, particularly those with haematological neoplasms that may themselves impair cellular immunity. Acute lymphocytic leukaemia was the prominent disorder reported as predisposing to PCP before 1970 [67], although the disease also arises during the course of chemotherapy for lymphomas as well as other neoplastic diseases. The infection is unlikely to occur until 1 month of chemotherapy has elapsed. Treatment with fludarabine is thought to carry a particular risk of PCP [86].

PCP following organ transplantation is most likely from the onset of the second to the sixth month following the procedure, during which time immunosuppression is usually at its highest, although the infection may occur beyond these boundaries if immunosuppression is also required preoperatively or if it has been intensified at a later stage because of rejection [2]. In most centres, the incidence of PCP in those transplant patients who do not take prophylaxis is reportedly 10–12%, whereas in those who do the risk is largely eliminated [2].

Of the group receiving immunosuppressive therapy for other conditions, patients with Wegener's granulomatosis appear to be at particular risk of PCP, an incidence of 6% having been reported in one large retrospective group who did not receive prophylaxis [87]. All these patients were receiving a corticosteroid as well as another immunosuppressive agent. Further groups at risk include those receiving potent immunosuppressive treatment for other antineutrophil cytoplasmic antibody-positive vasculitis, connective tissue disorders such as systemic lupus erythematosus, polymyositis/dermatomyositis, rheumatoid arthritis and severe skin diseases [88].

A review from a single large North American centre of 116 cases of PCP occurring in patients who were not infected with HIV found that the first episode of PCP was associated with haematological malignancy in 30% of cases, organ transplantation in 25%, inflammatory disorders in 22%, solid tumours in 13% and other miscellaneous conditions in 10%. Over 90% of patients had been treated with systemic steroids, the median daily dose being up to 30 mg, although one-quarter of patients had received about half this dose [89]. The incidence of PCP in such susceptible groups may be reduced by the use of

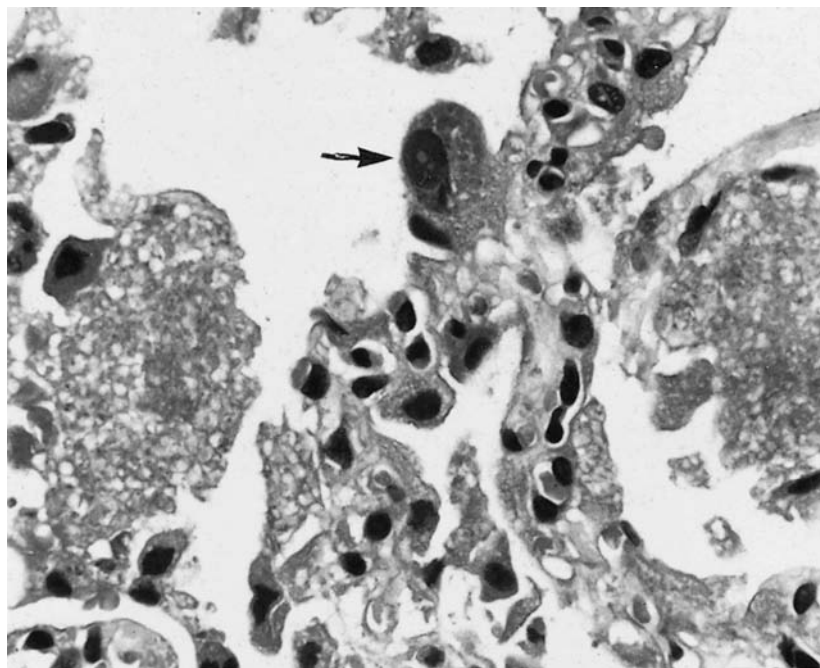
chemoprophylaxis and also by control of the retroviral load in patients with HIV infection.

### Pathophysiology

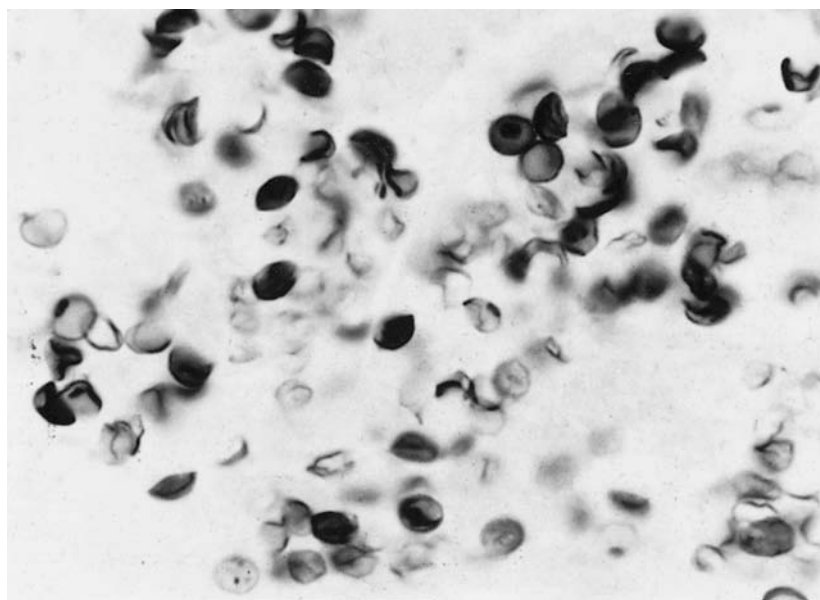
*P. carinii* is an obligate extracellular pathogen. The trophozoite is believed to become attached to alveolar epithelial cells (principally type I pneumocytes) by mechanisms that include the formation of fibronectin bridges, following which the cell membrane of the invading organism interdigitates with the surface epithelium of the host cell to form a more intimate attachment, a process which may take 2 days. In the immunocompetent host, the invading organisms are phagocytosed by alveolar macrophages, although there are also humoral responses with the production of IgG and IgM antibodies against various *P. carinii* antigens. Experimental studies using immunosuppressed rodents imply that, given favourable circumstances, the organism enters a slow proliferative reproductive phase, so that it may take several weeks before large numbers of organisms have been produced. These developments result in cellular damage to the alveoli, with destruction of type I and subsequent proliferation of type II pneumocytes. Disruption of the epithelial barrier causes increased alveolar–capillary membrane permeability so that the alveolar spaces tend to fill with a foamy, vacuolated, proteinaceous, eosinophilic exudate (Fig. 52.11) containing cellular debris, surfactant and the cysts of *P. carinii*, which are up to 7 µm in diameter.

As with yeasts, the cyst walls of *P. carinii* contain β-1,3-glucan that allows them to take up fungal stains such as Grocott–Gomori methenamine silver nitrate, which marks the cyst walls black and is the most valuable histological *P. carinii* 'search stain' (Fig. 52.12). The alveolar exudate also contains numerous trophozoites. Although these do not take up the foregoing stain and are less easily seen with light microscopy, they may be shown as minute dots in the alveolar spaces with polychromatic stains such as Giemsa or the rapid modified Wright–Giemsa (Diff Quik), as may the intracystic sporozoites. Immunofluorescent staining with conjugated anti-*P. carinii* monoclonal antibodies also demonstrates brightly stained cysts and is a very useful microbiological search technique (see p. 1368).

The foregoing alveolar changes are associated with a patchy inflammatory interstitial infiltrate, which may become more chronic with interstitial and intraluminal fibrosis. Increased phospholipase activity may result in the degradation of surfactant with subsequent microatelectases, which are likely to contribute to physiological shunting, reduced lung compliance and hypoxaemia [70,78]. Atypical histological findings in PCP may occur and include modular forms with granuloma formation, cavitation, local consolidation, hilar lymphadenopathy, interstitial microcalcification and vascular infiltration [64,90]. Small pleural effusions are sometimes found. The



**Fig. 52.11** Section of lung from AIDS patient showing alveoli containing granular material of *Pneumocystis* pneumonia and some larger cells (one arrowed) with inclusions typical of cytomegalovirus (haematoxylin & eosin  $\times 460$ ). (Courtesy of Dr Nick Francis.)



**Fig. 52.12** Higher power view of the granular material in Fig. 52.11 showing the cysts (Grocott methenamine silver  $\times 1040$ ). (Courtesy of Dr Nick Francis.)

pneumonic process more usually arises multifocally and is diffuse, although a predominantly upper lobe distribution may be encountered in patients who develop PCP despite prophylaxis with nebulized pentamidine [91–94], an observation explained by the relative alveolar hypoventilation that occurs in the uppermost parts of the lungs in the upright posture in humans [95]. Unusually, *P. carinii* infection may become disseminated in an extrapulmonary fashion to lymph nodes, bone marrow, spleen, liver, etc., so that virtually any organ system may become involved [96].

### Clinical features

Most patients have a low-grade fever, a dry cough and dyspnoea that progresses from mild breathlessness on physical exertion to tachypnoea at rest [64,97]. Less than one-third of patients produce sputum without induction (see below) and less than one-quarter experience chest pain [97]. The duration of symptoms from onset to diagnosis is highly variable, as some cases may be fulminant whereas others may be quite insidious. In general, PCP complicating HIV infection is more insidious, with a



median time from onset of mild symptoms to diagnosis of 4 weeks, whereas the same condition complicating other disease states tends to be more acute in its onset and development [98]. Patients with initially mild and insidious symptoms may postpone a visit to the physician until later in their illness but nevertheless present in a sick and uncomfortable state. On physical examination the patient may be febrile and tachypnoeic. Added sounds such as scattered crackles or, less commonly, wheezes may be heard but are absent in over half of cases. Patients may present with spontaneous pneumothorax and this occurrence in HIV-positive patients is highly suggestive of underlying PCP with subpleural cyst formation. Patients with HIV infection usually have noticed moderate to severe weight loss and oropharyngeal thrush may be present with other stigmata of HIV infection. In patients with typical clinical features of PCP but in whom HIV status is not known, a careful assessment of risk factors for HIV infection should be made. However, a lack of risk factors does not exclude a diagnosis of PCP and therefore the possibility of this treatable condition should not be neglected in 'low-risk patients'.

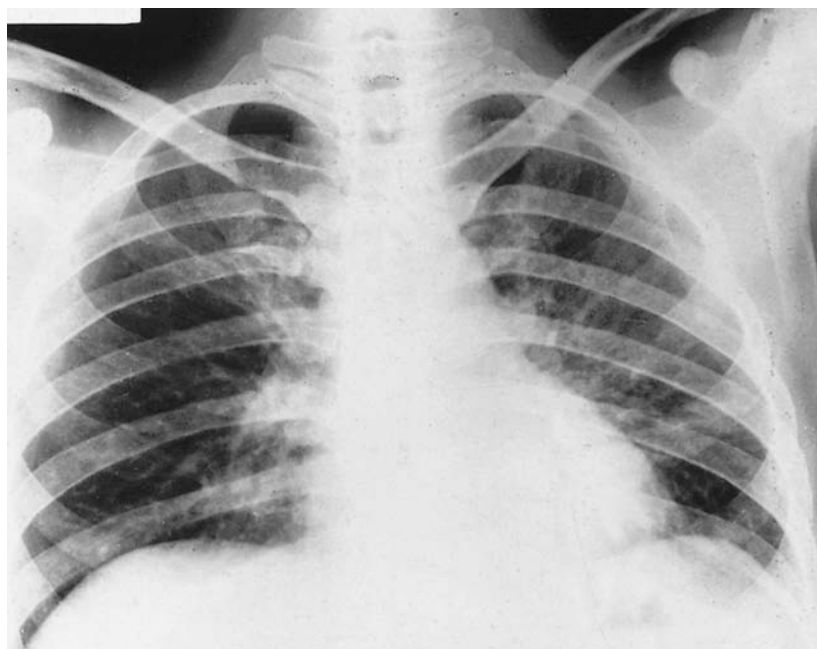
### Investigation and diagnosis

Whether it is desirable to investigate all patients with suspected PCP to a definite microbiological conclusion is somewhat controversial. On the one hand, there is the desire to be sure of the diagnosis before submitting the patient to a potentially toxic antimicrobial regimen, on the other the wish to initiate treatment as speedily as possible while sparing the patient uncomfortable and potentially

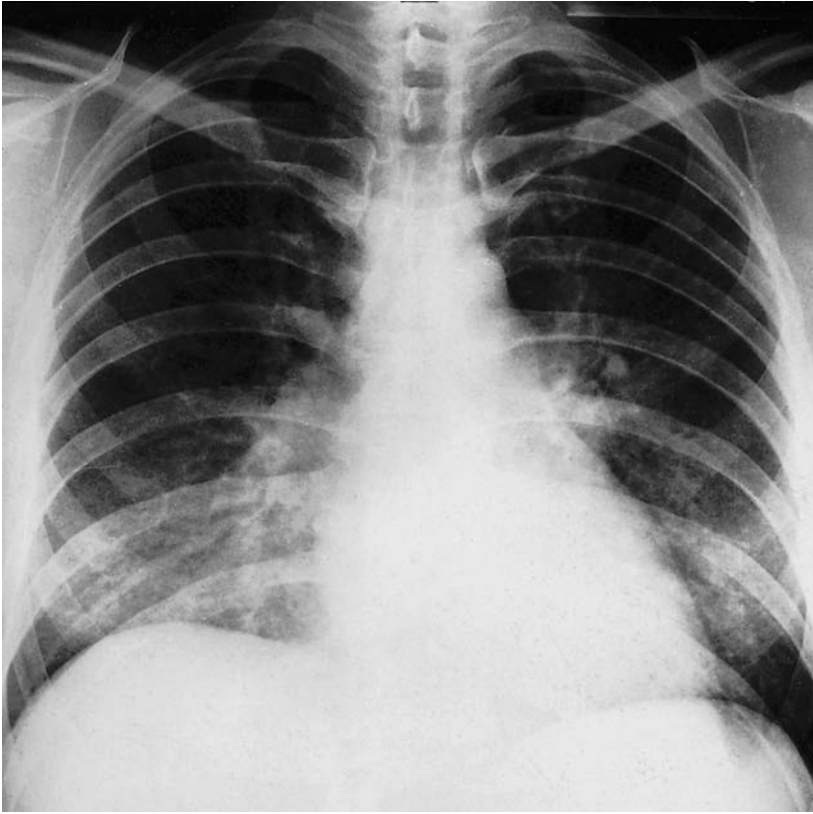
hazardous tests. Very often some sort of compromise has to be reached depending on the individual circumstances of the case and the facilities available in the institution. Sometimes the diagnosis of PCP seems so probable that treatment may be started without confirmation. Such a situation is illustrated by the patient known to be HIV-positive and who presents with a typical history of exertional dyspnoea, a non-productive cough, arterial hypoxaemia and whose chest radiograph shows diffuse bilateral hazy interstitial infiltrates, with no features to suggest bacterial pneumonia [99]. There is evidence that such an empirical approach is not associated with any worse outcome [100], although it should be realized that the diagnostic yield from BAL, should this subsequently become necessary, may decline within a few days of treatment [101].

### Diagnostic imaging

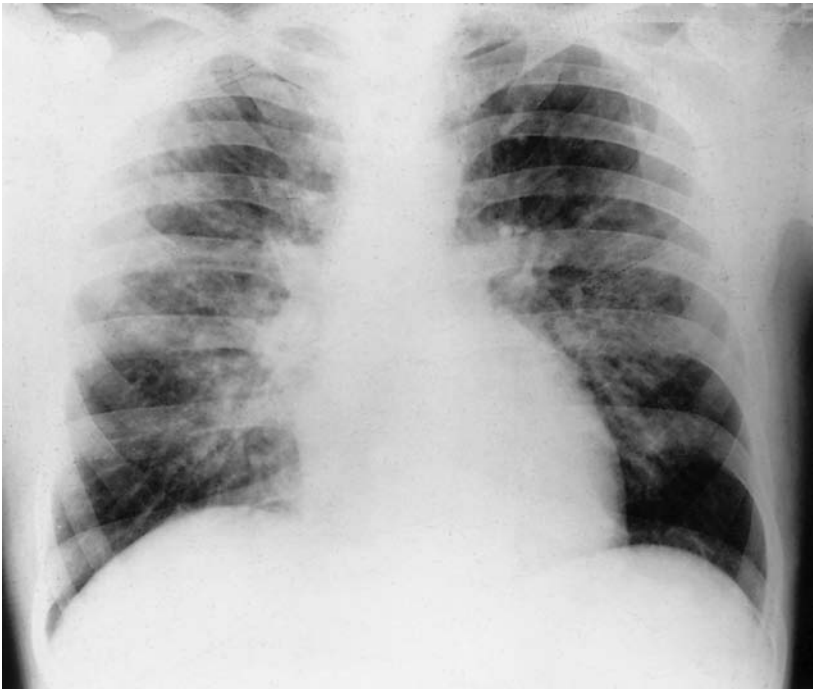
Patients with early PCP may sometimes develop mild symptoms before the appearance of any definite chest radiographic abnormality. This is more frequently found in HIV-positive than HIV-negative patients so that a normal chest film does not rule out the diagnosis of PCP [93]. The most typical early abnormality in PCP is that of bilateral, hazy, ground-glass, perihilar infiltrates with sparing of the lung peripheries (Figs 52.13 & 52.14). As the disease progresses, more homogeneous consolidation with air bronchograms may develop. These typical appearances may occur in up to 80% of all cases [93]. Ultimately the lungs may become massively consolidated and seemingly airless (Figs 52.15 & 52.16). The radiographic



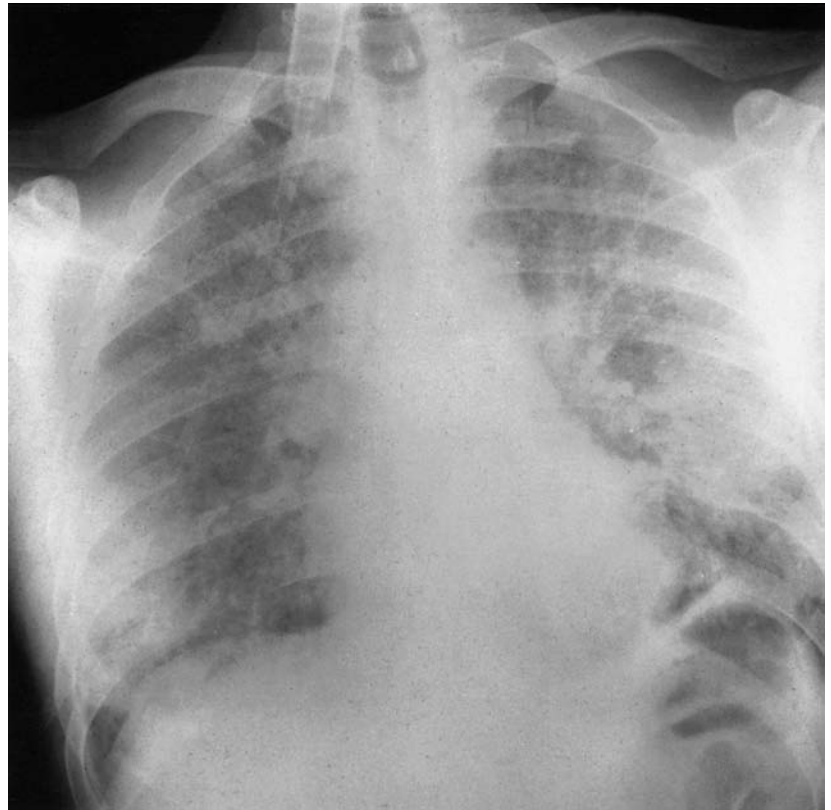
**Fig. 52.13** Early *Pneumocystis* pneumonia showing perihilar infiltrates and loss of vascular definition. (Courtesy of Dr Diana Buchanan.)



**Fig. 52.14** Bilateral reticulonodular infiltrates in *Pneumocystis* pneumonia. (Courtesy of Dr Diana Buchanan.)



**Fig. 52.15** More extensive bilateral infiltrates in *Pneumocystis* pneumonia with apparent peripheral sparing. (Courtesy of Dr Diana Buchanan.)



**Fig. 52.16** Extensive infiltration in severe *Pneumocystis* pneumonia. (Courtesy of Dr Diana Buchanan.)

changes in PCP have been reviewed and less common appearances include (i) more focal infiltrates; (ii) nodular appearances, sometimes with cavitation (coarse multiple nodules in the HIV patient usually indicate disseminated Kaposi's sarcoma and sometimes fungal disease); (iii) selective upper lobe involvement that may mimic mycobacterial disease, this sometimes occurring in patients who have developed PCP despite nebulized pentamidine prophylaxis; (iv) subpleural cyst formation (also associated with pentamidine prophylaxis) and sometimes leading to secondary spontaneous pneumothorax; (v) hilar lymphadenopathy; and (vi) small pleural effusions and changes consistent with bronchiectasis [90,93,94]. With successful treatment there is gradual clearing of the diffuse infiltrates over a period of weeks or even months as the patient improves, radiographic resolution commonly lagging behind clinical improvement.

High-resolution CT may be useful in excluding *Pneumocystis* pneumonia when the history is suspicious but the chest radiograph remains normal, in which case an incidence of PCP of 12% has been reported [102]. Such scans may show bilateral ground-glass opacification, sometimes with sparing of the subpleural lung tissue. Less commonly, there may be some lobular inhomogeneity that can result in a mosaic pattern in which ground-glass involvement is interspersed with normal lung appearances. However, CT need not be carried out as a matter of routine in more typical cases as the images may not add clinically

useful information to that obtained from plain radiographs. Subpleural cysts may sometimes be clearly shown. Nuclear medicine scans using gallium-67 or indium-111 have also been used in the investigation of PCP in some centres, although the uptake of these investigations, which lack specificity and are both expensive and cumbersome, has not been widespread [64,103].

#### Non-microbiological investigations

The CD4<sup>+</sup> count is a very useful predictor of the likelihood of PCP in patients with HIV infection; it has been found that PCP is unlikely to develop in HIV-infected patients with CD4<sup>+</sup> counts above  $0.2 \times 10^9/L$ , whereas patients with counts below this level have a greatly enhanced risk [84]. A number of other tests have been found to have a helpful negative predictive value despite a low specificity, so that a normal result makes PCP unlikely but an abnormal result could be due to a number of different conditions and does not rule it out.

Serum lactate dehydrogenase levels are usually raised in PCP [104], although it has been suggested that this non-specific finding may simply correlate with the degree of radiographic abnormality irrespective of the pathogen [105].

Similarly, the finding of a normal diffusing capacity (DLCO) for carbon monoxide in a patient at risk of PCP who has mild symptoms and a chest radiograph that looks

normal makes this diagnosis highly improbable, whereas the finding of a reduced *DLCO* or one that shows a downward trend in such a patient is suspicious enough to lead to further investigation for PCP [106].

An exercise test with simple monitoring of oxygen saturation by pulse oximetry may also be useful for excluding PCP in doubtful cases, since treadmill testing in 85 HIV-positive patients suspected of having PCP found that a 3% fall in saturation with exercise was 100% sensitive with a specificity of 70% [107]. Once again this test may be used to screen outpatients with normal or minimally abnormal chest radiographs and normal resting saturations, in which case a failure to desaturate with exercise effectively rules out PCP [64].

Arterial blood gas analysis is an essential assessment of severity, as with any pneumonia, although in the early stages of PCP is likely to be normal. Patients with PCP are commonly anaemic as a result of their underlying disease or its treatment. The total white cell count is more often normal or low rather than raised. Hypoalbuminaemia is not uncommon.

## Microbiological investigations

### *Induced sputum analysis*

Most patients with PCP do not produce sputum. In those few that do, a good specimen should be submitted to the microbiology department and the physician should make sure that the laboratory staff are aware of the nature of the clinical problem in order that the material be dealt with quickly and to best effect.

Sputum production may be induced in the majority of patients whose coughs are dry [7]. The specimen is obtained by having the patient breathe a mist of nebulized saline, which causes coughing. A hypertonic (2.7–5%) saline solution is conventionally used, a jet nebulizer being driven at a flow rate of at least 6 L/min and being applied to the face with a mask. Ultrasonic nebulization may be used as an alternative. The mouth should first be prepared by teeth cleaning, mouth rinsing and gargling in order to reduce any proteinaceous debris to a minimum, as this might otherwise obscure the organism. The procedure is at best unenjoyable and some patients find it distinctly unpleasant, so that it needs to be supervised by motivated staff, ideally an experienced physiotherapist, in order that an adequate specimen is obtained [108]. Sensible precautions should be taken to protect other patients from the dissemination of microorganisms during this process. Since the differential diagnosis often includes infection with *M. tuberculosis*, it is advisable to perform the investigation in a negative air flow room with attention paid to the safety of staff and visitors. A small percentage of patients may develop nausea, vomiting or wheeze and some may develop arterial desaturation [109]. It is never-

theless usually possible to obtain a satisfactory sample, although sputum induction is poorly tolerated by the more breathless subject and may prove impossible in up to 20% of patients. Although the test has been claimed to be very sensitive (up to 92%) by some groups [110], its usefulness is highly dependent on procedures being meticulously followed from the bedside to the laboratory. A sensitivity for PCP in HIV-positive patients of 28% was found on adequate samples by an experienced group in 1991, compared with 73% for BAL (see Chapter 8) [108]. Many centres now report higher sensitivities for both tests [110] so that the more invasive BAL may be avoided in a significant number of patients. A high sensitivity (63%) for induced sputum analysis has also been reported in patients with PCP due to disease other than HIV infection [111], although it might be expected that the yield in this group would be lower, as the alveolar burden of *P. carinii* is not usually as high in the absence of HIV infection [112].

Many laboratories now examine sputum for *P. carinii* using a direct immunofluorescent test (DIFT), which employs anti-*P. carinii* monoclonal antibodies and which demonstrates brightly stained cysts and results in significantly improved sensitivity compared with standard staining methods [113]. However, a negative induced sputum analysis by no means excludes PCP and it is usual for BAL to be carried out in such patients.

### *More invasive sampling techniques*

Bronchoscopic sampling is appropriate for cases of suspected PCP in whom induced sputum analysis has been negative or as the initial investigation in centres where the positive yield from induced sputum is too low to make the test worth while. One retrospective review of all cases of suspected PCP in a large North American centre over a 4-year period found that a positive diagnosis was made bronchoscopically in 50% of patients in whom induced sputum had been negative, PCP being confirmed in over half of these, other common diagnoses including tracheobronchial Kaposi's sarcoma (diagnosed by its visual appearance), tuberculosis and cryptococcal pneumonia [114]. There have been reports of diagnostic sensitivities of over 90% for PCP using both BAL and transbronchial lung biopsy, although these high success rates have generally been achieved in populations with a high prevalence of HIV-positivity. Some centres add transbronchial lung biopsy to BAL as a matter of routine, in the belief that it increases the likelihood of reaching a positive diagnosis, particularly as a significant number of patients may turn out to have diagnoses other than PCP; thus a retrospective European study involving 142 immunocompromised patients found that the *overall* diagnostic yield was 68% for transbronchial lung biopsy compared with 36% for BAL [115]. However, the same authors found that when the diagnosis was found to be PCP, there was little difference

in yield between transbronchial lung biopsy and BAL [115]. Many centres therefore use BAL without biopsy as the initial invasive diagnostic procedure of choice when the chance of PCP seems high, and use transbronchial biopsies only in selected cases. Thus a retrospective study covering a 3-year period in a large North American centre investigated the bronchoscopic results in patients with suspected PCP. Paired samples of both BAL fluid (examined using monoclonal antibody DIFT) and transbronchial lung biopsies (examined using conventional silver staining) showed that the one-fifth of patients in whom samples were adequate had PCP and that the sensitivity for DIFT on BAL fluid was 95% compared with 43% for silver staining on biopsies [116]. These and other seemingly conflicting results reported in the literature may result from methodological variables as well as from differences in the patient populations studied, so that individual clinicians may wish to modify their own approach according to the results of local audit. A decision to obtain histology for transbronchial biopsy may become necessary if less invasive methods have not produced a definitive diagnosis or if the patient is failing to respond to empirical antimicrobial therapy. It carries an increased risk of pneumothorax and haemorrhage. Brush biopsy does not increase the yield. It may occasionally be necessary to obtain a larger block of tissue by thorascopic or open lung biopsy (see Chapter 8).

Although the diagnostic yield may be increased by the use of PCR to detect *P. carinii* DNA in specimens such as induced sputum or BAL fluid [117,118], this costly investigation, which is not routinely available, may mislead as positive results may be obtained in the presence of residual non-viable organisms that may persist for some weeks after successful treatment of PCP.

### Supportive treatment

Patients who die as a result of PCP do so because of worsening tissue hypoxia, so that immediate steps should be taken to assess the level of hypoxaemia and to correct it appropriately. This basic respiratory support is provided by high-flow oxygen administered using standard face masks. If  $P_{aO_2}$  cannot be adequately maintained using high-flow oxygen via a mask with a reservoir bag, then the addition of continuous positive airway pressure by mask should be considered, provided that a pneumothorax has been excluded [119]. This may be well tolerated since sputum production is often minimal and it presumably improves oxygenation by splinting open small airways. Nasal positive-pressure ventilation may also improve gas exchange and avoid intubation. Patients who continue to deteriorate despite these measures remain tachypnoeic and become increasingly exhausted with worsening hypoxaemia ( $P_{aO_2} < 6.7$  kPa, 50 mmHg) and eventually become hypercarbic. An individual decision has to be

made in this situation about whether to intubate and mechanically ventilate the patient [120]. Ideally, this should be based on a knowledge of the patient's underlying disease and its prognosis, the patient's quality of life and any wishes that he or she might have expressed. Suffice to say that although the mortality is high in patients with PCP who require ventilation, particularly those with HIV infection [121], the authors have nevertheless seen successful outcomes, particularly in patients whose predisposing disease was controlled and whose performance was not significantly reduced before the onset of the pneumonic symptoms.

### Antimicrobial treatment

Pentamidine isethionate (see Chapter 9) is an antiparasitic agent that has been used for over 50 years in the treatment of African trypanosomiasis (sleeping sickness) and leishmaniasis (kala-azar). It was found to be effective against *P. carinii* in the 1950s, and PCP is the only respiratory application for this drug. The use of pentamidine increased both as a result of the AIDS pandemic and the increasing use of immunosuppressant therapy in medicine. In the 1970s, co-trimoxazole, a combination of trimethoprim and sulfamethoxazole (sulphamethoxazole) (see Chapter 9), emerged as an alternative drug for treating PCP, having been found to be as effective as pentamidine but with fewer side-effects when used in children [122]. Although there have been no large comparative trials of the two, there is evidence that both response time and survival are better with co-trimoxazole [123], which has subsequently been adopted as the treatment of choice for PCP both in HIV infection and other disease [124]. Adverse effects with co-trimoxazole remain a major problem in view of the high doses that have to be used. This is particularly so in those patients with AIDS, in whom side-effects are reported in 50–80% of cases leading to discontinuation of the drug in as many as 57% [97,125], whereas the adverse side-effect rate is lower (10–20%) in other immunosuppressed patients [97].

It is accepted practice to treat the iller, more hypoxic patient intravenously, the drug of choice being co-trimoxazole, with pentamidine as a second-line agent if co-trimoxazole cannot be tolerated. Intravenous/trexate trimetrexate/folinic acid (see Chapter 9) may be used as a third-line agent for patients who are intolerant of, or unresponsive to, co-trimoxazole and pentamidine [97].

The patient with mild disease ( $P_{aO_2} > 10$  kPa, 75 mmHg) may be treated with oral therapy, co-trimoxazole being the drug of choice. Orally administered alternatives for the intolerant patient are dapsone–trimethoprim, atovaquone or clindamycin–primaquine. The main drug regimens are illustrated in Table 52.8. Treatment of PCP in patients with HIV infection should be followed by lifelong prophylaxis.

Drugs	Dosage	Route
<i>First line</i>		
Co-trimoxazole	90–120 mg/kg daily in three to four divided doses	Oral or i.v.
<i>Second line</i>		
Pentamidine	3–4 mg/kg daily over 1–2 h once daily	i.v.
<i>Alternatives</i>		
Trimetrexate	45 mg/m <sup>2</sup> trimetrexate once daily 20 mg/m <sup>2</sup> calcium folinate four times daily	i.v. i.v. or oral
Dapsone–trimethoprim	100 mg dapsone once daily 15 mg/kg daily trimethoprim in two to four divided doses	Oral Oral
Atovaquone	750 mg two to three times daily	Oral
Clindamycin–primaquine	See text	i.v. and oral or oral

**Table 52.8** Antimicrobial treatment for *Pneumocystis carinii* pneumonia (see text for details).

### First-line treatment with co-trimoxazole

The conventional dose of co-trimoxazole required to treat PCP is 20 mg/kg daily of trimethoprim and 100 mg/kg daily of sulfamethoxazole, usually expressed as 120 mg/kg daily of the combined preparation. It is usual to administer co-trimoxazole as three to four divided doses and to treat for at least 2 weeks in the case of non-AIDS-associated PCP and for 3 weeks in the presence of HIV infection, provided that the therapy is tolerated and that a clinical response is taking place. In all but the milder case of PCP ( $\text{PaO}_2 > 10 \text{ kPa}$ , 75 mmHg), the course of co-trimoxazole is usually given intravenously for the first 10 days or so, using the same 120 mg/kg daily schedule. The manufacturer's recommendation is that the intravenous fixed combination preparation should be diluted 1/25 in 0.9% saline or 5% dextrose solution, i.e. 125 mL to one 480-mg co-trimoxazole ampoule (5 mL), and infused over 90–120 min. Despite this recommendation, it is probably safe to reduce the volume to 75 mL 5% dextrose per 480-mg ampoule if volume overload is likely to be a problem [126]. Patients with PCP receiving intravenous co-trimoxazole may deteriorate before they start to improve (see p. 1372) and a significant improvement in oxygenation may not be seen for 4–9 days. Patients with HIV-associated disease tend to respond more slowly than those without, so that it should not be assumed that therapy with co-trimoxazole has failed in such cases until about a week has passed [127]. Before switching treatment, it also has to be borne in mind that apparent deterioration may be caused by superadded pulmonary infection with bacteria or other pathogens, by coexisting disease such as Kaposi's sarcoma or lymphoma, or by complications such as pneumothorax or pulmonary oedema due to fluid overload. Once clear clinical improvement occurs, the course may be com-

pleted orally as the drug combination is well absorbed in the absence of gastrointestinal disease [125].

Milder cases may be treated orally from the start [64] provided that they have no problems with absorption, and this may be done under outpatient supervision. It is common practice to achieve this by prescribing 1920 mg (as two double-strength 960-mg tablets) three or four times daily. In patients who are finding it difficult to tolerate the drug, it may prove possible to reduce the total daily dose by 25%, from the usual 120 mg/kg daily to 90 mg/kg daily, without losing efficacy [128]. Dosage reductions are also made in renal insufficiency. The full dose may be given if the estimated creatinine clearance (see Chapter 9) is greater than 30 mL/min, the dose being halved in the range 15–30 mL/min and omitted completely if less than 15 mL/min. It is possible to assay drug levels of trimethoprim and sulfamethoxazole in such situations in order to attempt to maintain the trimethoprim level in the range 5–8 µg/mL and the sulfamethoxazole level in the range 100–150 µg/mL.

The necessity for 3-week courses has been questioned and it may be possible to conclude treatment after 2 weeks in the face of adverse effects if the patient has apparently responded and provided that secondary prophylaxis is started at the conclusion of the course [129]. It is advisable during treatment to check urea/creatinine and electrolytes, blood count and liver function tests at least twice weekly because of the likelihood of adverse effects.

Adverse effects (see Chapter 9) are common when high-dose co-trimoxazole is used in the above fashion to treat PCP, particularly when the patient has AIDS, in which case the drug may need to be discontinued in about 30% of cases [130]. Side-effects usually become evident after 1–2 weeks of treatment and include nausea and vomiting (25%), anaemia and neutropenia (40%), thrombocytopenia

(5%), abnormalities of liver function (10%), rashes (20%) and fever (25%) [123,124]. The drug need not be discontinued for mild rashes, which may be managed with antihistamines without progression [131]. Patients who have had co-trimoxazole rashes in the past have been successfully rechallenged on subsequent occasions, although severe systemic reactions may occur so caution should be exercised [131]. Rashes with involvement of the mucous membranes or those associated with the formation of bullae are reasons for discontinuance, as is intractable pruritis. The potential for marrow depression may be increased by other drugs such as zidovudine and ganciclovir, which should be stopped while treatment with high-dose co-trimoxazole is in progress. Trimethoprim has a mild potassium-sparing diuretic effect that may produce hyperkalaemia. Uraemia, hypocalcaemia and hyponatraemia sometimes occur. As with other antibiotics, *Clostridium difficile* colitis may occur. Patients with a previous history of a rash and fever in relation to co-trimoxazole have been given 8-day courses of desensitization, involving three or four times daily oral dosing with initially tiny concentrations of co-trimoxazole in solution prepared by diluting the standard oral suspension (240mg/5mL) [127]. One practical method is to start with a 1/10<sup>6</sup> dilution on day 1, giving 1, 2, 4 and 8 mL doses at 6-h intervals, then continuing with the same volumes at 6-h intervals but reducing the dilution by a tenth power each day until day 7 when a 1/1 dilution of 20mg sulfamethoxazole and 4mg trimethoprim is reached. On day 8 the standard oral suspension is given as 1, 2 and 4 mL for the first three doses, culminating in one double-strength tablet for the fourth dose. Such desensitization should not be attempted in patients who have previously experienced a serious skin reaction such as Stevens–Johnson syndrome or toxic epidermal necrolysis [132]. The overall rate of intolerance to co-trimoxazole is reduced in patients ill enough to require adjuvant corticosteroids (see below) [133].

### Second-line intravenous treatment with pentamidine

Intravenous pentamidine (see Chapter 9) may be used as an alternative treatment in patients who are intolerant or unresponsive to co-trimoxazole. It is probably as effective as co-trimoxazole but is more toxic [123]. It is given as a single daily dose of 3–4 mg/kg diluted in 250 mL of 5% dextrose solution (infused slowly over 1–2 h to prevent hypotension) and continued for 3 weeks in patients with AIDS; those with non-HIV-related PCP are sometimes treated for 2 weeks. Adverse effects from pentamidine are sometimes avoided by switching therapy after about 10 days to a less toxic oral regimen, such as trimethoprim in combination with dapsone or atovaquone singly, in order to complete 3 weeks of treatment. Nebulized pentamidine in doses of up to 8 mg/kg daily has been used to treat less

severe PCP but patients respond more slowly, the mortality rate is significantly higher and relapse is more common; thus this route of administration is rarely used other than for prophylaxis [127,134].

As with co-trimoxazole, adverse effects are frequent and include renal impairment (60%), leucopenia (45%), nausea and vomiting (25%), hypotension (25%) and hypoglycaemia/hypocalcaemia (20%) [123]. Fewer side-effects are encountered if 3 mg/kg daily is used. Hypotension is avoided by the slow infusion rate and blood pressure should be monitored as should serum urea/creatinine, electrolytes, glucose and calcium. Other side-effects are described in Chapter 9.

### Alternative intravenous treatment with trimetrexate–folinate

Trimetrexate (an analogue of methotrexate) may be used as third-line treatment in hospitalized patients who are intolerant of both co-trimoxazole and pentamidine or in whom these drugs have failed. However, some experts use trimetrexate–folinate alone or in combination with dapsone as a second-line treatment, in preference to the more toxic pentamidine, in patients intolerant of co-trimoxazole or in whom this drug has failed [125]. Trimetrexate has its effect by preventing *P. carinii* from synthesizing folate. The folinate component of the regimen prevents or reduces myelosuppression, the microbe itself being unable to take up this supplement as it lacks a folate transport system.

The dose of trimetrexate is 45 mg/m<sup>2</sup> once daily intravenously for 21 days and that of calcium folinate (leucovorin) 20 mg/m<sup>2</sup> daily intravenously (at a separate site) or orally as four divided doses for 24 days [135]. Neutropenia is the main adverse effect, this being attenuated by folinate. Other possible adverse effects include oral and gastrointestinal mucosal ulceration, hepatic and renal dysfunction and peripheral neuropathy. However, the combination may be better tolerated than co-trimoxazole [136]. In one trial, trimetrexate–folinate proved less effective than co-trimoxazole, with a 69% survival compared with an 84% survival for co-trimoxazole at 7 weeks [135]. It is possible that the efficacy of trimetrexate–folinate may be improved by the addition of oral dapsone and this approach is being investigated.

### Alternative oral treatment using dapsone–trimethoprim

This orally administered combination may be used in patients with mild to moderate PCP ( $P_{aO_2} > 9.3$  kPa, 70 mmHg) who are intolerant of co-trimoxazole or in those cases with more severe intolerance to co-trimoxazole once the condition has been brought under control with pentamidine. The regimen is dapsone 100 mg daily as one dose, trimethoprim 15 mg/kg daily in two to four divided



doses for 21 days [127,137]. The response rate appears to be similar to that achieved with co-trimoxazole with fewer side-effects.

Adverse effects include rashes, nausea and vomiting, haemolytic anaemia, methaemoglobinaemia, neutropenia, thrombocytopenia and disturbances of liver function, hyponatraemia and mild hyperkalaemia. Dapsone results in the production of hydrogen peroxide that may reduce haemoglobin to methaemoglobin, a useless molecule that cannot carry oxygen and which may result in cyanosis. This process is accelerated in subjects who have glucose 6-phosphate dehydrogenase (G6PD) deficiency, so that dapsone should not be used in patients with this condition; patients who are not G6PD deficient are unlikely to become symptomatic from any associated methaemoglobinaemia. There are reliable screening tests that demonstrate decreased red cell G6PD activity in the blood of such patients. Although used in co-trimoxazole-intolerant patients, dapsone-trimethoprim should not be tried in those who have developed a serious skin rash or type I hypersensitivity reaction to co-trimoxazole.

#### Alternative treatment using clindamycin-primaquine

This combination (unlicensed for PCP in the UK) is an alternative in patients with mild to moderate PCP ( $P_{aO_2} > 9.3 \text{ kPa}$ , 70 mmHg) who are intolerant of co-trimoxazole and dapsone-trimethoprim; clindamycin is administered first intravenously and then orally and primaquine orally. It is also being increasingly used in the sicker patient as an alternative to intravenous pentamidine. Clindamycin may be given at a dose of 600 mg (450 mg if body weight  $< 60 \text{ kg}$ ) intravenously every 6 h for 10 days, then 450 mg orally four times daily for 11 days, primaquine being given at a single dose of 15 mg (30 mg base) for the whole 21-day course. A trial comparing this regimen with co-trimoxazole in patients with HIV-associated PCP of this severity showed similar rates for response, adverse effects and survival following completion of treatment for both groups [138]. Clindamycin-primaquine is probably of similar efficacy to dapsone-trimethoprim [139].

Adverse effects with clindamycin-primaquine are generally mild. They include nausea, vomiting, abdominal discomfort, diarrhoea (including *C. difficile* diarrhoea), disturbances of liver function, methaemoglobinaemia (primaquine especially in G6PD-deficient subjects, who may develop haemolytic anaemia and who should be screened out) [125] and fever. Rashes may occur in about 20% of recipients and neutropenia or other haematological toxicity in about 25% of patients with AIDS treated for PCP [124,130].

#### Alternative oral treatment using atovaquone

This orally administered compound is probably best

reserved for patients with mild PCP ( $P_{aO_2} > 10 \text{ kPa}$ , 75 mmHg) who are intolerant of co-trimoxazole and second-line oral regimens such as dapsone-trimethoprim or clindamycin-primaquine. It has good activity against *P. carinii* but its efficacy in clinical practice is impaired by relatively poor absorption, although this may be improved if the drug is taken with fatty food. It has a higher failure rate than co-trimoxazole [140]. It is best avoided in patients with malabsorptive problems, including those with diarrhoea [140]. The dose is 750 mg in tablet form taken with food three times daily, or 750 mg twice daily as a suspension, for 3 weeks. Side-effects are infrequent, possibly reflecting its poor absorption, although rashes (often transient), nausea, vomiting, disturbances of liver function and diarrhoea may occur, the latter further impairing absorption.

#### Adjunctive corticosteroids

It was found by serendipity that a patient with PCP recovered after receiving oral corticosteroids [141]. There followed a small trial that showed improvement when patients with respiratory failure received methylprednisolone as an adjunct to conventional therapy for PCP [142]. After this, a double-blind placebo-controlled trial was carried out that also used early adjunctive high-dose methylprednisolone in a similar group of ill, hypoxic and tachypnoeic patients with PCP. It had to be discontinued when it became statistically obvious that the group receiving placebo and co-trimoxazole were more likely to develop worsening respiratory failure and less likely to survive than the group receiving steroids. Similar improvements were then found in a further double-blind placebo-controlled trial when high-dose prednisolone rather than methylprednisolone was used, except that in this study patients who deteriorated initially on placebo improved when switched to steroids [143]. The accumulation of this and other evidence showed that early high-dose corticosteroids given as an adjunct to conventional antimicrobial treatment in patients with moderate to severe PCP can be expected to significantly reduce the chances of deterioration and death [127]. Patients with mild disease at presentation ( $P_{aO_2} > 10 \text{ kPa}$ , 75 mmHg) probably do *not* benefit from this intervention [144].

The mechanism by which corticosteroids produce these benefits is unknown but it has been suggested that they blunt the early inflammatory response associated with drug-induced death of *P. carinii* that might otherwise lead to deterioration before improvement sets in. A consensus view is that steroids should be used in patients with a  $P_{aO_2}$  of less than 9.3 kPa (70 mmHg) at the onset of treatment and that this intervention is probably of no value if delayed for more than 72 h. An appropriate regimen is prednisolone 40 mg twice daily for 5 days, 20 mg twice daily for 5 days, followed by 20 mg daily until completion

of the course of antimicrobial. Methylprednisolone may be used at 75% of the dose of prednisolone in patients who cannot take oral medication [127]. Whether or not a similar approach is applicable to patients who have PCP in the absence of AIDS is unknown, as most of the published work refers to HIV-positive patients. There is evidence to suggest that the early use of steroids has reduced the incidence of acute respiratory failure and the need for mechanical ventilation in patients with PCP, whereas those who progressed to respiratory failure requiring mechanical ventilation despite receiving steroids seem to fare worse as a group than those who had ventilation for PCP in the years prior to the introduction and general use of steroids in this situation [145].

One concern about adjuvant corticosteroids is that they could make matters worse if used inappropriately, for example in the presence of mycobacterial or CMV infection in the severely immunosuppressed patient [146].

### Prophylaxis

Patients belonging to the 'at-risk' categories described above should receive PCP prophylaxis. This may take the form of primary prophylaxis, intended to prevent the initial attack of pneumonia in a predisposed individual, or secondary prophylaxis, intended to prevent relapse after the successful treatment of a first episode. In the case of HIV infection this should be for life, since prior to the introduction of prophylaxis 60% of patients would experience a relapse within a year [147] and the median survival after the first attack of PCP was only 11 months [148]. There are now convincing data to indicate that PCP prophylaxis has had a significantly beneficial effect on the morbidity, mortality and healthcare costs of HIV [149–151]. It is currently recommended that prophylaxis in HIV infection should be given to patients in whom:

- 1 the CD4<sup>+</sup> count falls below  $0.2 \times 10^9/L$ ;
- 2 the CD4<sup>+</sup>/total lymphocyte ratio is less than 1:5;
- 3 there is oropharyngeal thrush or an unexplained fever for two or more weeks even if the cell counts exceed the values given above;
- 4 there is another AIDS-defining diagnosis, such as Kaposi's sarcoma, cerebral toxoplasmosis or cryptococcal meningitis;
- 5 there has been recovery from a previous episode of PCP [64,152].

The prophylactic agent of choice is oral co-trimoxazole. Alternative regimens use dapsone or nebulized pentamidine (Table 52.9). In practice it is common for a patient with HIV infection to start with one drug regimen and to switch to another because of poor tolerance or interaction with other drugs.

Pregnancy is not a contraindication to PCP prophylaxis. Co-trimoxazole remains the drug of choice and may be used in pregnancy, although some physicians prefer to

**Table 52.9** Antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia.

Drugs	Doses
Co-trimoxazole	960 mg once daily* <i>or</i> 480 mg once daily* <i>or</i> 960 mg three times a week
Dapsone	100 mg once daily <i>or</i> 50 mg twice daily
Dapsone–pyrimethamine	Dapsone 50 mg once daily Pyrimethamine 50 mg once a week Calcium folinate 25 mg once a week <i>or</i> Dapsone 200 mg once a week Pyrimethamine 75 mg once a week Calcium folinate 25 mg once a week
Pentamidine (nebulized)	300 mg once monthly (appropriate nebulizer, see text)

\* Regimens of first choice.

Routes of administration oral except for pentamidine.

withhold systemic treatment in the first trimester because of theoretical concerns about teratogenicity, in which case they may opt for nebulized pentamidine in these first 12 weeks because little of it is systemically absorbed.

### Co-trimoxazole

Co-trimoxazole is the most effective form of primary prophylaxis for PCP in HIV infection and is taken as one double-strength tablet (960 mg) once daily, this being the regimen of first choice [152]. This results in a low attack rate of PCP of about 0.5% per year in patients with HIV infection [153]. Three-times weekly dosing with one double-strength tablet may bring the attack rate up to about 1.8% per year but produces almost a 50% reduction in toxicity and thus is an acceptable alternative regimen if higher doses cannot be tolerated [153]. However, there is the risk that intermittent dosing may produce difficulties with compliance and therefore loss of efficacy. There is also strong evidence for the efficacy and substantial clinical benefit of one single-strength tablet (480 mg) daily and this is the preferred regimen if daily double-strength tablets cannot be tolerated [152]. When side-effects have not been severe an alternative is to attempt desensitization (p. 1371), this having been successful in over 70% of patients with some regimens [132]. The efficacy of co-trimoxazole may be better maintained in the face of a falling CD4<sup>+</sup> count in HIV infection than is the case with other prophylactic drugs. Resistance of *P. carinii* to co-trimoxazole has so far not been a problem. It also provides protection against toxoplasmosis, as well as bacterial upper and lower respiratory tract infections [152,153]. Its main drawback is its propensity to produce adverse effects such as rash (20%), fever, nausea and vomiting,

neutropenia, anaemia or abnormalities of liver function, all leading to reduced compliance so that between one-fifth and half of patients may need to switch therapy [127]. It is nevertheless still reasonable to persist with or resume co-trimoxazole prophylaxis in a patient who has previously experienced mild intolerance to this compound, although not if a skin reaction has been associated with mucositis, the formation of bullae or exfoliation [70]. It has not yet been shown whether it is best to reintroduce co-trimoxazole that has been discontinued at the same dose, at a lower dose, at a gradually increasing dose or whether desensitization should be tried. Co-trimoxazole has been found to provide more effective primary and secondary prophylaxis than nebulized pentamidine [154,155], although it is possible that this difference may only become evident once the CD4<sup>+</sup> count has dropped below  $0.1 \times 10^9/\text{L}$  [156]. Trimethoprim alone is not an effective prophylactic agent. Co-trimoxazole is also regarded as the most effective prophylactic therapy against PCP in other immunosuppressed groups, for example in transplant recipients one single-strength 480-mg tablet is prescribed for up to 12 months after transplantation. This has reduced the incidence of PCP following transplant from 10–12% to virtually zero, while also reducing the risk of infection by other pathogens, including *Listeria monocytogenes*, *Nocardia asteroides* and *Toxoplasma gondii* [2]. This dose may also be prescribed in other categories of non-HIV-infected immunosuppressed patients.

### Dapsone

Dapsone 100 mg daily (as a single dose or as 50 mg twice daily) may also be used as prophylaxis in patients who are intolerant of co-trimoxazole (and who may fail desensitization to it). Some studies have found dapsone to be as effective as co-trimoxazole [156,157]; however, its efficacy appears to diminish as disease advances so that the attack rate of PCP is about 7% per year once the CD4<sup>+</sup> count has fallen to less than  $0.1 \times 10^9/\text{L}$  [127,156]. Dapsone 50 mg daily is sometimes combined with pyrimethamine 50 mg per week and with calcium folinate (leucovorin) 25 mg per week, this combination having been found to be of similar efficacy to nebulized pentamidine in primary PCP prophylaxis but with more adverse effects [152]. An alternative is dapsone 200 mg, pyrimethamine 75 mg and calcium folinate 25 mg, all once weekly. Combinations that contain both dapsone and pyrimethamine are also protective against cerebral toxoplasmosis but not against bacterial infections. The incidence of adverse effects is broadly similar to that encountered with co-trimoxazole [157]. Although some data suggest a low incidence of side-effects in patients switched to dapsone after intolerance to co-trimoxazole [158], other data have shown that a high proportion of dapsone-treated patients become intolerant to it [156]. Nausea, rashes, fever, pancreatitis, liver enzyme

disturbances, leucopenia, methaemoglobinaemia and haemolytic anaemia in patients with G6PD deficiency may occur. Twice-weekly dosing produces fewer side-effects but carries a higher failure rate, as does a reduction in the dose to 50 mg daily [153,156]. Dapsone has been found to provide more effective primary prophylaxis than nebulized pentamidine, although it is possible that this difference may only become evidence once the CD4<sup>+</sup> count has dropped below  $0.1 \times 10^9/\text{L}$  [156]. There are concerns about the possible teratogenicity of pyrimethamine, which should be avoided in pregnancy.

### Aerosolized pentamidine

Aerosolized pentamidine was the first form of PCP prophylaxis to be used in HIV-infected patients and was shown to be effective in a placebo-controlled trial [159]. It is conventionally used at a single dose of 300 mg monthly. The type of jet nebulizer and the flow rate used are important in achieving adequate lung deposition, as the optimal particle size for alveolar deposition is 1–2  $\mu\text{m}$ . The production of this size of particle diminishes deposition in the more proximal respiratory tract and therefore reduces adverse effects. The system with which there is the most experience is the Respirgard II jet nebulizer (Marquest). This should be driven by air or oxygen at a flow rate of 6–8 L/min [160,161]. The System 22 Mizer (Medic-Aid) was also validated for use with pentamidine but is no longer available. Although other systems may be effective, this has yet to be clearly shown in published work. The principal advantage of nebulized pentamidine as prophylaxis is the relatively low incidence of adverse effects compared with other options such as co-trimoxazole or dapsone [154,156]. The main disadvantage is reduced efficacy compared with standard doses of co-trimoxazole or dapsone, this becoming particularly evident in AIDS when the CD4<sup>+</sup> count falls below  $0.1 \times 10^9/\text{L}$  [154–156]. Other disadvantages include the inability of topical pentamidine to prevent bacterial infection, cerebral toxoplasmosis or extrapulmonary *Pneumocystis* that arises as a result of haematogenous dissemination [147,152,155]. The inhalation of a nebulized solution is less convenient than swallowing a tablet and is five to ten times more expensive. It is best administered in a small room or booth with extraction to the exterior of the building because of the potential risk of the dissemination of tuberculosis [161]. Nebulized pentamidine is usually well tolerated. Cough is common and wheeze may occur in about 10% of recipients [162], although these may be prevented or diminished by first giving a dose of  $\beta$  agonist such as 200  $\mu\text{g}$  salbutamol from a standard metered-dose inhaler or 2.5 mg from a nebulizer. The patient may complain of an unpleasant metallic taste or nausea, as indeed may also be the case with parenteral administration, although nebulized pentamidine is usually free from the systemic side-effects seen when the

parenteral route is used (see above and Chapter 9) as little of it is absorbed [147]. It remains an important form of prophylaxis for patients who are intolerant of co-trimoxazole and dapsone and who are at low risk of cerebral toxoplasmosis [155,163], although nowadays most patients manage one of the oral regimens satisfactorily.

## Complications

Patients who develop frank respiratory failure as a consequence of PCP commonly display the clinical features of ARDS, with a virtual radiographic 'white-out' and severe hypoxaemia resulting from the shunting of blood through areas of unventilated lung [164,165]. A few of these patients recover if mechanically ventilated [120,121]. Pneumothoraces may occur in patients with PCP, presumably as a result of the rupture of necrotic subpleural blebs; indeed PCP has become a leading cause of spontaneous pneumothorax in populations with a high prevalence of AIDS [90,166,167]. Small pleural effusions may also occur in association with PCP but are unusual [90, 166]. Haemoptysis and hypertrophic pulmonary osteoarthropathy are unusual associations that have been described in association with atypical histological patterns such as nodular forms with granuloma formation, cavitation, local consolidation and vascular infiltration [64,90,168,169]. Hyponatraemia as part of the syndrome of inappropriate secretion of antidiuretic hormone has been described with PCP, as indeed it has with other pneumonias [170]. Haematogenous extrapulmonary spread of *Pneumocystis* is uncommon but can occur in virtually any organ system [171]. It was found to have occurred in approximately 3% of patients with AIDS coming to necropsy at one North American centre [172].

## Outcome

Widely varying mortality rates for PCP of 5–43% have been reported in patients with AIDS [97]. Assuming a reasonable level of competence in the management of patients with PCP, mortality is chiefly influenced by the severity of the infection at presentation. This is reflected by the duration of symptoms prior to presentation (>4 weeks), the presence of tachypnoea (>30/min), the level of hypoxaemia ( $P_{aO_2} < 6.7$  kPa, 50 mmHg) and the extent of chest radiographic change [134,173]. Haematological and biochemical parameters that have been shown to predict poor outcome include a leucocytosis ( $>10.8 \times 10^9/L$ ), hypoalbuminaemia ( $<35$  g/L) or a raised serum lactate dehydrogenase ( $>300$  iu/mL) [134,173]. Mortality does not necessarily increase between the first and recurrent episodes of PCP, one cohort study of over 200 patients reporting mortality rates of 14%, 16% and 12% for the first, second and third episodes of PCP respectively [174]. Mortality is also greater in older age groups and in patients in whom pulmonary copathogens, such as bacteria, mycobacteria, *Cryptococcus* or *Toxoplasma*, are found [70,173]. The same may be true in patients receiving adjunctive steroids and from whom CMV is recovered from BAL fluid [146]. Patients who worsen after 5 days or who fail to improve after 7–10 days of treatment with appropriate medication may require treatment with an alternative drug regimen but in this group the mortality rate rises to 75–100% [97]. A prospective study of the first episode of PCP in 102 patients with AIDS found the mortality rate to be 28%, rising to 79% in those who required mechanical ventilation [173]. A relatively high mortality rate of 34% was reported in a recent retrospective survey of 116 non-HIV-infected patients with underlying diseases complicated by PCP [89]. A survival rate of 52% has been reported in a group of 29 patients who had extrapulmonary PCP [175].

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# PULMONARY MANIFESTATIONS OF SYSTEMIC DISEASE

ANTHONY SEATON

Many of the diseases discussed in this book have systemic manifestations or may demonstrate a major pulmonary component of a primarily systemic disease. This chapter considers diseases primarily of other organs in which lung manifestations may occur and, in some cases, may be an important or presenting feature. For convenience, they are divided into inherited and acquired diseases, although it is clear that many in the latter category may manifest because of an inherited susceptibility, while those in the former category may also be influenced by environmental factors.

## Inherited disorders

The most important of these is cystic fibrosis, dealt with separately in Chapter 30. Less common, occurring as a potentially clinically important genotype in about 1 per 1000 Europeans, is  $\alpha_1$ -antitrypsin deficiency. Other inherited disorders are sickle cell disease (common in certain racial groups), neurofibromatosis, tuberous sclerosis, Ehlers-Danlos, Marfan and cutis laxa syndromes, Shwachman's disease and Hermansky-Pudlak syndrome.

### $\alpha_1$ -Antitrypsin deficiency

The relatively short glycoprotein  $\alpha_1$ -antitrypsin is synthesized in the liver hepatocytes [1]. The molecule is shaped like a shepherd's crook, with a reactive methionine group on an exposed part of the handle of the crook [2]. This amino acid binds tightly to protease, inactivating it. However, the methionine can be readily oxidized and inactivated itself, a mechanism that fits well with the concept that, in defending itself against attack, the lung may need to produce oxidases and also allow elastase activity to continue. However, marked overproduction of oxidases (e.g. from leucocytes stimulated by cigarette smoke or in Gram-negative septicaemia) can result in inactivation of  $\alpha_1$ -antitrypsin and other closely related enzymes such as antithrombin and complement

inhibitors, thus contributing to the severity of the disease process.

Many genotypes of  $\alpha_1$ -antitrypsin deficiency have been described but the clinically important ones in terms of lung disease are PiZZ and PiSZ [3-6]. The former results from homozygous inheritance of a gene causing substitution of a single glutamic acid responsible for the primary bend in the crook. This alters the shape of the molecule, preventing hepatocytes from transporting it into the blood. Thus  $\alpha_1$ -antitrypsin accumulates in these cells, where it may be visible as inclusion bodies and where it is probably responsible for the other serious manifestations of the disease, namely neonatal jaundice, infantile cirrhosis and a usually mild adult portal cirrhosis. The PiZZ genotype results in levels of  $\alpha_1$ -antitrypsin in the blood of about 15% of normal. The homozygote PiSS results in levels of about 60% of normal and is not usually associated with clinical disease; neither are the heterozygotes PiMZ and PiMS, which are associated with levels 60 and 80% of normal respectively. The PiS variant results from inheritance of a gene that codes for replacement of a different glutamic acid in the  $\alpha_1$ -antitrypsin molecule that acts as a signal for splicing; this substitution causes decreased synthesis of a normally functioning molecule. The PiSZ genotype is associated with levels of  $\alpha_1$ -antitrypsin of about 40% of normal and may be associated with clinical lung disease.

Details of the clinical features of  $\alpha_1$ -antitrypsin deficiency are given in Chapter 23. It is worth pointing out here that study of the biochemistry and genetics of this relatively rare lung disease has given rise to the most plausible theory of the causation of emphysema and is now leading to prospects of treatment with genetically engineered substitute antitrypsin. For the moment, however, the mainstay of management is encouragement to stop smoking.

### Neurofibromatosis

Two types of this condition are recognized, both inherited

as an autosomal dominant [7]. It occurs in about 1 in 2500 births. Perhaps half of all cases are the results of new mutations, a fact that is very important in genetic counselling. If a family have a child with evidence of the condition, they will wish to know the risks associated with a future pregnancy. If there is no evidence of the condition in other family members (and careful examination for minimal evidence is necessary), a new mutation in the child is likely. On the other hand, if other family members have evidence of the disease, there is an even chance of a further child having it. Two types are now recognized, either of which may cause thoracic spinal nerve manifestations. Type 1 is von Recklinghausen's disease and is caused by a mutation on the long arm of chromosome 17q that codes for a GTPase-activating protein known as neurofibromin [8,9]. This condition may be complicated by kyphoscoliosis, pheochromocytoma, malignant change in fibromas, pathological bone fractures and mental retardation. The type 2 disease causes mainly bilateral acoustic neuromas and other intracranial lesions such as gliomas and meningiomas, cataracts and retinal abnormalities but may involve spinal nerves. It is caused by a mutation on chromosome 22q coding for a protein called schwannomin [10].

Since incomplete penetrance is common, the type 1 gene may be expressed by a range of clinical manifestations, from a few *café-au-lait* patches (six is regarded as the minimum for diagnosis), through multiple small subcutaneous nodules, to a serious crippling condition with multiple plexiform skin tumours with gross skin thickening and involvement of the spinal canal and central nervous system. Unfortunately, the severity of manifestations in the parent is no indicator of the abnormalities to be expected in the offspring, 50% of whom are likely to show some features of the disease. Similarly, type 2 disease may present with multiple tumours early in life or in much more benign form with few lesions later in life; there is some evidence that the severity of manifestations depends on the type of mutation [10,11].

Thoracic manifestations are usually confined to chest wall neurofibromas associated with intercostal nerves and which sometimes show the dumb-bell appearance, with enlarged intervertebral foramen associated with an extension into the spinal canal (see Chapter 45). Occasionally, however, the condition is associated with diffuse pulmonary fibrosis and bullous emphysema [12], and may present as pneumothorax.

### **Tuberous sclerosis**

This condition occurs in about 1 per 10 000 births in the UK and is also inherited as an autosomal dominant, although many cases occur as a new mutation and severe disease may be transmitted by someone with minimal evidence [13,14]. Two mutations have been identified: on chromo-

some 9q encoding a protein called hamartin; and on chromosome 16p encoding tuberlin, a GTPase-activating protein [15,16]. The clinical manifestations vary considerably and are due to the presence throughout the body of abnormal hamartomatous malformations. Skin lesions (ranging from irregular depigmentation to multiple warty nodules), central nervous nodules (causing epilepsy and mental retardation) and hamartomas of kidney, heart, bone and other organs may be present. Lung lesions include multiple nodular hamartomas and a patchy fibrosis that pathologically shows associated muscle hyperplasia as well [17]. Carney's triad, i.e. pulmonary hamartomas, gastric leiomyosarcoma and paraganglioma, is mentioned in Chapter 42 [18]. Patients with diffuse pulmonary disease often present with pneumothorax. Pleural effusion has been described [19].

The diagnosis is made from the presence of typical associated lesions, especially mental retardation, the warty facial adenoma sebaceum, the yellowish rough 'shagreen patch' over the lower spine, subungual fibromas, retinal fibromas, and bone lesions showing increased radiographic density. In patients with diffuse lung disease, the prognosis is poor once symptoms are present. However, one patient has been described in whom mild stigmata of tuberous sclerosis were associated with diffuse lymphangioleiomyomatosis and who responded partially to treatment with tamoxifen [20]. Two others with a similar syndrome seem not to have responded [21]. Such treatment would be justified on a trial basis in such patients in the absence of any more promising therapy. If it were to be used, it would be of interest to look for oestrogen receptors in the lung biopsy.

### **Marfan's syndrome**

This condition is characterized by excessive height and disproportionately long limbs and digits, dislocation of the lens and cardiovascular abnormalities including aortic regurgitation, dissecting aneurysm due to medial degeneration of aorta, and mitral valve prolapse [22]. Joint dislocations may also occur in relation to lax ligaments. Like the above two conditions, it is inherited as an autosomal dominant, in this case due to a mutation on chromosome 15 that encodes the protein fibrillin, important in elastin-containing tissues [23,24]. The presentation is variable in severity but many patients die in early middle age of cardiovascular problems [25]. The manifestations of the disease result from reduced tensile strength of connective tissues in the suspensory ligament of the lens and major blood vessels.

Apart from aortic dissection and regurgitation, the thoracic manifestations are not usually very important. Scoliosis of mild degree is common but pulmonary function is generally normal when allowance is made for any spinal deformity [26]. However, pneumothorax is more common

in such patients than in the general population and both upper lobe bullae and upper lobe fibrosis have been described in patients with the syndrome. Aspergillomas may complicate bullae.

### **Ehlers–Danlos syndrome**

This is a name given to what is now known to be a group of at least nine separate inherited disorders of collagen characterized by abnormal skin, lax ligaments and hyper-extensible joints. Different types are inherited differently, although most are transmitted as autosomal dominants. It is not certain how commonly thoracic problems occur in this syndrome but haemoptysis, recurrent sinusitis and pneumonia, pneumothorax, tracheomegaly and pectus excavatum have been described more frequently than might be expected [27–29].

### **Cutis laxa syndrome**

This syndrome includes a number of inherited abnormalities of elastic tissue, characterized clinically by the development in childhood of abnormally lax and inelastic skin. The patient has characteristically loose skin around the eyes and on the ear lobes, and biopsy may show short fragmented elastic fibres with normal collagen in the skin. At least three types are recognized. The most severe is transmitted as an autosomal recessive and the skin lesion is present at birth. Severe emphysema leading to death may occur in infancy. Autosomal dominant inheritance is associated with a milder condition without pulmonary disease, while X-linked inheritance is associated with urinary tract, skeletal and joint abnormalities. Although the recessive type usually appears to be fatal in early childhood, some patients with what seems to be this variant have survived to adolescence. Severe emphysema in a child should always raise the suspicion of this condition [30–33].

### **Hermansky–Pudlak syndrome**

This is a rare condition in which albinism, a platelet aggregation defect and chromolipid inclusions in bone marrow macrophages are found [34–36]. It is inherited as an autosomal recessive. The gene has been identified on chromosome 10q and encodes a transmembrane polypeptide that is probably a component of many cytoplasmic organelles [37,38]. The patients complain of bruising, menorrhagia and bleeding after dental extraction. In a few instances, the condition has been accompanied by evidence of interstitial lung fibrosis. Accumulations of chromolipid have been demonstrated in lung macrophages, and it has been suggested that these or chronic lung haemorrhage and haemosiderosis may cause the fibrosis [39,40]. However, it seems more likely that growth factors released in the lung

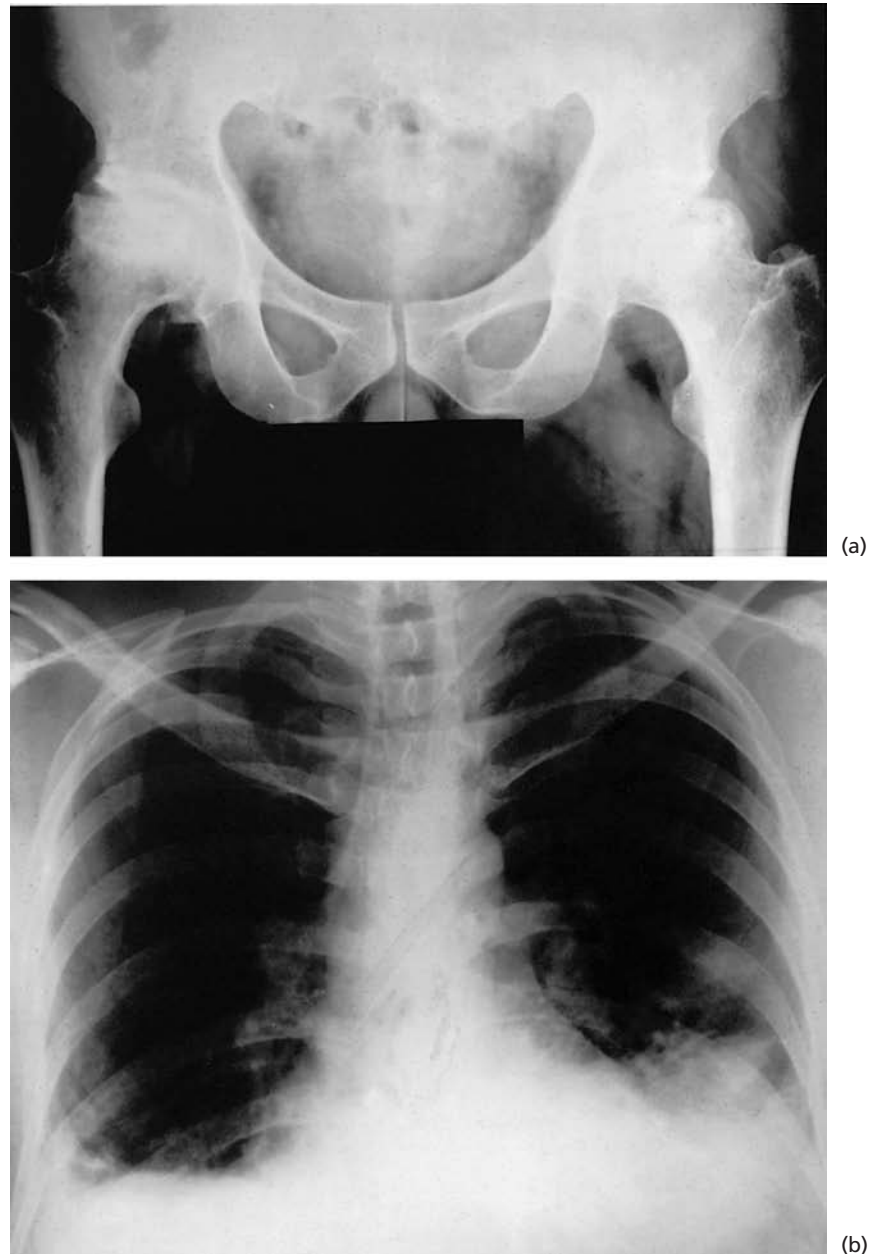
may be responsible, and platelet-derived growth factor, produced by lung macrophages, has been found in raised concentrations in lavage fluid from patients with the syndrome [41].

### **Sickle cell disease**

In contrast to the other conditions in this section, sickle cell disease is very common, occurring in about 1 in 200 births in affected racial groups from West and Central Africa, Greece, Turkey, the Middle East and India. Homozygotes (sickle cell disease) inherit haemoglobin S from both parents and exhibit the disease, while heterozygotes (sickle cell trait) have a mixture of haemoglobins S and A and only show evidence of sickling when stressed by hypoxia. The full syndrome also occurs in heterozygotes having haemoglobin S combined with other variant  $\beta$ -globin haemoglobins, such as haemoglobin C or  $\beta$  thalassaemia. Haemoglobin S has a valine substituted for glutamic acid in the  $\beta$  chain due to a mutation on chromosome 11.

The homozygous disease varies in its manifestations and tends to be milder in people of the Indian races than in Africans. It is characterized by sickling crises, in which vascular occlusion, bone marrow aplasia or sequestration of blood in liver and spleen occur as a result of the deformation of red cells, and which usually present with bone or abdominal pain. Relatively frequently (in up to 20% of crises) the disease presents as an acute chest syndrome [42,43]. This typically starts with bone pain in the thoracic cage, often accompanied by pleurisy, tachycardia and tachypnoea. Inspiratory crackles and signs of consolidation tend to occur later; radiographic shadowing usually appears first at the bases and in severe cases spreads throughout the lungs. The episode is accompanied by fever and falls in haemoglobin and, in severe cases, platelet count. Pains in the abdomen and other bones may be a feature. The episode may be fatal, and pathologically the lungs show evidence of alveolar wall necrosis with obstruction of capillaries by sickled red cells [44,45]. Bone marrow and fat emboli may also be found in the pulmonary vessels.

Apart from the acute chest syndrome, patients with sickle cell disease may be at increased risk of infections [42], including pneumonia, though this diagnosis may often be made in error when infarction occurs [46]. There may also be a greater risk of pulmonary embolism in pregnancy. Heterozygotes rarely develop symptoms unless exposed to hypoxic conditions, such as in unpressurized aircraft or under unwary anaesthesia. The author has seen one such patient from the Middle East whose first crisis, induced by climbing in the Himalayas, caused ischaemic necrosis of the hips and whose second crisis occurred during surgery for that condition, resulting in pulmonary infarction (Fig. 53.1).



**Fig. 53.1** Radiographs of patient from the Middle East who developed (a) ischaemic necrosis of the femoral heads on climbing in the Himalayas and (b) infarcted lung following operation. Sickle cell trait was responsible.

For details of the management of sickle cell disease, the reader is referred to the book by Sergeant [47]. In terms of prevention of episodes, the patient should be advised about the dangers of anaesthesia and diving and the avoidance of reduced oxygen tension during climbing and aircraft flights. The chest syndrome is managed by the use of narcotic analgesics, preferably by infusion pump, intravenous fluids, oxygen and broad-spectrum antibiotics in case of infection. Exchange transfusion is used if the patient does not improve on this regimen; blood is withdrawn in 100-mL volumes and the same amount of donor blood replaced up to about 2 L in adults every day until the proportion of haemoglobin S in the patient's blood is less

than 20% [43]. This may also be used before anaesthesia for major surgery. Increasing hypoxaemia should be treated by assisted ventilation if oronasal administration is unable to provide an adequate  $F_{IO_2}$ . In desperate cases, extracorporeal membrane oxygenation has proved life-saving [48].

There is some evidence that patients with sickle cell disease develop a restrictive pattern of lung function and pulmonary hypertension as a consequence of repeated episodes of pulmonary sickling [49]. However, the assessment of lung function may be difficult because of bodily disproportion caused by disturbance of bone growth in childhood, and specific formulae for

prediction of vital capacity, total lung capacity and diffusing capacity (DLCO) in such patients have been published [50,51].

### Immune deficiency syndromes

Many inherited abnormalities of immune defences have been described. Some, such as severe combined immunodeficiency disease, present with T-lymphocyte dysfunction and infections, including *Pneumocystis carinii* pneumonia in infancy. Others, such as Shwachman's syndrome, may present in childhood with recurrent infections and pancreatic insufficiency, mimicking cystic fibrosis [52]. The hereditary antibody deficiency syndromes may present as severe episodes of recurrent infections in infancy (such as X-linked hypogammaglobulinaemia) or as a more chronic bronchial sepsis and bronchiectasis in children and adults (such as IgA deficiency). Many of these conditions may also occur as a secondary phenomenon in adult life and may be associated with chronic bronchial sepsis or susceptibility to pneumonia. For further information on diagnosis and management, the reader is referred to relevant texts [53,54].

### Niemann–Pick disease and other sphingolipidoses

These are rare hereditary diseases of sphingolipid metabolism caused by lack of specific enzymes and characterized by accumulations of abnormal lipid deposits in nervous and other tissues [55,56]. In several of them reticular radiographic shadowing on the chest film and pathological accumulations of lipid together with a fibrotic reaction have been described in the lung. Hepatosplenomegaly, mental changes, a cherry-red macula and 'sea-blue' histiocytes in the marrow are other common features. Some of these conditions occur in a mild form compatible with survival into middle age.

### Acquired disorders

#### Connective tissue diseases

Pulmonary manifestations occur frequently in the connective tissue diseases [57,58]. There is considerable overlap between the different diseases, between the associated pulmonary manifestations and between the same pulmonary conditions in the absence of obvious collagen disease. Thus classification of the disorders is rather arbitrary and is likely to remain so until their aetiology is better understood. Those considered in this chapter are summarized in Table 53.1.

**Table 53.1** Respiratory manifestations of connective tissue diseases.

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<i>Rheumatoid disease</i>
Pleural effusion/fibrosis
Bronchopleural fistula
Pulmonary nodules and diffuse fibrosis
Caplan's syndrome
Bronchiolitis obliterans
Recurrent infections
Eosinophilic pneumonia
Pulmonary hypertension
Shrinking lung
Amyloidosis
Bronchocentric granuloma
Cricoarytenoid obstruction
Bronchiectasis
<i>Systemic lupus erythematosus</i>
Pleurisy/pleural effusion
Acute pneumonitis
Pulmonary haemorrhage
Interstitial fibrosis
Lymphocytic interstitial pneumonitis
Pulmonary hypertension/embolism
Segmental atelectasis
Diaphragmatic dysfunction
Infections
Drug reactions
Amyloidosis
<i>Systemic sclerosis</i>
Pulmonary fibrosis
Pulmonary hypertension
Aspiration pneumonia
Ventilatory failure
Relapsing pneumonitis
<i>Sjögren's syndrome</i>
Xerotrachea
Pulmonary fibrosis
Lymphocytic interstitial pneumonitis
Pulmonary lymphoma
<i>Ankylosing spondylitis</i>
Restricted chest movement
Upper lobe fibrosis
<i>Dermatomyositis/polymyositis</i>
Interstitial fibrosis
<i>Polyarteritis</i>
Pulmonary arteritis
<i>Mixed connective tissue disease</i>
Pleurisy/effusion
Interstitial fibrosis
Pulmonary arteritis
<i>Giant cell arteritis</i>
Pulmonary arteritis
<i>Behçet's syndrome</i>
Pulmonary arteritis/infarction
<i>Relapsing polychondritis</i>
Tracheal stenosis
Recurrent infection

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### Rheumatoid disease

Pulmonary fibrosis was first described in association with rheumatoid arthritis in the late 1940s [59,60] and Caplan [61] recognized the association of arthritis and fibrotic nodules in the chest in coal-miners in South Wales in 1953. It is now clear that the lungs and pleura may manifest many different effects of rheumatoid disease and of its treatment, although all are rare except for fibrosis and pleural effusion [62].

### Pleural disease

An occasional patient with rheumatoid disease develops pleural effusion [63]. The condition is more common in men, usually in middle age, and rarely the effusion precedes evidence of joint disease. It is usually unassociated with symptoms but may cause pleurisy or, if unusually large, breathlessness. It tends to recur after aspiration. The fluid usually has a high protein and low glucose content, the latter being a useful diagnostic clue [64,65]. Another typical abnormality is a high pleural fluid/blood ratio of neurone-specific enolase, a ratio that is about unity in most conditions causing effusion but which rises to 10 or more in rheumatoid patients [66]. The effusion may appear chylous due to a high cholesterol content (Fig. 53.2). Rheumatoid factor may be present in high titre, sometimes higher than that in serum. Cytology may show large numbers of polymorphonuclear leucocytes, epithelioid cells and leucocytes containing dense granules similar to those found in joint fluid [67]. Pleural biopsy may show palisaded histiocytes characteristic of the rheumatoid nodule.

Small effusions require no treatment and may resolve

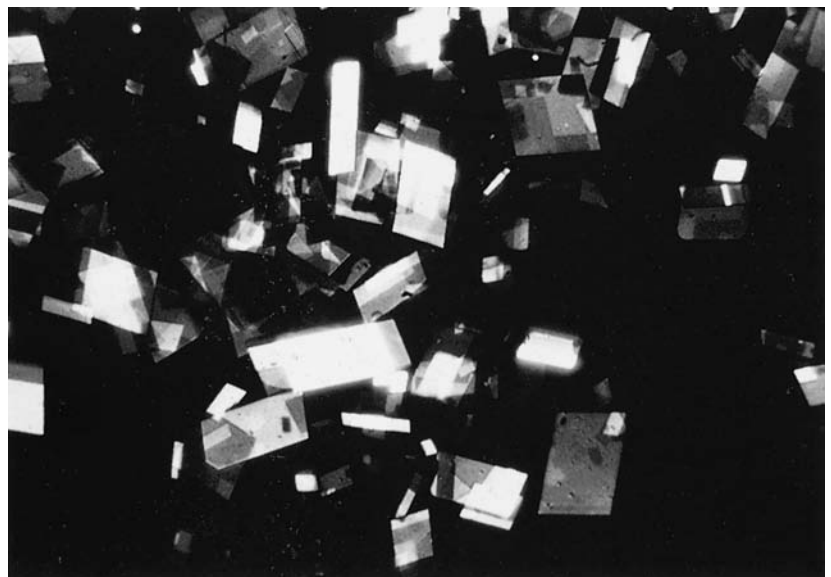
spontaneously leaving pleural thickening. Larger ones should be aspirated; if they recur, chemical pleurodesis should be carried out. Persistent effusions may cause quite extensive pleural fibrosis and restriction of lung movements, and in such cases pleurectomy needs to be considered. The efficacy of corticosteroid treatment is not established for the management of rheumatoid pleural effusion. Some patients have appeared to respond and others not; a short trial is justified in patients with disease that recurs after aspiration before proceeding to pleurodesis.

Apart from effusions, patients with rheumatoid disease quite commonly show evidence of pleural thickening or adhesions at autopsy. In some cases these may be the residua of an undiagnosed effusion. Rarely, a pulmonary nodule may cavitate and rupture into the pleural space, causing pneumothorax and bronchopleural fistula [68]. Such episodes are likely to require surgical intervention to excise the nodule and to carry out pleurodesis.

### Pulmonary nodules

Single or multiple nodules, usually about 1–3 cm in size though sometimes up to 10 cm, may appear on the chest film of patients, again usually male, with rheumatoid disease [69,70]. They are the least common lung manifestation of this disease. They tend to be subpleural in distribution and typically cavitate, leaving a very thin hair-line cavity that often gradually disappears (Fig. 53.3). Occasionally, nodules appear in patients without rheumatoid disease and on excision prove to be typical rheumatoid lesions; such patients may develop joint symptoms later [71].

There is no obvious relationship between the develop-

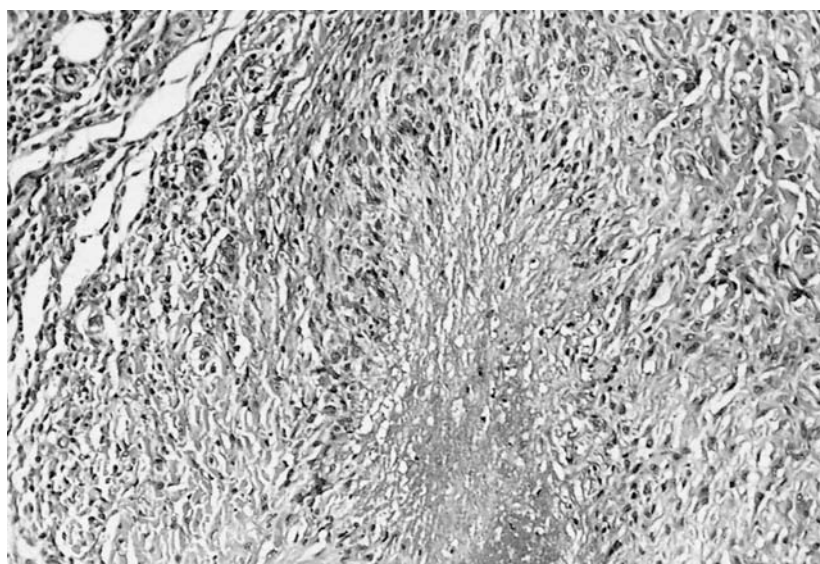


**Fig. 53.2** Cholesterol crystals in pseudo-chylous effusion from patient with rheumatoid disease ( $\times 350$ ).





**Fig. 53.3** Chest film of cavitating rheumatoid nodules in both upper lobes. Patient had long-standing seropositive rheumatoid disease.



**Fig. 53.4** Rheumatoid nodule showing central necrosis, a zone of palisaded histiocytes and surrounding fibrous tissue and few chronic inflammatory cells (haematoxylin & eosin  $\times 150$ ).

ment of nodules and the severity of the underlying rheumatoid disease, although there seems to be an association with the presence of subcutaneous nodules and with high titres of rheumatoid factor. Histologically they resemble subcutaneous nodules, with central necrosis surrounded by palisaded histiocytes and with a peripheral zone of chronic inflammatory cells (Fig. 53.4).

In general these nodules require no treatment, although excision is sometimes necessary because of anxiety that one might be neoplastic. As mentioned above, rupture into the pleura may cause bronchopleural fistula or be associated with pleural effusion, necessitating surgery.

The occurrence of such nodules in the lungs of coal-miners is called Caplan's syndrome [61]. At one time this strange immunological feature was thought to be a possible explanation of the development of progressive massive fibrosis. However, it is now apparent that

Caplan's syndrome is of rare occurrence in miners and is only very occasionally the cause of massive fibrosis.

### *Pulmonary fibrosis*

The best-known pulmonary complication of rheumatoid disease is pulmonary fibrosis [72–74]. Most commonly this occurs as a chronic and only slowly progressive diffuse interstitial disease, maximal in the lower zones and not causing significant disability in a patient usually handicapped by joint disease. Evidence on lung function testing of some pulmonary fibrosis may be found in 30–40% of all patients with rheumatoid disease. It is more common in men. However, this description of a relatively mild condition should not blind the clinician to other possibilities since the clinical picture extends to include an aggressive and rapidly progressive arteritic type of disease, sometimes associated with digital arteritis [75]. Anything from

this through desquamative interstitial pneumonitis to a burnt-out basal fibrosis may be seen.

Pulmonary fibrosis in patients with rheumatoid disease is indistinguishable either clinically or investigationally from the cryptogenic type, except for the necessary presence of evidence of the systemic disease. Up to one-third of patients with cryptogenic pulmonary fibrosis have positive rheumatoid factor in the absence of clinical evidence of rheumatoid disease, and it seems likely that the two conditions are both responses to the same cause [76]. What that is, of course, remains obscure. Finger clubbing occurs in about 50% of patients and repetitive inspiratory crackles are heard at the bases [77]. There is no clear relationship between the severity of the rheumatoid arthritis and that of the lung disease, although subcutaneous rheumatoid nodules are often present and the titre of rheumatoid factor may be high in patients with fibrosis [77,78].

Radiological appearances vary from an acute exudative pattern, through diffuse nodular and irregular, predominantly lower zone, infiltrates, to honeycombing (Figs 53.5 & 53.6). As stated above, the rate of progression is very variable. Little is known of the pathogenesis of the lung lesion, which represents a chronic inflammatory reaction with T lymphocytes and neutrophils [79]. Further discussion of the pathogenesis can be found in Chapter 31. The pathology is of interstitial fibrosis with some chronic

inflammatory cells [80], and bronchoalveolar lavage shows changes similar to those in cryptogenic pulmonary fibrosis. Immune complexes have been demonstrated in the lung in some cases but evidence of arteritis is usually absent [81,82].

Another, quite distinct, manifestation of rheumatoid lung disease is progressive upper lobe fibrosis and cavitation [83,84]. This may be unassociated with symptoms and present simply as an abnormal radiograph. However, bleeding from bronchiectatic cavities or infection of the damaged lung are not infrequent complications, while aspergilloma may also occur. The condition may mimic tuberculosis or other mycobacterial infection, chronic sarcoidosis or chronic allergic alveolitis and may cause diagnostic confusion if the clinician is not aware that it occurs. In one case it has been associated with bronchiolitis obliterans in the upper lobe airways, and the authors of this report suggested that this may play a pathogenic role; however, the presence of extensive rheumatoid disease in large airways in this patient may have been equally relevant [85]. A similar condition is well recognized in association with ankylosing spondylitis (see below). There is some evidence that the condition, when associated with rheumatoid disease, may stop progressing when the patient is treated with steroids, azathioprine or penicillamine [84,86,87].

Rheumatoid lung fibrosis is diagnosed when the above



**Fig. 53.5** Chest film of 60-year-old woman with mild rheumatoid disease and an acute progressive pulmonary fibrosis showing honeycombing of left lung and irregular fibrosis in right lung. There was some regression of change in the right lung after steroid therapy.



**Fig. 53.6** More chronic type of rheumatoid lung showing diffuse fine fibrosis and arthritic shoulder.

clinical features occur in a patient with rheumatoid disease. The harder one looks, the more one is likely to find evidence of disease in patients with rheumatoid arthritis, although the significance of early changes in *DLCO*, high-resolution CT or isotopic lung scans in terms of prognosis is not clear [88]. It is wise to assess the rate of progression of the lung lesion by repeating measurements of *DLCO* over several months before embarking on treatment. If no change occurs and in view of the toxic side-effects of the drugs, it is advisable simply to reassess function at, say, 6-monthly intervals and to withhold treatment. If the patient presents with evidence of more active disease, with diffuse patchy pneumonitis radiologically, or if there appears to be deterioration in lung function, a trial of high-dose prednisolone should be given, the effect being monitored by measurements of lung volumes and *DLCO*. If this is unsuccessful, consideration may be given to the use of azathioprine, cyclophosphamide or penicillamine, all of which have been used with apparent success in occasional cases, though none can be regarded as being of established value. In general, radiographic and CT changes of a fine irregular type, with loss of lung volume, indicate mature fibrosis and no response to therapy, whereas a more fluffy or ground-glass appearance may indicate more active inflammation and a better response.

#### *Bronchiolitis obliterans* (see also Chapter 29)

Airways obstruction appears to occur excessively frequently in patients with rheumatoid disease, even in as many as 30% of non-smokers with the disease [89,90]. However, in some patients a severe and rapidly progressive form of airways obstruction occurs, with widespread inspiratory crackles and often a mid-inspiratory squeak on auscultation [91–93]. The chest film may be normal or show only overinflation. Lung function shows severe airflow obstruction, a reduced *DLCO* but normal *Kco* and raised residual volume and total lung capacity measured plethysmographically; helium dilution often shows normal volumes, presumably because of inability of the gas to equilibrate with trapped air in the time available. There is a strong suspicion that in some cases the syndrome has been provoked by treatment with penicillamine [94,95] though patients have been seen who have not had this drug. The course of the condition may be progressive, with death from respiratory failure occurring within 2–3 years of onset [91]. At necropsy there is widespread fibrous obliteration of bronchioles, which are the site of an intense chronic inflammatory infiltrate. However, milder and much less rapidly progressive disease may also occur, with survival for over 10 years after the onset of symptoms [94]. There is no convincing

evidence that corticosteroids are effective in preventing progression of the condition.

### *Other pulmonary syndromes*

Pulmonary infection appears to occur relatively frequently in patients with rheumatoid arthritis [96], and the development of polyarthritis and positive rheumatoid factor has been described in patients with bronchiectasis and cystic fibrosis [97]. The significance of these observations is unclear. Conversely, bronchiectasis has been described sufficiently frequently in patients with rheumatoid disease for it to be thought that there may be a causative link or a common aetiological factor [98,99]. Chronic eosinophilic pneumonia with fever, weight loss, dyspnoea and pulmonary infiltrates has been described rarely in rheumatoid disease [100,101]; it responds to treatment with corticosteroids. Pulmonary hypertension [102,103], progressive loss of lung volume perhaps due to diaphragmatic dysfunction [104], secondary diffuse pulmonary amyloidosis [105], sclerosing mediastinitis [106] and bronchocentric granulomatosis [107–109] have all been described on rare occasions in association with rheumatoid disease. Finally, severe rheumatoid disease may affect the cricoarytenoid joints of the larynx, provoking upper airways obstruction (Fig. 53.7). One such patient treated by the author required a permanent tracheostomy.

### **Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is a condition occurring nine times more frequently in women than in men, with a prevalence in Californian females of 1 in 700; it is also more common in the black races, being diagnosed in 1

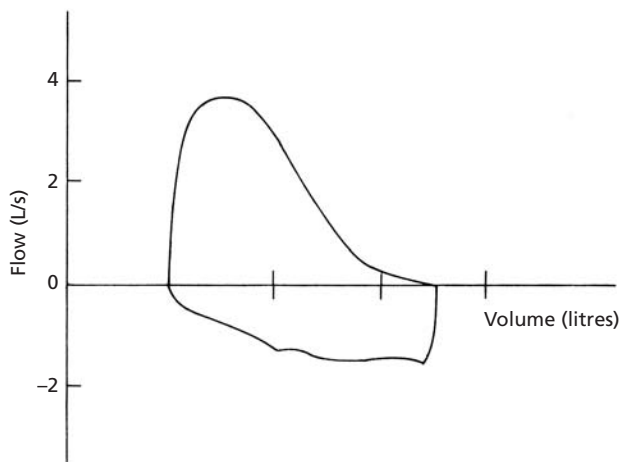
in 245 black women in the same state [110]. The systemic features of the disease include facial rashes, discoid skin lesions, photosensitivity, hair loss, arthropathy and renal and central nervous system lesions. Diagnosis is based on the presence of such clinical manifestations together with lupus cells in the blood, positive antinuclear antibody and antibody to double-stranded DNA. The clinical spectrum of the disease is wide, varying from acute fulminant cases with widespread arteritis and renal failure to a mild condition with transient rashes and occasional systemic involvement [111]. The known causes are few; the syndrome may follow the use of certain drugs (e.g. hydralazine, phenytoin, procainamide, chlorpromazine, penicillamine) [112] and occurs to excess in patients exposed to quartz [113,114]. It is probably influenced by both genetic and hormonal factors [115], and there is some evidence of viral transmission in animals [116]; nevertheless, in most individual patients the aetiology is obscure.

As with rheumatoid disease, SLE is also associated with a wide range of pleuropulmonary complications (see Table 53.1) [117–119]. Pleurisy or pleural effusion is the most common, occurring in about half of all patients. Pulmonary infiltrates are not infrequent and may be due to primary involvement of the lung acinus by SLE, pulmonary haemorrhage, superimposed infection or infarction, or complications such as amyloidosis or lymphocytic interstitial pneumonitis. 'Shrinking lung', originally thought to be due to progressive pulmonary disease but now usually related to bilateral elevation of myopathic diaphragms, occurs occasionally.

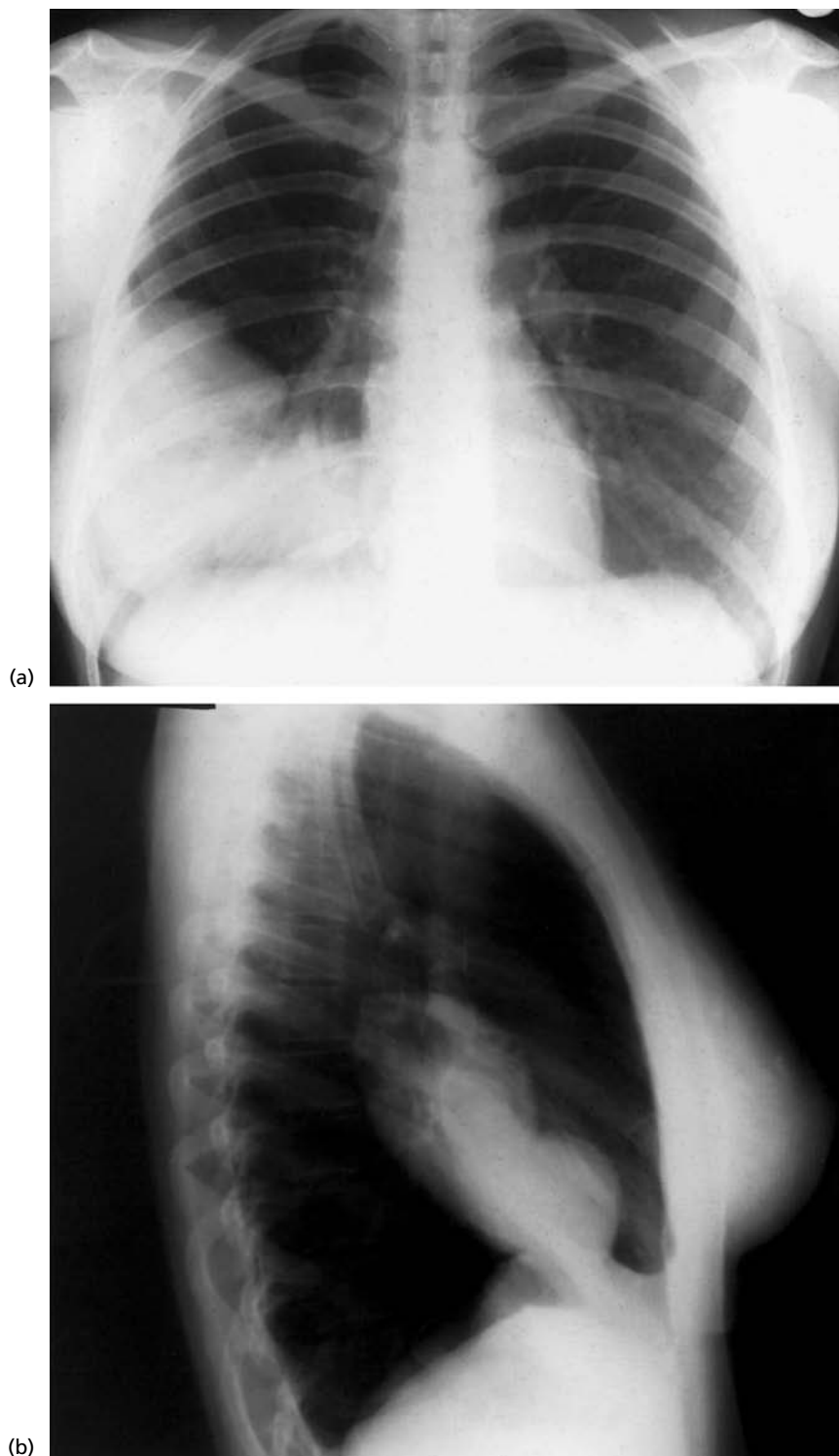
### *Pleurisy and pleural effusion*

One of the most frequent clinical features of SLE, pleurisy and pleural effusion may be unilateral or bilateral and may occur just once or repeatedly [120,121]. Mild episodes may present with bilateral pain, a friction rub and no radiographic abnormality, or small bilateral effusions. More severe cases may be associated with breathlessness and persistent effusions (Fig. 53.8). Diagnosis is made from the clinical and haematological features of the disease. In the case of an effusion, the fluid is usually an exudate and has a normal glucose (though this may rarely be low) and a moderately high count of mononuclear or, sometimes, polymorphonuclear leucocytes. Immune complexes, reduced levels of complement C3 and C4, lupus cells and antinuclear factor may be present in the fluid. Pleural biopsy changes are usually non-specific, although fibrinoid deposition and haematoxylin-staining bodies may be seen. More usually the pleura is oedematous, infiltrated with mononuclear cells and covered with a fibrinous exudate [122].

The normal course is for spontaneous resolution, aided by aspiration. Pain may be relieved by non-steroidal anti-



**Fig. 53.7** Flow–volume loop from patient with severe rheumatoid disease and cricoarytenoid involvement showing attenuated peak flow and inspiratory flows.



**Fig. 53.8** (a) Posteroanterior radiograph of patient with systemic lupus erythematosus showing pseudotumour in right lower zone. (b) Lateral radiograph shows this to be an effusion encysted in the oblique fissure.

inflammatory drugs. In severe or persistent cases, high-dose oral steroids are usually effective. The main problem is reassuring oneself that the lesion is not due to infection or infarction, both of which occur frequently in SLE. The former may be excluded by culture of sputum, blood and pleural fluid. The latter should be suspected if the patient has the lupus anticoagulant (see below).

#### *Lupus pneumonitis*

This presentation of SLE, which occurs in some 12% of patients, usually mimics a bacterial pneumonia, the patient being ill, febrile and breathless [123–125]. Pleurisy, cough and sometimes haemoptysis may occur. Inspiratory crackles may be heard over the lung and the patient may

be hypoxaemic. Pneumonic infiltrates are most frequently bilateral and basal but may be diffusely distributed and patchy. Occasionally, however, the radiograph may be apparently normal, suggesting that the episode is largely confined to the pulmonary vessels [126]. Pleural effusions may be present also.

Diagnostic difficulty arises in two respects. If the patient was not previously known to have SLE, the episode is understandably thought to be an acute infection and the diagnosis only made after antibiotics prove ineffective, bacteriology is negative and the typical haematological features are detected. On the other hand, if the patient is known to have SLE, the problem is whether the illness is acute lupoid lung or a secondary infection. Here the tendency is to assume the former, a diagnostic decision that may literally prove fatal if the patient has pyogenic or opportunist infection. Almost one-third of patients with SLE now die of infections (see below). In this situation, careful microbiological assessment should be carried out and, if necessary, both antibiotic and anti-SLE therapy used.

Lupus pneumonitis is often a severe, potentially life-threatening, disease. Pathologically, the lungs show non-specific inflammatory changes at necropsy, including mononuclear and polymorphonuclear cell alveolitis, alveolar wall oedema and sometimes an arteritis of small vessels with lymphocytes and plasma cells. Some studies have shown alveolar deposition of immunoglobulin and the presence of antinuclear antibodies in alveolar walls and capillaries [127,128], although at present lung biopsy is not helpful in making a positive diagnosis. It may of course be useful in excluding opportunist infections.

Once the diagnosis is made, the condition should be treated vigorously. There is usually a good response to high-dose (60mg or more daily) prednisolone and this should be started immediately. If response does not occur within 2–3 days or if there is evidence of renal involvement, it would be the author's practice to add cyclophosphamide. When the patient has improved, the drugs may be slowly reduced in dosage. Lung function (volumes and DLco) and renal function should be monitored, stopping the cyclophosphamide first and reducing the prednisolone to as low a maintenance level as keeps the patient free of recurrence. Each patient needs to be treated as an individual, the dose of therapy being titrated against the clinical response; it is not possible to be dogmatic about treatment.

### *Pulmonary haemorrhage*

SLE is one of the causes of acute diffuse pulmonary haemorrhage [129–132] (see Chapter 51). The patient typically presents with malaise, cough, dyspnoea and haemoptysis, which may be no more than a little streaking of the sputum or may be massive. The chest film shows bilateral, often

quite extensive consolidation, and the diagnostic clue comes from the finding of a low haemoglobin. Clinically it is indistinguishable from Goodpasture's syndrome, although antiglomerular basement membrane antibodies are not detectable.

The condition may prove fatal despite treatment and has an approximately 50% mortality rate. Appropriate oxygenation, transfusion of blood and high-dose corticosteroid and cyclophosphamide therapy are recommended when the diagnosis is suspected. If there is doubt about the diagnosis, plasmapheresis may be tried, though the evidence in the literature suggests that this does not influence survival [132].

The pathological findings, apart from extensive alveolar haemorrhage, are of non-specific alveolitis and, in some patients, an extensive neutrophil inflammatory infiltrate of small arteries, arterioles and capillaries [132,133]. Pulmonary haemorrhage may also occur in SLE secondary to uraemia or thrombocytopenia, in which case the pathological changes are simply those of haemorrhage and haemosiderosis.

### *Chronic interstitial fibrosis*

Some evidence of chronic alveolitis is found in a majority of patients with SLE subjected to necropsy, though in some cases these may be secondary to infection or infarction, and during life abnormalities of lung function in terms of DLco and of the ratios of lymphocytes in alveolar lavage fluid are not infrequent [134]. Such findings do not necessarily indicate progressive lung disease and may regress [135]. Clinical evidence of chronic interstitial fibrosis, indistinguishable clinically, functionally and radiologically from the cryptogenic disease, is found rarely in SLE. Nevertheless, there are enough reports in the literature to make it clear that the association does occur occasionally and that it is associated with immune complex deposition in alveolar walls [136–138]. While it would be sensible practice to treat such patients with steroids and immunosuppressants after appropriate assessment of the severity and rate of progress of the disease, anecdotal reports suggest that it does not usually respond and has a relatively poor prognosis. Again, each case should be treated on its merits; it would be surprising if mild, non-progressive cases did not occur.

### *'Vanishing lung' syndrome*

These patients present with increasing exertional dyspnoea and inability to take a full inspiration when they have their chest film taken. Lung function shows a restrictive pattern but usually no abnormal auscultatory signs are present in the chest. Diaphragmatic excursion is seen to be limited on screening and transdiaphragmatic pressure may be much reduced. The condition is probably due to respiratory myositis [139–142].

Some evidence of diaphragmatic weakness or elevation has been shown to be present in up to one-third of patients with SLE being studied in hospital, and is thus a relatively common feature of the disease. In symptomatic patients, a good response with improvement in diaphragmatic function has followed treatment with prednisolone.

### *Other pulmonary syndromes*

It is quite usual to see radiological signs of linear atelectasis in SLE, often related to pleurisy, elevated diaphragms or infection [143–145]. No treatment is required except that for the primary condition. Patients with SLE are at increased risk of infection, probably largely due to the use of immunosuppressant and corticosteroid drugs; almost one-third of patients who die of SLE have evidence of serious pyogenic or opportunist infection at death [146,147]. *Pneumocystis* pneumonia, candidiasis, toxoplasmosis, aspergillosis and mycobacterial infections may be seen, as well as staphylococcal pneumonia. There is some evidence that alveolar macrophage function may be suppressed in SLE, rendering such patients more than normally liable to these infections [148].

Pulmonary embolism is a particular risk in patients with SLE with the lupus anticoagulant. This is an antiphospholipid antibody present in a small number of patients and is associated with central nervous system disease, recurrent abortions and thromboses [149,150]. It also causes a false-positive venereal disease reference laboratory (VDRL) test for syphilis. It interferes with the transformation of prothrombin to thrombin and thus causes a prolonged partial thromboplastin time. However, paradoxically, it causes an increased susceptibility to thromboses, probably as a result of its inhibition of the release of arachidonic acid metabolites from cell membranes and therefore the loss of their inhibitory effects on platelet aggregation.

Perhaps also related to the presence of the lupus anticoagulant is the development of pulmonary hypertension, which occurs in a small number of patients with SLE [151,152]; in one report, five of six patients with pulmonary hypertension had the anticoagulant. Associated vasculitis and Raynaud's disease may also be factors in the aetiology of pulmonary hypertension.

The differential diagnosis of diffuse or patchy pulmonary infiltrates in SLE should include four other possibilities: (i) some of the drugs used in its treatment (cyclophosphamide and azathioprine) may occasionally cause interstitial pneumonitis (see Chapter 55); (ii) occasionally patients with SLE develop lymphocytic interstitial pneumonia, with dense patchy infiltrates and a relatively benign course (see Chapter 40) [153]; (iii) a patient with, or even without, chronic renal involvement may rarely develop secondary amyloidosis involving the

lung parenchyma (see Chapter 51) [154]; and (iv) pulmonary oedema secondary to renal failure may also occur (see Chapter 27).

### **Systemic sclerosis**

Systemic sclerosis is a multisystem disease characterized by fibrosis of the epidermis and dermis (scleroderma), Raynaud's phenomenon and fibrosis of other organs including the kidneys, lungs, heart, gastrointestinal tract and skeletal muscles [155]. It occurs in 5–20 people per million per annum and is about three times more common in women than men. The peak incidence is between the ages of 20 and 60. There are no known geographical differences in incidence, although it does seem to be more frequent in manual workers and a number of environmental factors have been associated with an increased risk of the condition. The prognosis depends very much on which organs are involved. A relatively benign variant, scleroderma, involves only the skin, causing disfigurement and discomfort but not threatening life. However, most patients develop renal, cardiac and/or lung involvement and this reduces the 5-year survival to about 70%. One variant, known by the acronym CREST, is characterized by finger-tip calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and skin telangiectasis. The skin involvement is more limited, usually being confined to the face and hands, and visceral involvement occurs later or not at all. Nevertheless, lung fibrosis or pulmonary hypertension are common accompaniments eventually.

The patient with systemic sclerosis usually presents with tight shiny skin on the hands and face, often spreading eventually all over the body. The rapidity of progression is very variable and unpredictable. Renal involvement is the main cause of death. The renal lesion appears to be a vasculitis of small arteries, with endothelial swelling, intimal thickening and a perivascular cuff of mononuclear cells, leading to intimal sclerosis and fibrinoid change and secondary kidney avascularity and infarction. These changes mimic those occurring in accelerated hypertension, which is a complication of the disease, but are not secondary to it as they may be present even if the blood pressure is normal. Similar arterial and arteriolar changes are present in the skin, where a diminution in the numbers of capillaries has also been demonstrated.

The development of renal disease is of serious import, since renal failure and malignant hypertension are likely to occur and cause death within a few years. Almost equally serious is cardiac involvement, which may present as cardiac tamponade due to pericardial effusions or fibrosis, as heart failure due to patchy myocardial fibrosis (probably also related to small vessel disease) or as syncopal attacks due to cardiac conduction disturbances



[156–159]. Lung involvement is the other important cause of death [159].

Other organs that may be involved include the oesophagus (which characteristically lacks peristaltic activity, causing dysphagia and reflux), the small intestine (leading to malabsorption), the thyroid (fibrosis) and, very occasionally, the central nervous system and cranial nerves. Systemic sclerosis may also be associated with Sjögren's syndrome, primary biliary cirrhosis and other collagen diseases.

### *Aetiology and pathogenesis*

There is no strong evidence of genetic factors in the aetiology of systemic sclerosis [155,159]. On the other hand, there are several well-recognized environmental factors. The disease is more common in manual workers and has been associated with exposure to quartz in mining and quarrying and to vinyl chloride and other chlorinated hydrocarbons, and to ingestion of contaminated cooking oil in the notorious Spanish toxic oil syndrome [114,160–163]. A scleroderma-like syndrome has also been described during treatment with both bleomycin and L-tryptophan [164]. However, in most individual patients the aetiology is obscure.

Whatever the primary cause, the most obvious pathological lesions occur in small blood vessels and the organs they supply. It has been suggested that the initial damage caused by a number of different factors may be to the endothelial lining of those vessels, which in turn allows proteins and toxic substances access to the perivascular tissues where an inflammatory reaction leading to fibrosis occurs. A frequent feature of the disease, occurring in up to 90% of patients, is the finding of circulating antinuclear antibodies, usually of the speckled or nucleolar type; evidence suggests that the presence of anti-Scl 70 antibody is a strong predictor of lung disease in systemic sclerosis [165]. Further studies of the occurrence of such antibodies in populations exposed to quartz would be of considerable interest, since it is likely that they are produced in response to liberation of antigenic material from damaged cells.

### *Pulmonary fibrosis*

Most patients with systemic sclerosis and the CREST variant ultimately develop lung involvement [166,167]. Pulmonary fibrosis presents as gradually increasing dyspnoea. Cough is rarely an important symptom. Bilateral inspiratory crackles are often present but their absence is not inconsistent with the diagnosis. The radiograph simply shows fine irregular, predominantly basal, fibrosis (Fig. 53.9). In some patients dyspnoea seems out of proportion to the radiological changes, and in these individuals it is likely that pulmonary vascular disease (see

below) is the predominant lesion. As in idiopathic fibrosis, CT allows estimation of the extent and to some degree the stage of the disease [168,169].

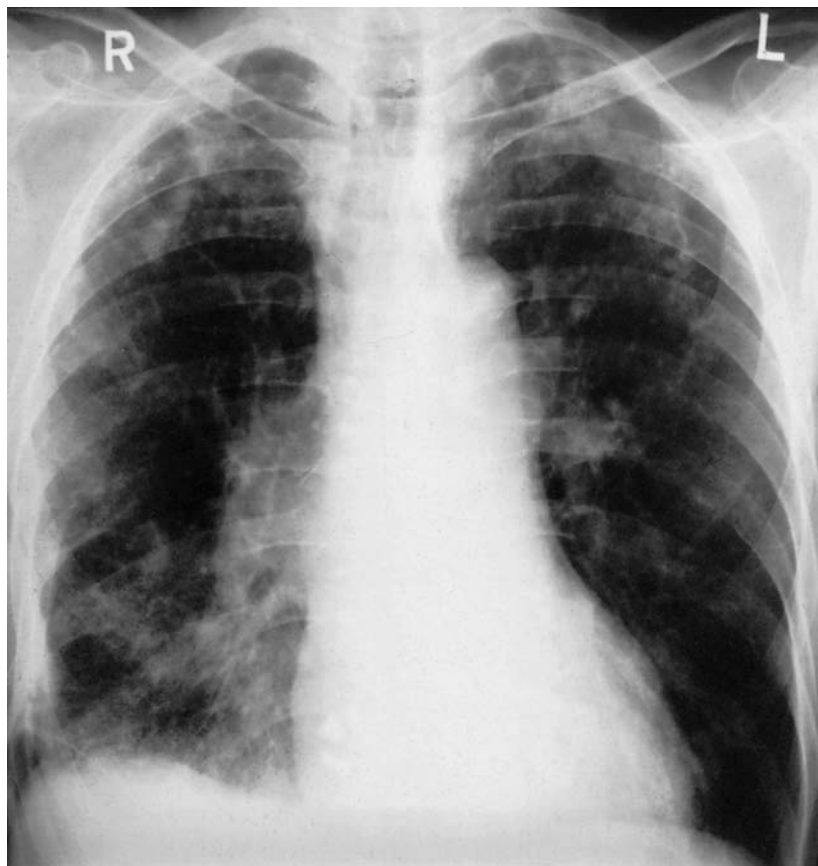
Lung function testing in the presence of radiographic and clinical abnormalities is likely to show a restrictive pattern with reduction in *DLCO*, although this does not usually fall below about 60% of predicted values [168,170]. Not infrequently *DLCO* alone is reduced, and if this reduction is severe it again suggests vascular involvement. Gallium scans may show abnormal uptake, though this is of no diagnostic value. Bronchoalveolar lavage may show further evidence of lung inflammation with increased numbers of neutrophils and eosinophils, the former being associated with a more progressive condition [171–174].

The pathological findings are of banal alveolar wall fibrosis, predominantly in the lower zones, with relatively little inflammatory cell infiltrate. Secondary bronchiolectasis may be present. Arteriolar and small arterial narrowing by intimal thickening may be present [167,175]. Recent investigations of pathogenesis have identified increased local expression of endothelin receptors in scleroderma interstitial tissue [176]; endothelins are peptide mediators involved in regulation of cell proliferation. In addition, another mediator called tissue factor, which may be involved in fibrin deposition in the lung as it is in the clotting cascade, has been found in type II pneumocytes of patients with this condition [177]. However, the mechanisms of this and other forms of lung fibrosis remain obscure.

The presence of clinical evidence of interstitial fibrosis and reduced lung function in a patient with systemic sclerosis implies a reduced life expectancy, with about a 60% 5-year survival rate [166]. However, in general the fibrosis tends to be less rapidly progressive than the idiopathic form [178] and death is due to pneumonia or other, non-respiratory, complications of the disease [159]. Cor pulmonale is rare at necropsy.

### *Pulmonary hypertension*

In contrast to pulmonary fibrosis (but recognizing that overlap between the two conditions occurs), pulmonary hypertension is a very serious and progressive complication of systemic sclerosis, particularly in the CREST syndrome [179–181]. The patient again presents with breathlessness, but this tends to be rapidly progressive. There may be crackles in the lungs, although often there are no signs. Evidence of pulmonary hypertension, such as right ventricular heave and gallop rhythm and large jugular *a* waves, may be present. The lungs may look normal or avascular and the main pulmonary arteries may be dilated. The ECG shows evidence of right ventricular preponderance. Lung function testing shows a lowered *DLCO*, often of severe degree. Such patients are very likely



**Fig. 53.9** Chest film of patient with silicosis and massive fibrosis in upper lobes who developed secondary systemic sclerosis and fine lower lobe fibrosis related to this disease. Rib fractures at right base were traumatic.

to have the antinuclear antibody anti-Scl 70, perhaps indicative of a general tendency towards vascular damage.

Pulmonary hypertension in systemic sclerosis portends a particularly bad prognosis. The patients develop cor pulmonale and most are dead within 3 years. Widespread obliterative changes are present in small arteries and arterioles and extensive arteriovenous anastomoses may be demonstrated at necropsy.

#### *Other pulmonary syndromes*

The dysphagia and gastro-oesophageal reflux associated with oesophageal disease in systemic sclerosis may be responsible for nocturnal aspiration of stomach contents and recurrent aspiration pneumonias (see Chapter 13). The rigid skin together with involvement of the muscles of respiration may cause ventilatory failure, with a restrictive pattern of lung function; in such circumstances some reversibility of the muscle weakness may occur after treatment with corticosteroids [182]. Another, very rare, syndrome responsive to corticosteroid treatment is relapsing organizing pneumonitis, which has been described in association with the CREST syndrome and primary biliary cirrhosis [183]. It presents with breathlessness and confluent areas of consolidation on the chest radiograph. Finally,

in all patients with chronic pulmonary fibrosis there appears to be an increased risk of the development of adenocarcinoma or alveolar cell carcinoma of the lung.

#### *Treatment*

With the two exceptions mentioned above, corticosteroids do not seem to be of much value in the management of systemic sclerosis unless there is evidence of overlap with other connective tissue diseases. However, there is evidence that treatment with D-penicillamine improves prognosis, may prevent development of renal and possibly lung involvement and may improve *DLCO* [184,185]. It would now be reasonable policy to treat such patients with this drug, starting with 250 mg daily and increasing the dose every fortnight to about 1.8 g daily for 2 months, then tapering it again gradually to 500 mg daily. Treatment should be continued for about 2–5 years. Side-effects include digestive disturbances, nephropathy, rashes and bone marrow suppression, some of which may require cessation of treatment. In the absence of response, little is lost by trying immunosuppressive treatment and again uncontrolled evidence suggests that cyclophosphamide may sometimes be associated with improvement in lung function [186].

There is some largely speculative evidence that patients

with pulmonary hypertension may respond to pulmonary vasodilators if treated early enough [187,188]. Hydralazine, calcium blockers and angiotensin-converting enzyme inhibitors have been tried, generally without success. Nevertheless, in view of the poor prognosis of this syndrome, carefully monitored trials of such therapy in individual patients are justified. General measures include keeping the extremities warm, lanolin for softening the skin, metoclopramide and H<sub>2</sub> antagonists for dysphagia and reflux and, perhaps, peripheral vasodilators.

### **Sjögren's syndrome**

Sjögren's syndrome is characterized by a combination of dry eyes, mouth and other mucous membranes and lymphocytic infiltrates of salivary and mucous glands [189]. It is much more common in women and is often associated with rheumatoid arthritis, SLE, Raynaud's disease, scleroderma and other connective tissue disorders. In about 50% of cases, however, it is the only disease present and is called primary Sjögren's syndrome. It is of unknown aetiology, although there is a well-described association with HLA-DR3 and it may also occur in patients with either human immunodeficiency virus infection or graft-versus-host disease following marrow transplantation. Various other viral infections, including inevitably Epstein-Barr virus, have been suspected of causing the condition but no consensus has been reached.

When Sjögren's syndrome is combined with other diseases, the lungs may show any of the manifestations of those diseases. However, there is clear evidence that a proportion of patients with primary Sjögren's syndrome, ranging in different studies from 9 to 75%, develop lung involvement [190–192]. The variation in these estimates of prevalence probably reflects partly selection of the subjects and partly how thoroughly abnormalities have been sought. It seems likely that careful evaluation of symptoms, chest radiograph and lung function in patients with Sjögren's syndrome shows respiratory involvement to be present in the majority.

### **Pulmonary involvement**

Many patients complain of a persistent dry cough with associated dry tracheobronchial mucosa [190–193]. This abnormality may be present in isolation or combined with other pulmonary lesions and has been called xerotrachea. It is associated with impaired mucociliary clearance [194]. Airways narrowing, which may be severe enough to cause reduction of forced expiratory volume in 1 s or which may only be detectable by tests of flow rates at low lung volumes, occurs in a proportion of patients. Interstitial lung disease occurs in up to one-third of patients and may present in one of two broad groups: interstitial fibrosis or

diffuse lymphocytic infiltrates [195]. These conditions present no different clinical or pathological features from those occurring in the absence of Sjögren's syndrome, the patient complaining of breathlessness and radiography and CT showing diffuse irregular or patchy infiltrates respectively [196]. However, it should be noted that there is a well-recognized risk of the lymphocytic infiltrate in the lungs developing into a malignant lymphoma or reticulum cell carcinoma of highly undifferentiated type [197]. Not surprisingly, in view of the lack of airway secretions, respiratory infections and pneumonia occur relatively frequently in Sjögren's syndrome.

### **Treatment**

No curative treatment is available for Sjögren's syndrome and local measures may be necessary for symptomatic relief. The finding of abnormal lung function in a patient with the syndrome should prompt further investigation, but it would be wise not to rush to treatment of interstitial disease with immunosuppressant drugs until follow-up makes clear whether clinically significant progression is occurring. In most cases it is not [198]. Pulmonary infiltration by lymphocytes often responds to prednisolone if thought necessary; a dose of 60 mg daily is given until improvement occurs and then tapered to a maintenance dose [197]. Azathioprine has also been used with reported initial response [195]. It is not known whether this treatment prevents progression to lymphoma; if this tumour develops, appropriate chemotherapy is necessary.

### **Ankylosing spondylitis**

Ankylosing spondylitis is a condition in which progressive inflammation of spinal joints leads to ankylosis. It occurs predominantly in young adult males [199] and 90% of its victims carry the HLA-B27 antigen [200]. Beyond this strong genetic predisposition, the provoking cause or causes are not known. Apart from ankylosis of the spine, which may range in severity from involvement of sacroiliac joints only to development of a completely rigid bamboo spine, the joints of the chest wall, hips and knees may be involved, as may other large joints [201]. Some 20% of patients develop iritis and about 4% a proximal aortitis with aortic valve regurgitation. Amyloidosis may occasionally occur in patients with long-standing disease.

The patient usually presents with low backache, often referred down the backs of both legs, with stiffness in the mornings and on resting. The condition normally progresses only slowly and does not alter life expectancy or cause severe disability. However some patients run a more rapid course, early development of systemic signs or of limb joint involvement indicating that this is the case.

### Lung involvement

The lungs are usually only involved in patients with a long history of joint disease [202–205]. Two conditions are recognized. Firstly, if there is severe involvement of the thoracic cage, a restrictive pattern of lung function may occur and rarely this may be sufficient to cause dyspnoea. Usually, however, the function of the diaphragm allows adequate ventilation [206]. Secondly, some 1% of patients with long-standing, though not necessarily severe, disease may develop upper lobe fibrosis (Fig. 53.10). Again this is rarely progressive or disabling but provides a diagnostic puzzle if the association is not known. The author has seen it occur in a patient whose only evidence of ankylosing spondylitis was sacroiliac joint fusion and HLA-B27 positivity; others have also reported this, indicating that the fibrosis is clearly not secondary to a rigid chest wall [207]. The bronchiectasis that occurs secondarily to the fibrosis may become the seat of aspergillomas and thus the cause of haemoptysis. Locally invasive aspergillosis has been reported [208]. Colonization with *Mycobacterium kansasii*, *M. avium-intracellulare* and *M. scrofulaceum* has also been reported [205,207,209], though in such cases it would be difficult to know whether the mycobacteria or the ankylosing spondylitis are the cause of the upper lobe disease.

In general, no treatment is required for the pulmonary complications of ankylosing spondylitis. The important point is to be aware of the association with upper lobe fibrosis so that the patient is spared unnecessary treatment for tuberculosis.

### Other connective tissue disorders

Although respiratory muscle weakness and respiratory failure may occur in acute forms of dermatomyositis, direct lung involvement is rare in the dermatomyositis–polymyositis syndrome [210–212]. When it occurs, a subacute diffuse interstitial fibrosis with an active inflammatory component is usual. Often this is responsive to steroid treatment [213], although occasionally rapidly progressive fibrosis resistant to steroids and immunosuppressants may occur [214,215]. Bronchiolitis obliterans organizing pneumonia and diffuse alveolar damage have also been described [216]. Dermatomyositis is of course also one of the paraneoplastic syndromes associated with lung cancer. The pulmonary aspects of polyarteritis nodosa and related syndromes have been described in Chapter 38. ‘Mixed connective tissue disease’ is the term used to describe an illness showing features of several of the other conditions, rheumatoid, SLE, systemic sclerosis and polymyositis [217]. Not surprisingly, pulmonary fibrosis and pleurisy with effusions may be features of the syndrome, occurring in about one-quarter of the patients [218]. Management is along the lines indicated for the

individual diseases above, and there is some evidence that the interstitial lung involvement may respond to corticosteroids. Giant cell arteritis may very rarely be associated with a granulomatous interstitial pneumonitis or with involvement of intrapulmonary elastic arteries [219,220].

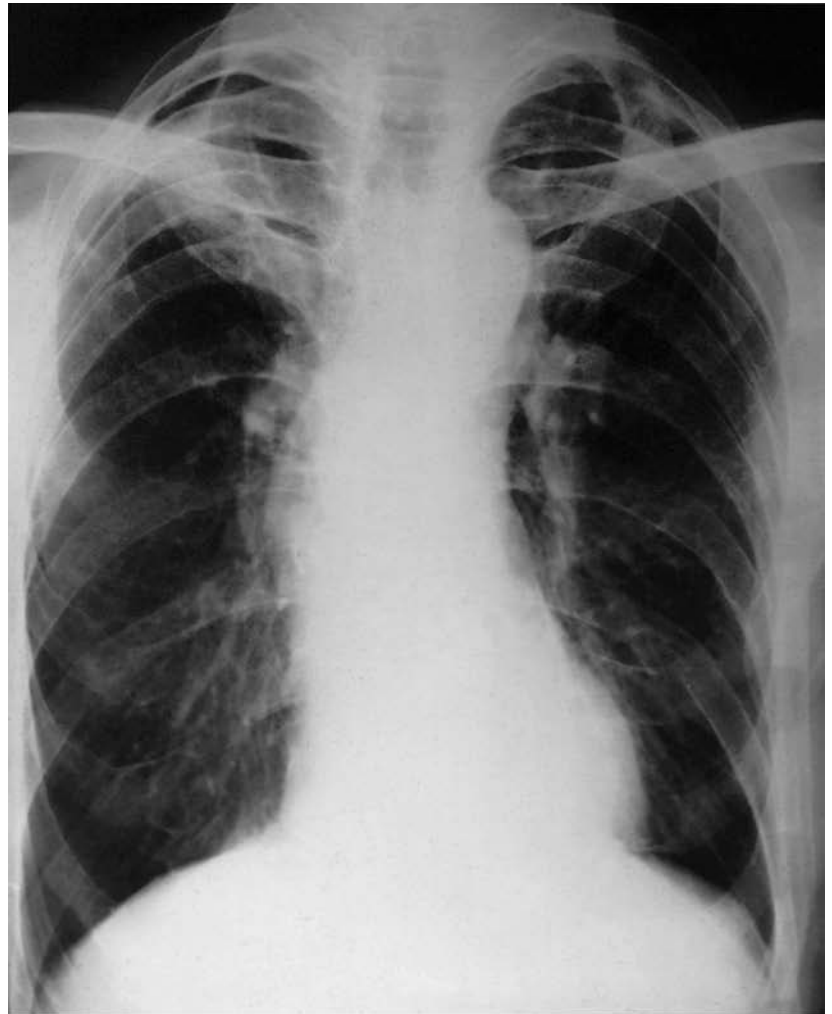
Behçet’s syndrome, a condition of unknown aetiology characterized by recurrent oral and genital ulceration, iritis, thrombophlebitis and arteritic lesions in other organs, occasionally involves the lung [221,222]. When it does, the lesions appear to be multiple recurrent infarcts with haemoptysis, caused by pulmonary arteritis and aneurysm formation. Haemoptysis may be fatal and anti-coagulants are contraindicated. Recommended treatment is with high-dose prednisolone and cyclophosphamide; if haemoptysis and thrombosis persist, stanozolol or phenformin have been suggested to enhance fibrinolysis [223]. The Hughes–Stovin syndrome may be a variant of this disease; it is characterized by recurrent thrombophlebitis and pulmonary artery vasculitis and aneurysm formation [224,225].

Relapsing polychondritis is a rare condition in which recurrent episodes of inflammation, probably mediated by autoantibodies, occur in cartilage [226–230]. It is sometimes associated with rheumatoid and other collagen diseases. Inflammation and destruction of ear and nasal cartilage, episcleritis and laryngotracheobronchial damage may occur. The latter results in airway involvement by inflammatory cells, destruction of cartilage, narrowing of the lumen and increased collapsibility. The patient complains of breathlessness and stridor may be audible. The progress of the condition may be slowed by high-dose corticosteroids, but once tracheal narrowing has occurred by fibrosis the patient is likely to suffer recurrent respiratory infections and increasing breathlessness.

### Some other systemic disorders with lung involvement

#### Rheumatic fever

Apart from the acute pulmonary effects of heart failure during rheumatic fever, a specific pulmonary infiltrative condition, rheumatic pneumonia, may occur. The patient complains of cough, dyspnoea and pleurisy and there may be haemoptysis. The radiograph may show patchy mottling or appearances suggestive of pulmonary oedema. The pathological lesions are patchy, and include alveolar wall infiltration with leucocytes, capillary endothelial necrosis and intra-alveolar haemorrhage and exudation [231]. Hyaline membranes have been described and organization with fibrosis may occur. Corticosteroids are recommended for treatment on an anecdotal basis.



(a)



(b)

**Fig. 53.10** (a) Upper lobe fibrosis with elevated hilar shadows in man with (b) sacroiliac ankylosis.

### Syphilis

Diffuse consolidation of the lung may be a feature of fatal congenital or of tertiary syphilis [232–235]. Gummas may occur in trachea, bronchi or lung, where their diagnosis nowadays is a matter of considerable surprise to the pathologist examining a biopsy or specimen of lung removed under suspicion of being a carcinoma. Diffuse pulmonary fibrosis, cavitation and bronchial stricture have been described. The offending organism, *Treponema pallidum*, is sensitive to penicillin.

### Ulcerative colitis

Minor abnormalities of pulmonary function, often of an obstructive type, are quite frequent in ulcerative colitis [236], although the disease may also be associated with lung disease separate from the well-known association of alveolitis with sulfasalazine (sulphasalazine) treatment (see Chapter 55). Most commonly there appears to be an inflammatory reaction affecting the airways, which may simply cause a persistent cough or may present as bronchiectasis or bronchiolitis obliterans [237–241]. In some patients the condition has presented as a progressive bronchiectasis following colectomy. It is distinct from smoking-related bronchitis and is well described in non-smokers. The pathological changes are basal cell hyperplasia, basement membrane thickening and submucosal inflammatory cell infiltration. Although the aetiology is obscure, it is likely that the disease represents a bronchial reaction to whatever environmental or immunological factor is causing the colitis. Interestingly, there is evidence of response to corticosteroids, either inhaled or systemic, unless there is a marked infective element [239]. There is also a report of an acute interstitial pneumonitis in association with ulcerative colitis and pyoderma gangrenosum, also responsive to corticosteroids [242].

### Crohn's disease

Occasionally Crohn's disease, or regional enteritis, coexists with sarcoidosis, although despite the histological similarities between the two conditions this is very rare [243]. Apart from this, there are reports of interstitial lung disease, lung functional abnormalities and airway inflammation in association with Crohn's disease in both adults and children [239,244,245], though this appears to be less common than with ulcerative colitis. Amyloidosis involving the lungs may also occur [246].

### Coeliac disease

There seems to be a complex relationship between coeliac disease and interstitial lung disease [247–251]. Occasionally, a syndrome of lung restriction indistinguishable from

idiopathic fibrosis has been described in patients with coeliac disease. Moreover, it has been suggested that coeliac patients may be at excess risk of bird fancier's lung, although it should be noted that they often have bird antibodies in their blood derived from eggs in the diet and distinct from the true avian antibody associated with bird fancier's lung. It seems likely that there is a true but rare association of interstitial fibrosis with coeliac disease, the aetiology being obscure.

### Whipple's disease

This condition of arthritis, weight loss, fever and steatorrhoea is characterized by fat-filled foamy macrophages and sarcoid-like granulomas in the intestinal wall and other affected tissues. It occurs mainly in middle-aged men and is caused by a Gram-positive bacillus also called after Whipple [252]. Some patients have been described as having patchy interstitial lung infiltrates and restrictive lung function [253].

### Acute pancreatitis

Pleural effusion is a well-recognized accompaniment of acute pancreatitis (see Chapter 43). A proportion of patients acutely ill with pancreatitis may develop adult respiratory distress syndrome, and it is thought that this is due to release of inflammatory mediators in ascitic fluid that induce production of interleukin 1 and tumour necrosis factor in the lung [254,255]. Circulating pancreatic enzymes themselves may also be relevant and the author has seen one patient develop rapidly progressive lower zone emphysema after an acute attack of pancreatitis associated with very high amylase levels.

### Waldenström's macroglobulinaemia

This is a condition akin to myeloma that occurs predominantly in elderly males and which is characterized by malaise, a bleeding tendency, hepatosplenomegaly and the presence of a paraprotein, usually IgM, in the blood. It generally runs a benign course. However, these patients are liable to pulmonary infections and occasionally present with pulmonary infiltrates of lymphoid or plasma cells, showing characteristic staining for the paraprotein [256,257]. In such cases, treatment with chlorambucil, melphalan or cyclophosphamide may be successful.

### Renal dialysis and transplantation

Patients being treated for renal failure and those on immunosuppressants are at increased risk of pulmonary infection [258–262]. Patients on long-term dialysis may develop metastatic calcification and this has been reported

to involve the lung to sufficient degree to cause respiratory failure and death. The patient presents with increasing dyspnoea, usually starting some months after the start of dialysis, and very fine pin-point shadowing may be visible on the chest film. It has also been described in patients after successful renal transplantation. CT and radiophosphate imaging provide useful methods of diagnosis when, as is often the case, the chest radiograph shows non-specific shadowing. The mechanism is usually thought to be deposition of calcium magnesium phosphate in the lungs as a result of secondary hyperparathyroidism due to low levels of 1,25-dihydroxyvitamin D<sub>3</sub>, with reduced renal phosphate excretion. However, this seems unlikely to be

the case in patients with successful renal transplants, in whom the mechanism remains obscure.

### Neuromuscular disease

A wide variety of neuromuscular diseases, including muscular dystrophies, Parkinson's disease and myxoedema, may cause ventilatory insufficiency leading to recurrent infections through failure to clear secretions and to chronic respiratory failure. In selected patients, management has been much improved by domiciliary ventilatory support (see Chapter 58). These conditions are discussed in Chapter 45.

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# OCCUPATIONAL LUNG DISEASES

ANTHONY SEATON

Most of the diseases with which this book is concerned are probably caused by the inhalation of harmful matter, be it microorganisms, tobacco smoke, allergens or other particles. While these broad classes of substances may be encountered in the general environment, many of them occur also in the workplace in greater amounts as a result of industrial processes; a broad range of lung reactions may therefore occur as a result of workplace exposure.

## Historical aspects

It is likely that humans have suffered from occupational asthma since the change from hunting to agriculture as a means of providing food. However, the first recorded mention of breathlessness among handlers of grain was by Ramazzini, the father of occupational medicine, in 1713 [1]. The harmful effects of mining probably also date back to prehistory, when humans first started to dig underground for flints to make arrowheads and axes and thus exposed themselves to quartz dust. Certainly in Roman times it was recorded that mining was a dangerous trade, fit only for convicts and slaves. In 1556 Georgius Agricola [2] recorded the dangers of suffocation underground due to toxic fumes and pointed out that breathlessness due to inhalation of dust resulted in the premature death of many miners. However, these early accounts appear to have been sporadic and it was not until the Industrial Revolution in Britain that the coincidence of increasing amounts of occupational disease and adequate medical and scientific expertise allowed rapid progress to be made in their understanding. The diseases that came to attention at this time, in the eighteenth and early nineteenth centuries, were those afflicting knife grinders, pottery workers, coal-miners and stonemasons, the classical mineral pneumoconioses. By the middle of the nineteenth century, silicosis had been differentiated from tuberculosis [3] (which was of course rife in the new industrial cities at that time) and a peculiar black pigmentation of the lungs had been described in Scottish coal-miners [4]. Occupational exposure was also known to cause asthma occasionally [5].

In 1775, before the earliest descriptions of pneumoconiosis, cancer of the skin had been recognized by Pott as an occupational disease in the apprentices of chimney sweeps [6], and lung cancer was first described as an occupational disease in German metal miners in 1879 [7]. Indeed, it was as a result of the recognition that occupational factors were relevant to the genesis of cancer that scientists first started to study this disease and its mechanisms.

The twentieth century has seen an increasing recognition of the many lung diseases that can be caused by exposure to harmful substances in the workplace. Increasing use of asbestos from about 1900 until the middle of the century was clearly shown to be related to pulmonary fibrosis in 1930 [8], bronchial carcinoma in 1949 and mesothelioma in 1960 [9,10]. A range of other lung carcinogens, including radiation, arsenic, nickel, chromates and halo ethers, was described. The first of many causes of allergic alveolitis, inhalation of mouldy hay, was recorded in 1932 [11], and subsequently many other causes of this disease and of occupational asthma have been recognized. Berylliosis was described first in Germany in 1933 and in the USA in 1943 [12,13]. The public has been made dramatically aware of possible workplace hazards by a series of horrifying episodes of industrial gassings, the worst of which killed many thousands of people living around Bhopal in India in 1985, when a cloud of methyl isocyanate escaped from a factory producing pesticides [14].

## Types and frequency of disease

It is now clear that many of the broad types of bronchopulmonary disease may be caused or made worse by exposure to harmful substances in the workplace. Thus pulmonary fibrosis may result from exposure to asbestos or quartz, pulmonary oedema and bronchiolitis from inhalation of toxic gas, allergic responses from exposure to organic dusts and some chemicals acting as haptens, pleurisy from inhalation of asbestos, cancer from a range of carcinogens, and infection from workplace exposure to

microorganisms. The workplace may be only one factor in the causation of some of these conditions, which are discussed in more detail elsewhere in the book. A summary of lung responses to workplace hazards is given in Table 54.1.

It is difficult to know how widespread occupational lung disease is, even in advanced nations. Data obtained from workman's compensation and disability awards are likely to include only cases that fulfil quite strict criteria for diagnosis, usually from a rather selective list of conditions. Similarly, data from statutory notifications of disease are only representative of those required to be notified and again are often the tip of an iceberg. On the other hand, surveys of population samples are likely to have to rely largely on self-determination of the causes of illness and therefore probably overestimate prevalence. In the British Labour Force Survey of 1990, which questioned a random sample of the workforce in 60 000 households, some questions were added about occupational disease. The response indicated that of a workforce of about 20 million, some 30 000 people had asthma and 60 000 had other lung disease that they attributed to their work, in addition to a substantial number who thought that their lung disease was made worse by their work [15]. While these figures probably represent an overestimate, they should not be dismissed lightly, since patients often discover the relationship of their illness to work before their doctors. It might be argued that patients in general have an unsophisticated concept of disease causation, but often so do doctors. In particular, clinicians have a marked tendency to attribute disease to one cause, when epidemiology teaches that with most diseases there are multiple possible aetiological contributors. For example, it is usual

to attribute lung cancer or chronic airflow obstruction to smoking if the patient does indeed smoke. However, many epidemiological studies have shown that workers in a number of dusty industries have an increased risk of one or other of these diseases compared with non-exposed people of the same smoking status. Thus, although it can never be proved in an individual case with clinical certainty, in a population of dust-exposed workers there may be individuals who would not have developed disabling lung disease had they not been exposed to the workplace hazard. Who is to say that such people are wrong in attributing their illness to work rather than cigarettes when it is likely that both have played a part?

Perhaps the best information currently available comes from the UK SWORD survey, in which occupational and chest physicians report cases of what they think are occupationally caused lung disease on a regular and confidential basis [16,17]. Although almost certainly giving an underestimate because of failure to sample all those doctors who see such patients, this allows some estimate of incidence of such diseases to be made. Results from recent surveys have shown, as expected, that asthma and mesothelioma rank as the most commonly recognized conditions, being reported in about 950 and 650 patients each year respectively. There are good reasons to believe that the true incidences of these conditions in the UK are approximately 3000 and 1000 respectively. Two other conditions are apparently more common than was originally anticipated: acute inhalation injury, which is reported in about 300 people each year, and the syndrome of bronchial hyperreactivity following such exposures, sometimes called reactive airways dysfunction syndrome. The latter condition is responsible for a proportion, as yet undeter-

**Table 54.1** Lung responses to workplace hazards.

Type of disease	Postulated mechanism	Typical exposure
Diffuse fibrosis	Macrophage-mediated Delayed hypersensitivity	Asbestos Beryllium
Nodular fibrosis	Macrophage-mediated	Quartz, coal
Emphysema	Neutrophil elastase release	Coal, cadmium
Chronic bronchitis	Airway inflammation	Dusts and fumes
Acute bronchitis	Airway inflammation	Irritant gases and fumes
Airway hyperreactivity, bronchiolitis obliterans,		
Asthma	Airway hypersensitivity	Flour, wood, isocyanates
Byssinosis	Endotoxin complement activation	Cotton dust
Allergic alveolitis	Complement activation Cytokine release	Thermophilic actinomycetes
Bronchial carcinoma	DNA damage	Asbestos, chloromethyl ether
Pleural mesothelioma	DNA damage	Asbestos

mined, of reports registered under both asthma and inhalation injury categories. It is likely that the same relative frequencies of different occupational lung diseases as reported in SWORD are present in other industrialized countries, although the actual numbers will differ in relation to the efforts made nationally to prevent them.

## Deposition and clearance of particles

The details of the lung's defences are described in Chapter 4. In brief, the harmfulness of an inhaled particle depends on its inherent toxicity, its ability to penetrate to the site at which it can exert its effects and the amount retained in the lung. Penetration depends on the ability of the particle to overcome the physical forces tending to bring it into contact with the walls of the airways, namely sedimentation, impaction, interception, diffusion and electrostatic precipitation [18].

1 Sedimentation, or movement under the influence of gravity, proceeds at a rate that depends on the density and the square of the diameter of the particle; thus large dense particles fall rapidly and are deposited primarily in the nose, mouth and larger airways.

2 Impaction occurs when a particle fails to follow a change in direction of airflow and strikes the airway wall; it depends on the particle's momentum (the product of mass and velocity) so again large particles are filtered out by the larger airways.

3 Interception is a factor in the deposition of fibrous aerosols, when the ends of long thin particles strike the airway wall.

4 Diffusion occurs as a result of Brownian motion, due to bombardment of very small particles by gas molecules in the air, and is particularly important with respect to deposition on alveolar walls of particles of less than  $0.5\mu\text{m}$ . It is also the mechanism whereby inhaled toxic gases exert their effects on the airways and alveoli.

5 Electrostatic precipitation was until recently not thought to be important because of the conducting properties of mucus. However, studies in rats have shown considerably greater lung retention of highly charged compared with uncharged particles, suggesting that the effect of charge may be pathologically significant [19].

An indication of the likelihood of a particle's deposition in various parts of the respiratory tract in relation to its aerodynamic diameter, i.e. its diameter expressed in terms of it behaving as a sphere of unit density, is shown in Fig. 54.1 [20]. Another representation of lung deposition patterns is given in Fig. 54.2, which shows that the highest rate of alveolar deposition occurs with a particle size around  $0.02\text{--}0.06\mu\text{m}$  ( $20\text{--}60\text{nm}$ ). This is the size range of particles in fume and in the nucleation mode of ambient air pollution [21].

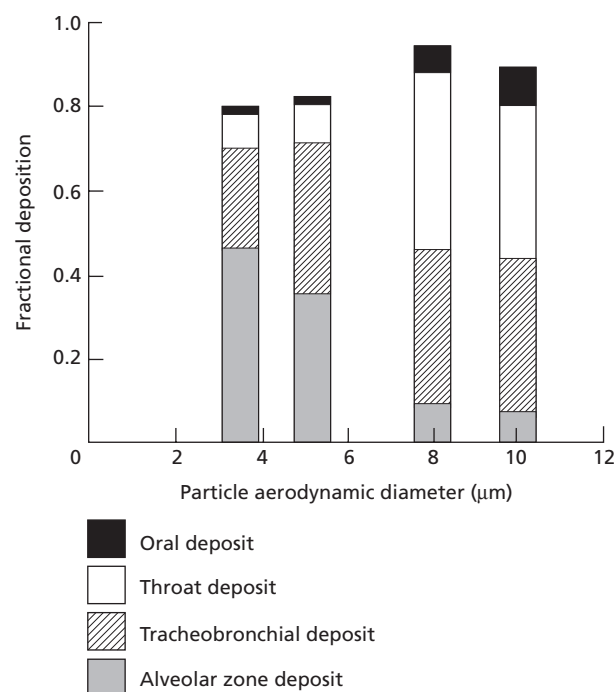
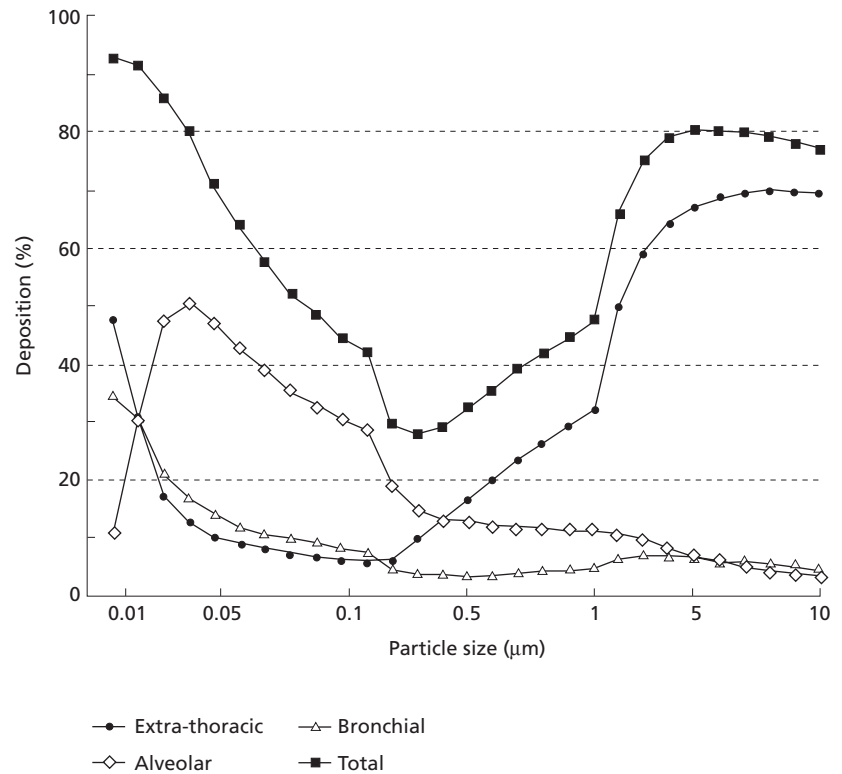


Fig. 54.1 Fractional deposition in different parts of the respiratory tract of particles of differing aerodynamic diameters. (From Emmett *et al.* [20].)

Knowledge of the physical behaviour of particles in the respiratory tract is particularly important in the design of dust-sampling instruments. These play a crucial part in monitoring the exposure of workers to aerosols in the workplace and, increasingly, in measuring exposures as part of epidemiological studies aimed at producing information about exposure-response relationships on which preventive action can be based (see Chapter 3). Such instruments are now available that can measure 'respirable' particles ( $<7\mu\text{m}$ ),  $\text{PM}_{10}$  ( $<10\mu\text{m}$ ) (Fig. 54.3) [22] and 'inspirable' particles that closely resemble in size those passing into the human nose and respiratory tract [23]; others can fractionate a mixed dust cloud into particles of different aerodynamic sizes. All these instruments allow the dusts to be weighed. However, not yet available is a simple method for measuring asbestos or other fibres in the air. These still have to be collected on a filter and then counted, a laborious and rather unreliable procedure [24].

Once deposited in the respiratory tract, the fate of a particle depends on the body's clearance mechanisms and on its ability to resist them. Larger particles, deposited on the airways, are generally cleared efficiently within 24 h by the mucociliary mechanism, though such clearance may be prolonged if the airways are damaged by cigarette smoke or fume inhalation [25,26]. Such cleared particles are either coughed up or swallowed. Particles reaching the acinus are beyond the region of cilia and production of mucus





**Fig. 54.2** Lung deposition and particle size: highest rate of deposition occurs with submicrometre-sized particles. (From Committee on the Medical Effects of Air Pollutants [21] with permission.)

and are cleared much more slowly [27]. Deposition occurs predominantly at bifurcations of alveolar ducts [28]. The mechanism of particle removal involves ingestion by alveolar macrophages [29] or type I alveolar epithelial cells [30]. Having ingested a particle, the type I alveolar cell either delivers it into the interstitial space of the alveolar wall, where it can be taken up by interstitial macrophages or flow with interstitial fluid into the lymphatics, or dies and passes into the alveolar lumen [31]. The macrophage also seems to have several options: it may migrate up to the mucociliary escalator, perhaps impelled by a flow of alveolar surfactant; move to the terminal airways due to a viscosity gradient [32]; or may pass between the alveolar epithelial cells, presumably temporarily unlocking the tight junctions by proteolytic enzyme action, into the interstitial space. It may then proceed into the lymphatics to pulmonary and hilar nodes, or pass back into the airways at the end of the terminal bronchiole, through lymphatic sumps [30]. It seems likely that all these mechanisms operate, though their relative importance has not been established. It is probable that alveolar clearance occurs over a prolonged period, the first particles being removed within 24 h but many remaining for months and even years [33]. The presence of dust pigment around the centre of the acinus is of course a finding familiar to all pathologists.

The harm exerted by the particle once inhaled depends on its biological, chemical and physical properties, and on the amount inhaled. Biological factors include its ability to

act as a sensitizer or to overcome attack by macrophages, for example allergens such as grass pollen (up to 100 μm in diameter) provoke a primarily nasal reaction of a hypersensitivity type, while mycobacteria cause alveolar disease by being resistant to killing by macrophages. Chemical factors include the effects of gases or particle surfaces on cell or lysosomal membranes, for example the cytotoxic effects of sulphur dioxide and quartz. Physical factors apply when the particle is too large to be removed, as with asbestos fibres which are only partially ingested by macrophages. In addition, recent studies of microfine particles of less than 50 nm diameter have shown paradoxical toxicity in rats at inhaled concentrations too low to cause pathological effects when the same concentration is inhaled in the form of larger, micrometre-sized respirable particles [34]; this strongly suggests that physicochemical factors associated with particle surfaces may be responsible for toxicity in particles associated with air pollution and fumes such as those derived from welding and metal cutting [35]. Finally, the total mass of dust inhaled is clearly important, in that the lung's defences presumably evolved to enable removal of the modest amounts of particulate matter found in the ambient air (mainly bacterial, fungal and floral) and not the large amounts of inorganic matter that may be inhaled in the workplace. Nevertheless, a measure of the efficiency of these mechanisms is that a coal-miner may easily inhale 4 kg of coal dust in a lifetime but at death only about 10–30 g remain in the lungs [36].



**Fig. 54.3** A personal respirable dust sampler. The filter holder with size-selective orifice is close to the breathing zone and connects to a battery-operated pump on the belt.

## Mineral pneumoconioses

The term 'pneumoconiosis' was coined by Zenker [37] to define a group of diseases caused by inhalation of dust. It usually implies a tissue reaction within the lung to the dust and, while strictly including diseases due to organic dusts, is generally used in relation to diseases and radiological abnormalities caused by mineral dusts. The most common pneumoconioses are coal-workers' pneumoconiosis, silicosis and asbestosis, although very many other types have been described, usually due to inhalation of mixed dusts containing silicates. They range in seriousness from asbestosis, which not only causes diffuse fibrosis but also increases substantially the patient's risk of lung carcinoma, through silicosis that causes progressive patchy nodular fibrosis, to conditions such as stannosis, siderosis and baritosis, which simply cause radiological change without physiological effects.

The inhalation of mineral dust may also have effects other than leading to pneumoconiosis, such as carcinogenesis and initiation of bronchitis or emphysema. These effects are discussed in subsequent sections.

## Coal-workers' pneumoconiosis

### Epidemiology

Coal-workers' pneumoconiosis is virtually confined to underground coal-miners, though it may occur in any place where a worker is exposed to high levels of coal dust in poorly ventilated conditions. Thus it has been described in coal trimmers, loading coal in the holds of ships, and in men and women sorting coal on surface screens. Coal is usually mined underground by one of two methods, long wall or room and pillar. In the former, used widely in Europe, all the coal in a seam is taken in a series of cuts by a machine across a face of up to 200m. The roof above, usually composed of quartz-bearing rock, is supported by a row of hydraulic supports that are advanced after each cut, allowing the roof behind to fall in. The faceworkers operate the coal-cutter and roof supports in the tunnel along the face, which is ventilated by air blown down an access tunnel (roadway), across the face and out through a return roadway. The height of the face may vary from 46 cm to 2.5–3m, depending on the height of the coal seam. Dust is generated largely by the coal-cutter but also by the movement of roof supports, by the collapse of the roof as these are moved forward, and by the transport of coal from the face. As the face progresses into the coal seam, so the roadways at either end are driven forward through coal as well as through the rocky strata. This may be done by powerful drilling machines, by placing and firing explosives or by other traditional tunnelling methods, all of which generate dust.

Room and pillar mining is used more widely in the USA. It involves driving a series of tunnels into the coal seam and linking them by cross-tunnels, leaving square pillars of coal to support the roof. Additional support is given usually by roof-bolting, where loose strata above the coal are fixed by drilling a bolt through them into firmer rock above. This form of mining is the more traditional and is used when there is sufficient coal for it to be economical to leave the pillars. It is the method widely used in mining for many other minerals.

From this brief description, it can be seen that miners may be exposed to dust not only from the coal seam but also from roof, floor and intrusions of rock (dirt bands) into the seam. Miners driving the roadway (known as hardheaders, tunnellers, rippers and brushers in different mining areas) are likely to be exposed to a mixture of mineral dusts. Other underground workers are also exposed to the same dusts, though generally more diluted, in the return roadway as well as to dust generated at points where coal is tipped from one transportation system (conveyor belt or bogie) to another. Therefore even miners working in the same colliery may show different types of pneumoconiosis depending on the work they do. It should be noted that ventilation of a mine by blowing air

in one end and out the other across a long face wall does not adequately ventilate blind tunnels off the main airstream. In room and pillar mining, curtains (brattices) are hung in appropriate places to direct the flow of air away from the area where dust is being generated. In blind tunnels, forced ventilation or extraction by ducting is necessary. Again, absence of these provisions puts some men at greater risk than others.

Understanding of coal-workers' pneumoconiosis is complicated further by the fact that coal and coal dust differ dramatically from place to place. Some coals, formed under very high pressure, are particularly hard and very high in carbon content (and therefore combustibility), anthracite being the hardest of these. They are known as high-rank coals. Softer bituminous and steam coals leave more ash when burnt and are said to be of lower rank. The ash remaining in the fireplace or a coal-fired boiler is a mixture of quartz, kaolinite, mica and other silicate minerals. These are also present in the dust the miner inhales and in the lungs at postmortem, influencing the risk of pneumoconiosis and the type of pathological reaction.

Immediately after the Second World War, some 3000 men per annum were being diagnosed as having coal-workers' pneumoconiosis in the UK [38]. The realization of this epidemic led to a series of investigations by the Medical Research Council and the National Coal Board that have gone a long way to understanding the epidemiology and aetiology of the disease [39,40]. These studies have shown that the risk of pneumoconiosis varies considerably from place to place, roughly in relation to the rank of coal, high ranks being the most dangerous [41]. They have also demonstrated a relationship between a miner's exposure to respirable dust and risk of disease (Fig. 54.4); the mean of these relationships in different collieries has been used as information on which to base dust standards for protection of the workforce in coal-mines [42,43]. Other studies have shown relationships between exposure to relatively high levels of quartz in the dust and rapidly progressive pneumoconiosis or probable silicosis [44], and between dust exposure and the risks of bronchitis and emphysema [45–48]. In the UK, this information has been used by the coal industry as a basis for preventive measures and each year very few active miners are diagnosed as having pneumoconiosis; increasingly these are older men, coal-workers' pneumoconiosis in this country being a rare disease in miners under the age of 50 [49]. The disease does of course occur throughout the world, wherever coal is mined. In western Europe and the USA in general, measures of dust control have resulted in a decreased prevalence of disease, although in newly emerging industrial nations such as China and India it is likely that new cases will be seen frequently unless appropriate preventive measures are taken.

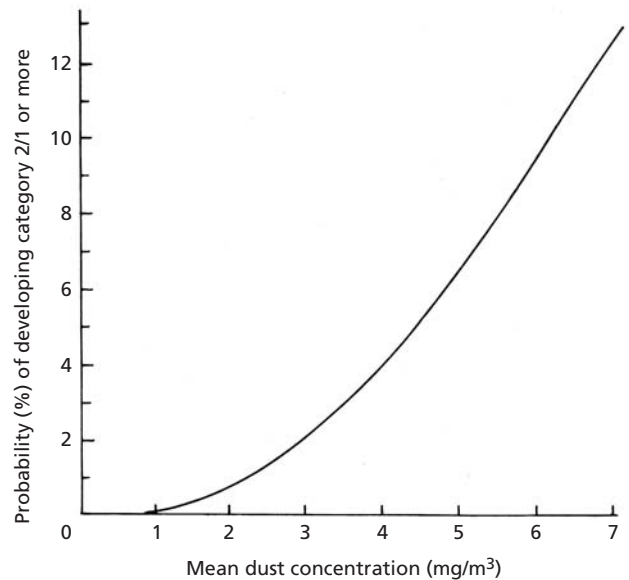
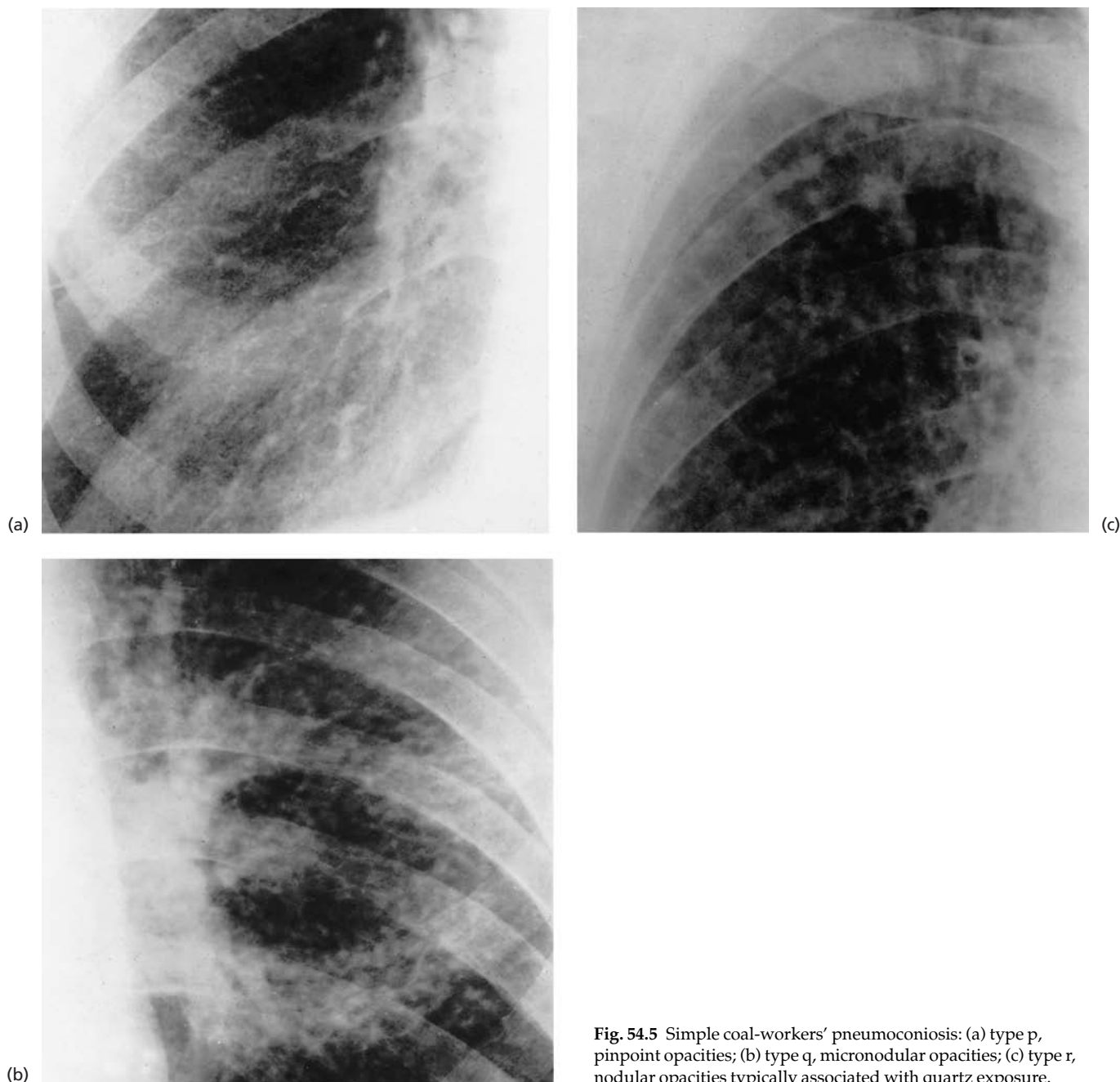


Fig. 54.4 Risk of category 2 simple coal-workers' pneumoconiosis in relation to average dust exposure over a working lifetime.

## Clinical features

### Chest radiography

The earliest sign of coal-workers' pneumoconiosis is nodular shadowing on the chest radiograph. These appearances are usually classified according to the International Labour Office (ILO) standard classification, which is described in Chapter 3 [50]. The nodules are most commonly of the q type (1.5–3 mm in diameter), though p (<1.5 mm) and r (>3 but <10 mm) lesions may occur, and it is quite usual to see examples of at least two of these types in any one miner's film. They are usually more profuse in the upper and middle zones. The profusion of nodules (categories 1–3) is an indirect measure of the miner's exposure to respirable dust and thus increases with increasing exposure, although progression of the p and q types does not occur after dust exposure has ceased. There is evidence that the larger nodules, which are usually relatively sparse, result from quartz exposure and represent silicotic nodules pathologically [36,51]. They may progress both in size and profusion after exposure has ceased. The very small p lesions seem to be related to the combination of pneumoconiosis and emphysema, while the q lesions represent overlapping coal macules [36]. Very rarely, the onset of severe emphysema may result in obscuration of rounded opacities, although spontaneous regression in the absence of emphysema does not occur in true coal-workers' pneumoconiosis. These distinctions between the radiological types of the condition are far from clear-cut since there is considerable interobserver and intraobserver variation in classifying films according to type of opacity. Typical examples are illustrated in Fig. 54.5.



**Fig. 54.5** Simple coal-workers' pneumoconiosis: (a) type p, pinpoint opacities; (b) type q, micronodular opacities; (c) type r, nodular opacities typically associated with quartz exposure.

The early nodular lesions are frequently accompanied by Kerley B lines. However, it has been recognized that coal-miners also develop other small irregular and linear shadows on their radiographs, similar to those occurring early in asbestosis [52]. These tend to occur more at the lung bases and to be of relatively low profusion, rarely more than category 1. There is evidence that their prevalence is related not only to exposure to respirable dust but also, unlike the rounded opacities, to age and cigarette smoking [53]. Pathologically and physiologically they seem to be related to the presence of emphysema

and airflow obstruction [52], and it is likely they represent paraseptal deposition of dust and the pathological reaction to it. There is no evidence that they are relevant to subsequent risks of progressive massive fibrosis (PMF).

The above description applies to simple coal-workers' pneumoconiosis, a condition in which only small opacities are present. However, a proportion of coal-miners develop so-called complicated pneumoconiosis (because originally it was thought that this was a consequence of complication of simple disease by tuberculosis) or PMF

[54,55]. This condition presents as a larger shadow, equal to or greater than 1 cm in maximum diameter, often initially in the right upper zone (Fig. 54.6). The lesion gradually grows, becomes more radiodense and causes distortion of adjacent lung and bronchi often with bullous emphysema. Frequently similar lesions appear in other parts of the lung and run a similar course. The course is very variable and often becomes arrested at a relatively early stage, although in some cases both lungs ultimately may be almost completely replaced by PMF and emphysema, with resultant cor pulmonale.

While a miner with a high category of simple pneumoconiosis is at greatest risk of developing PMF, it is now clear that simple pneumoconiosis need not be visible on a radiograph for PMF to occur [55]. Although simple pneumoconiosis does not normally progress or regress after dust exposure ceases, it has been shown that PMF commonly occurs after the miner has left the industry, sometimes as much as 20 years later [55]. This interesting fact suggests strongly that simple pneumoconiosis and PMF may be two separate diseases, both related to dust exposure. This is discussed further in the section on pathogenesis.

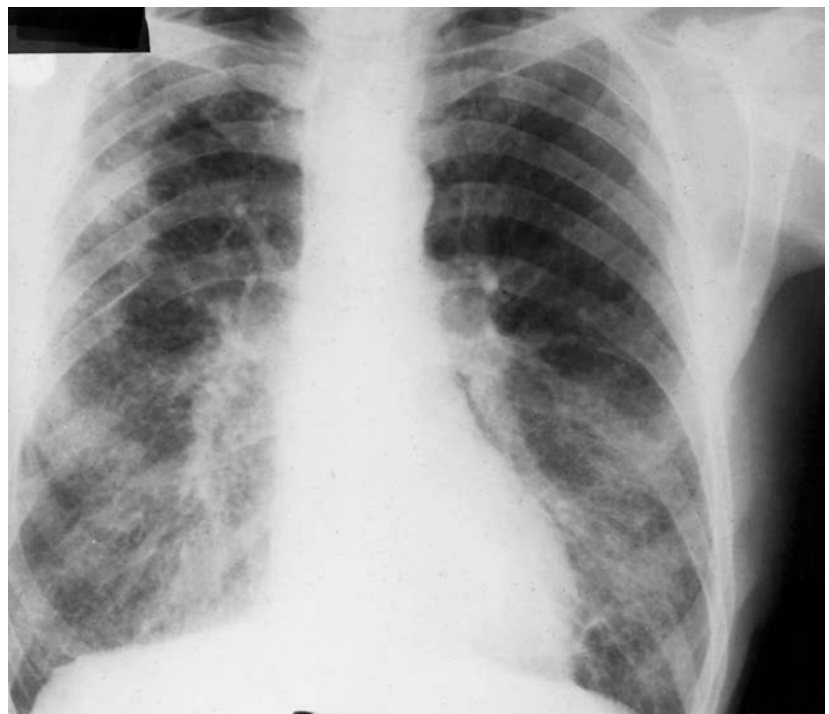
Massive fibrosis may present several different radiological appearances, of which at least two are relatively common and easily distinguished [56]. The most frequent appearance is as described above, initially rather indistinct and ovoid and gradually becoming more clearly demarcated and larger. This is particularly common in areas where high-rank coal is mined. The other type seems

to result from aggregation of the larger r-type nodules to give a multinodular appearance initially, though ultimately this may come to resemble the other type. These appearances seem most common in miners exposed to high levels of quartz [56,57].

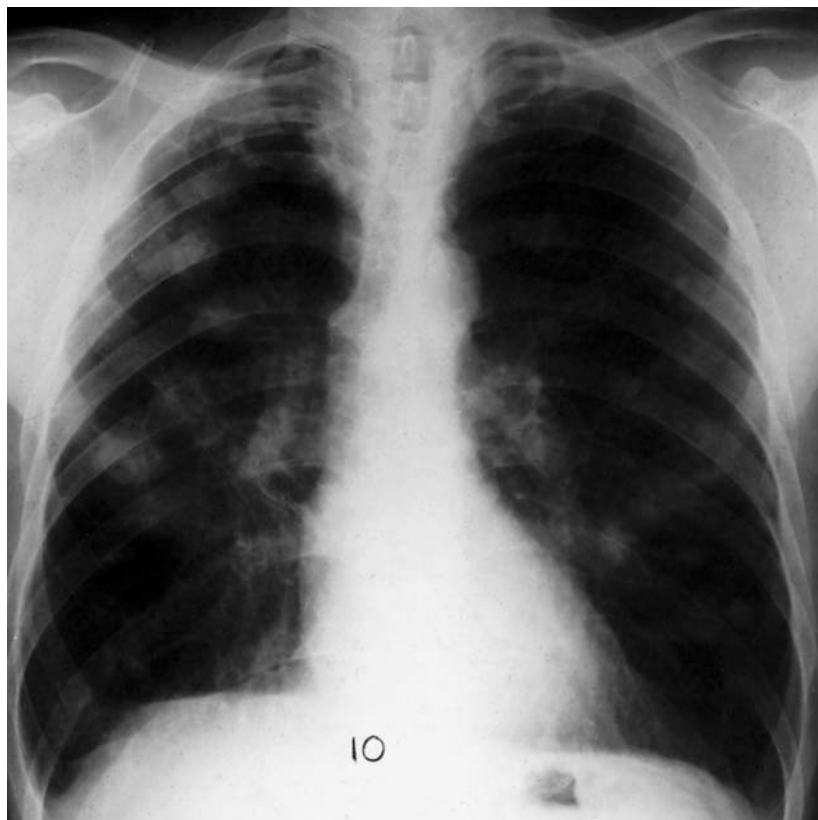
A few miners, especially those with rheumatoid arthritis or with rheumatoid factor in their blood, develop well-defined rounded lesions that grow to about 2–3 cm in diameter or rarely somewhat larger (Fig. 54.7). They are usually multiple and have a marked tendency to cavitate. They often occur on a background of no simple pneumoconiosis and in miners with a relatively low dust exposure. They are called Caplan's lesions and their combination with rheumatoid disease Caplan's syndrome, after the Pneumoconiosis Panel doctor who described them [58–60]. They do not have an ominous prognosis and cause no significant functional impairment, being unassociated with emphysema [61].

### *Symptoms and signs*

The miner with simple coal-workers' pneumoconiosis has no symptoms or signs attributable to the disease. This is a particularly important fact, not always appreciated by doctors tempted to link radiological abnormality (which may be extensive) with symptoms. This is not to say that miners with simple pneumoconiosis may not become breathless; they may and often do, but this is due to some other disease such as asthma, emphysema or heart failure. Failure to appreciate this may result in the patient not



**Fig. 54.6** Coal-workers' pneumoconiosis: extensive (category 3) simple pneumoconiosis with early massive fibrosis (stage A) in right upper zone.



**Fig. 54.7** Multiple rounded lesions of Caplan's syndrome in coal-miner with rheumatoid disease.

receiving treatment appropriate to the condition, sometimes for years. It is particularly unfortunate if this results in treatable conditions such as asthma being missed. Nevertheless, miners develop emphysema more often than other groups of workers with similar smoking habits, and this has also been shown to be related to their exposure to respirable dust [48] (see Pathogenesis).

The early stages of PMF likewise are insufficiently extensive to cause any symptoms or dysfunction. However, as the disease progresses the combination of the fibrous masses and the associated emphysema leads to increasing breathlessness. Cough is not typically a feature unless there is considerable bronchial distortion, and the breathlessness is unvarying and related to exertion. Ultimately the patient reaches the stage of hypoxic and often hypercapnic respiratory failure and cor pulmonale [62,63]. Mortality studies of coal-miners have emphasized their increased risks of dying of chronic bronchitis and emphysema, as well as pneumoconiosis [64].

There are certain other negative features of coal-workers' pneumoconiosis apart from absence of symptoms in the simple disease. These are an absence of physical signs (clubbing and crackles are not features), no increased risk of bronchial carcinoma [64,65] and no increased susceptibility to tuberculosis. However, coal-miners do run an increased risk of gastric carcinoma [64], for unknown reasons (although the author is inclined to

speculate that this may be related to exposure to water underground containing *Helicobacter pylori*), and seem to be unusually susceptible to infections with opportunistic mycobacteria [66] (perhaps for the same reason).

### Lung function

Several studies have indicated that coal-miners have somewhat lower forced expiratory volume in 1 s ( $FEV_1$ ) than control groups but that  $FEV_1$  does not decrease further in relation to increasing radiological category of pneumoconiosis [67,68]. This, together with the epidemiological demonstration of raised residual volume in coal-miners that increases in relation to category of pneumoconiosis [69], is consistent with the hypothesis that coal dust has an effect on airways or alveoli separate from the effect by which it causes pneumoconiosis. Studies on small numbers of miners with high categories of simple pneumoconiosis have shown changes in lung mechanics suggestive of either small airways disease or patchy emphysema [70,71]. However, in general it may be assumed clinically that a miner with simple pneumoconiosis, and without complicating chronic airways disease or emphysema, has an  $FEV_1$  and forced vital capacity (FVC) within the normal range. Diffusing capacity is also usually normal, though slight reduction may be associated with the p type of opacities, and this has been



taken to indicate that emphysema coexists with these lesions [72].

PMF may also be present without functional abnormalities. However, as the condition progresses and particularly if emphysema develops, function becomes impaired by a mixture of restriction of lung volumes and airflow obstruction [73]. Which of these is dominant depends on the size of the masses and the amount of emphysema, although severe airflow obstruction is a common feature in the late stages as a result of reduction in retractive forces across the lung, measurable as increased compliance. There is also reduction in gas transfer owing to loss of alveolar volume, and ultimately hypoxaemia and hypercapnia.

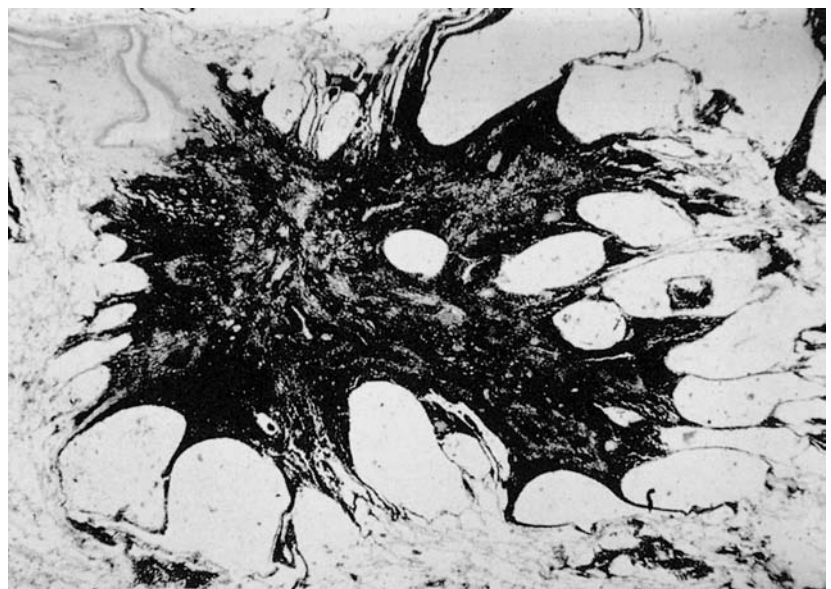
### Pathology

The earliest lesion is the accumulation of coal dust in macrophages at the centre of the acinus, around the respiratory bronchioles. This lesion grows to form the typical coal macule, a stellate structure often surrounded by emphysematous changes (Fig. 54.8). Macroscopically these lesions are dispersed throughout the lung and pigmented dust is seen to have accumulated in the lymph nodes also. The macules are impalpable. In addition, in more advanced simple pneumoconiosis, palpable, somewhat larger, nodules are visible that may be stellate or rounded. They are also composed of dust, disintegrating macrophages, reticulin fibres and reticuloendothelial cells but have a firm central portion of collagen. This may be irregular or, if quartz exposure has been an important factor, arranged in concentric whorls. If the miner has had heavy quartz exposure, typical silicotic lesions may be seen.

PMF is always associated with pathological evidence of simple pneumoconiosis, though the dust foci may be so sparse as to have been invisible radiologically. The lesions are black, usually irregularly shaped and limited in number. They may be sufficiently large to destroy a whole lobe or several lobes and cavitation may be present within them (Fig. 54.9). Histologically, at least two polar types may be recognized, although most examples exhibit features somewhere between the extremes [36]. The more frequent type consists of a peripheral zone of dust, macrophages and reticuloendothelial cells surrounding a relatively acellular central area consisting of collagen around the edges and amorphous, often necrotic, tissue centrally. This material is probably largely fibronectin [74,75], which has been shown to be the major protein component of PMF. Fibronectin is produced by macrophages and fibroblasts and its normal role includes binding cells together. It is a component of reticulin on light microscopy, in that it takes up silver stains and has a fibrous form. The PMF lesion typically contains elastic laminae, the ghosts of obliterated pulmonary vessels, and is usually surrounded by quite extensive emphysema.

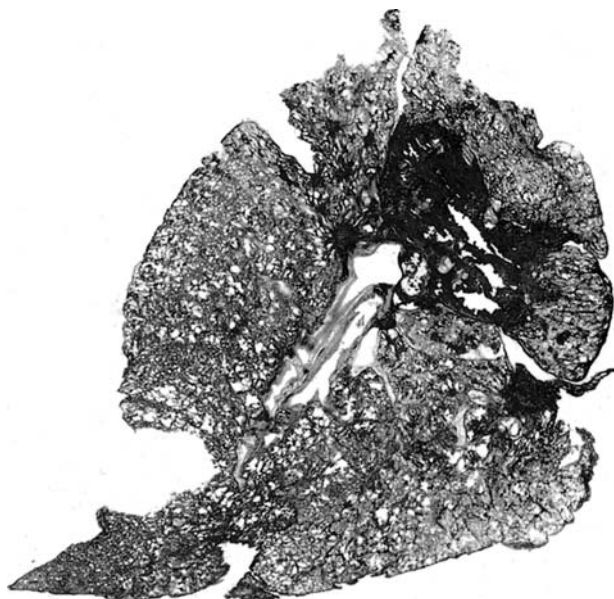
The other type of PMF lesion appears to be the aggregation of the fibrotic nodules described above. This is often seen clearly at the periphery of the lesion, and rings or bands of dust representing the edges of earlier lesions can be seen more centrally. Studies of the dust retained in lungs of patients with PMF suggest that the former lesion tends to be associated with exposure to large amounts of high-rank coal, while the latter type is more likely to occur in miners exposed to lower-rank coal with a high quartz and silicate content [36]. However, these relationships are not clear-cut.

A third lesion occurs less frequently than the other



**Fig. 54.8** Simple coal macule showing centriacinar accumulation of dust and cells with some surrounding emphysema.





**Fig. 54.9** Section of coal-miner's lung showing progressive massive fibrosis, diffuse centriacinar emphysema and relatively sparse coal macules.

two types of PMF, although at one time it was thought possible that this might be rather more common. This is the Caplan lesion, which superficially resembles a silicotic nodule in that it shows concentric pigmented and non-pigmented layers, the dust impregnation usually being relatively light [59]. There is often little background of simple pneumoconiosis and the lesions themselves are quite rounded and well demarcated. The rings consist of collagen, which often liquefies, and the whole lesion may cavitate. The periphery usually shows features constant with rheumatoid histology, with lymphocytes, plasma cells and sometimes palisaded histiocytes. These lesions are usually multiple and rarely grow larger than 5 cm in diameter.

### Pathogenesis

The development of simple pneumoconiosis is clearly related to two factors: the total quantity of dust inhaled and its composition [43,76]. However, these do not explain all cases and individual predisposition seems important also; this is probably related more to individual efficiency of dust clearance than to immunological differences between people, studies of which have proved unrewarding [77–79]. The composition of dust is important not only in determining the pathological type of lesion but also, almost certainly, whether pneumoconiosis occurs. Given the same levels of dust, different collieries show striking differences in prevalence of pneumoconiosis, even when factors such as migration of the workforce and differing coal and ash content have been allowed for [43]. Complex

interactions occur between different minerals in coal dust that may significantly alter their toxicity; for example, quartz may be rendered almost non-toxic when mixed with certain silicates such as illite [80]. Nevertheless, the essential mechanism of simple pneumoconiosis is likely to be dust-mediated damage to macrophages, release of cytokines accompanied by recruitment of polymorphonuclear cells, resulting in activation of fibroblasts and also local initiation of emphysema by elastolysis. This latter problem is discussed in the next section.

Equally, PMF has been shown to be related to total dust exposure and to dust composition: the more dust a miner is exposed to, the greater the risk [81]. High-rank dusts are particularly liable to provoke the amorphous type of PMF, while low-rank high-quartz dusts more commonly lead to the nodular aggregating type [43]. Why a miner's disease progresses from the simple lesion to PMF is still not clear. Sometimes it is due to progressive enlargement and aggregation of quartz-induced lesions. More commonly, however, it is a diffuse fibrosing and necrotic process with marked vasculitis and considerable accumulation of dust. Its preponderance in upper lobes and, intriguingly, its predisposition to affect taller miners speak for a mechanical cause [81]. Whether this is related to local impairment of clearance, lymphatic blockage, lymph node destruction or some other factor remains to be seen, although severe destruction of hilar nodes is almost universal in miners with PMF and progressive silicosis [82,83], and it is logical to suppose that blockage of this escape route for the dust is relevant to its accumulation in the lung and provocation of a chronic progressive inflammatory reaction there. Other theories of the aetiology of PMF now seem less likely. These include autoimmune factors, which only seem relevant to the rare cases of Caplan lesions, and tuberculosis, which is no longer relevant in the UK though it was probably important in the past. Atypical mycobacterial infection has not been investigated in detail yet. It seems unlikely but cannot be dismissed as a cause in some cases.

### Coal, bronchitis and emphysema

The relationship between exposure to coal dust and chronic bronchitis and emphysema has been extremely controversial. Physicians and pathologists in mining areas have for many years believed there to be a relationship but proof has been hard to come by. In particular, in recent years the prevalence of cigarette smoking in miners has tended to hide the risks of coal dust exposure. Nevertheless, recent evidence gives strong support to the hypothesis that coal dust causes both chronic bronchitis and emphysema, adding to the effects of cigarette smoking. This evidence may be summarized as follows.

- 1 There is an increased prevalence of cough, sputum and reduction in  $FEV_1$  in miners compared with controls [45,84].

2 The risk of cough and sputum increases with increasing dust exposure in smokers and non-smokers [40,85].

3  $FEV_1$  declines in relation to a miner's dust exposure [46,47,86–89].

4 There is more emphysema in the lungs of miners who have died suddenly of cardiac disease than of non-mining controls, even when matched for smoking habit [90].

5 The risk of a miner having some emphysema in the lungs at death is proportional to dust exposure during life, if there are some pathological changes of nodular pneumoconiosis in the lungs as well [48]. This relationship holds true even when the lungs of non-smokers are examined.

6 The risk of a miner dying of chronic bronchitis and emphysema increases in proportion to dust exposure [64].

The facts make a strong case for a relationship, and would fit with the hypothesis that coal dust acts as both a cause of fibrosis and an initiator of emphysema. A common pathway, via damage to macrophages and recruitment of polymorphonuclear cells, is an attractive explanation; this hypothesis has been supported by the finding that inhalation of coal-mine dust by rats at concentrations not far removed from those to which miners have been exposed causes a neutrophil alveolitis, impaired leucocyte chemotaxis and a rise in alveolar concentrations of proteolytic enzymes [91,92]. It is particularly interesting that this response occurs within weeks of the start of exposure in view of the epidemiological finding in humans of an accelerated loss of lung function in young miners over the first year or two of exposure underground, later slowing down [93]. One might speculate that it is in this period, before the lung's defences are adapted to dealing with dust, that the process leading to emphysema may be initiated in the susceptible.

Argument has centred around the relative importance of cigarettes and coal dust in causing emphysema and airflow obstruction. In practical terms this is a red herring, in that both contribute and their effects appear to be additive and dose-related epidemiologically (Fig. 54.10). Therefore, reductions of dust levels in coal-mines will reduce the numbers of workers becoming disabled, although it will not eliminate the problem. In the past, when fewer miners smoked and dust levels were exceedingly high, it is likely that coal dust was more important overall than smoking. Currently, the reverse is almost certainly true in the West. What the future holds depends on action by both industry and society.

### Management and prevention

There is no treatment for coal-workers' pneumoconiosis and, as for all occupational diseases, the emphasis should be on prevention. This is achieved by reduction of dust levels in coal-mines by a combination of improved ventilation and use of water to suppress the dust at its source.

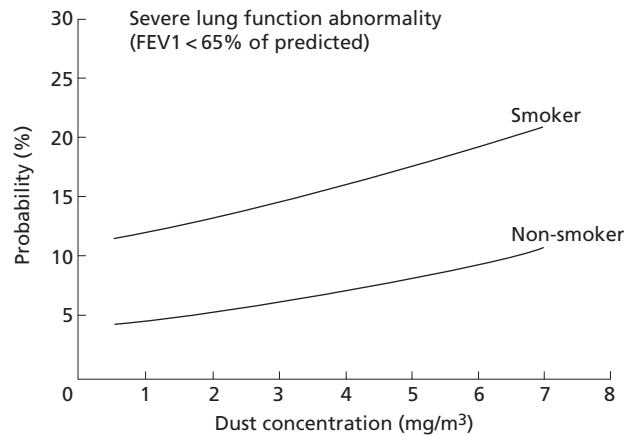


Fig. 54.10 Relationships between risk of acquiring a forced expiratory volume in 1 s ( $FEV_1$ ) of less than 65% of predicted and dust exposure and smoking. (Derived from data in Marine *et al.* [86].)

Special attention needs to be paid to areas where ventilation may be ineffective, such as the advancing ends of roadways. On long-wall faces, the air is driven around the face down one roadway and out the other. In room and pillar mines, curtains (brattices) are used to direct the flow of air. The effectiveness of these measures is monitored by measuring the dust concentration to which miners are exposed and in many countries this is done according to statutory obligations. In the UK, the maximum allowable concentration is  $7 \text{ mg/m}^3$ , measured as respirable dust ( $<7 \mu\text{m}$  diameter) 70 m back from the face in the return roadway, a concentration roughly equivalent to an average of  $4 \text{ mg/m}^3$  at the face. In the USA, dust is sampled within the breathing zone of face workers by personal monitors and a lower standard,  $2 \text{ mg/m}^3$ , is applied. Both these standards were based on epidemiological studies that predicted the average risk of category 2 simple pneumoconiosis after a lifetime's work at different dust concentrations (see Fig. 54.4). Tighter standards are generally applied for driving roadways where quartz levels may be high.

Whatever dust standard is applied, some miners will get pneumoconiosis because of variations in individual susceptibility. Therefore dust suppression should be accompanied by workforce radiographic monitoring. In the UK, chest radiographs are offered to all miners every 4 years and any worker showing signs of simple pneumoconiosis is offered work in less dusty conditions. This has the effect of reducing the risks of developing PMF. A further measure that may be taken is to offer miners personal protection by respirators, and this is the practice in the UK. However, this is not regarded as a substitute for good dust suppression.

These measures together have had a marked effect on the prevalence of pneumoconiosis in the UK and, with the

dwindling numbers of men employed in a contracting industry, simple pneumoconiosis and PMF are now very rare in working miners, although the latter is still seen in retired miners [55]. National statistics in other countries are harder to find, but there is no reason to suppose that similar results would not follow similar control measures.

In the UK and some other countries, an industrial injuries insurance scheme is run by the state, miners with pneumoconiosis being entitled to benefits. This is discussed in the final section of this chapter. In practical terms, the advice given to a miner who has developed pneumoconiosis depends on his age and the coal-mine in which he works. A miner developing simple pneumoconiosis under the age of 40 is very likely to develop PMF and to have his life shortened by it. Complete cessation of further dust exposure will reduce these risks. Between 40 and 55, the risks are correspondingly smaller and PMF, when it develops, may occur too late in life to cause appreciable disablement, so the management often involves offering work in conditions where the dust level is relatively low (and in the UK this offer is a statutory obligation). A man who develops simple pneumoconiosis in his last few years underground may usually be advised that the final year or two at the face will not affect his risks of PMF and premature death appreciably. These general guidelines may be modified in individual circumstances by knowledge of the dust conditions and pneumoconiosis risks in particular mines and mining areas.

**Silicosis**

**Epidemiology**

*Exposure to silica*

Silicon dioxide or silica is the most abundant compound in the earth's crust, where it is mostly found in the crystalline form known as quartz, a regular tetrahedron comprising a central atom of silicon that shares four oxygen atoms with adjacent silicon atoms. Quartz may be contaminated with other elements in trace amounts that give it colour and value as ornamental gemstones, such as agate, onyx and amethyst. Different spatial arrangements of the silicon dioxide molecule are responsible for other minerals: tridymite and cristobalite are formed by heating quartz and occur naturally in some volcanic rocks. Silica may also occur in microcrystalline and amorphous forms; the former consists of tiny crystals bonded together by amorphous silica as in flint, while the latter, probably relatively non-toxic, is not crystalline and occurs as diatomite, the petrified skeletons of minute prehistoric organisms. However, calcining (heating above 1200°C) of amorphous silica converts it into a toxic crystalline form.

Since silica occurs so abundantly, exposure to its airborne dust may occur in a very wide range of circum-

**Table 54.2** Some occupations in which exposure to quartz may take place.

Mining
Tunnelling
Quarrying
Stonemasonry
Sandblasting
Fettling and foundry work
Ceramics
Brick-making
Refractory kiln repair
Silica flour manufacture
Abrasive manufacture
Diatomaceous earth manufacture

stances. Some of the more important are recorded in Table 54.2. The most important numerically is cutting stone, in mining, quarrying, masonry and tunnelling. Almost all forms of mining entail a hazard of silicosis. Metal mining requires the extraction of metal-bearing ore, which is largely quartz. Even when the mineral being mined is itself a known cause of lung disease or radiological abnormalities, such as asbestos, tin or barium, the miner is usually at greater risk of silicosis. Tunnelling through granite, sandstone or other quartz-bearing rock entails an obvious hazard, although pure limestone and marble are not toxic. Stonemasonry and cleaning with abrasives are also well-known causes of silicosis. The practice of using a high-speed jet of sand for metal and stone polishing, known as sandblasting, is extremely hazardous and has been illegal in the UK since 1949. However, it continues in the USA and many other countries. Work in foundries, where molten metal is made into castings, may involve a risk of silicosis as the mould into which the metal is poured is usually made of sand bonded by resin. The sand is fused to the surface of the casting and often converted by the heat to the particularly toxic cristobalite. This is polished off the surface by a worker called a fettler, who is at potential risk of silicosis. Other foundry workers at risk are those who clean or replace the brick linings of the furnaces. These bricks (refractory bricks) are made of baked sandstone and there is also a risk of silicosis in the ceramic workers who produce them.

The production of china and earthenware involves the use of clays, usually with a low silica content, to which finely ground calcined flint may sometimes be added. The material is shaped and then fired in an oven. It is then polished, fettled and glazed, sometimes with a mixture containing powdered flint. It is clear that there are plenty of situations in this industry where silicosis may occur. Other industries with a risk of silicosis include production of silica flour, finely ground silica used as a filling in abrasives, toothpastes, polishes, paints, rubbers and plastics, production of calcined diatomaceous earths, glass-making, enamelling and production of gemstones.

### Prevalence

It is not possible to know how many workers have silicosis since notification procedures differ in different countries and many workers at risk are never surveyed by radiography. However, records in some countries, notably the UK and the Scandinavian countries, allow some overall estimates to be made. In the UK, with a working population of about 20 million, the number of workers being awarded state disablement pensions each year for silicosis fluctuates between 110 and 170. However, this figure excludes an unknown but almost certainly much larger number of workers with radiological change but no disability. The workers are predominantly from foundries, mines and quarries, refractory brick-works and potteries. A Swedish case register assessed the number of workers with radiological silicosis as having fallen from about 120 to about 70 per annum between 1950 and 1975; at the same time it was apparent that the age at which the disease was first diagnosed was progressively increasing [94]. In neither the UK nor Sweden, however, is the population at risk known.

It is likely that silicosis as it occurred in the first half of this century in mining, pottery work and sandblasting is now a very rare occurrence in developed countries. The disease prevalence has been modified in these and other industries by an increased awareness of risk and by legislative action leading to better dust suppression. For example, there has been good evidence of decreasing risk in Vermont granite workers [95], Scottish granite stonemasons [96] and diatomaceous earth workers [97,98]. On the other hand, in some industries complacency about risks has allowed poor control of exposures with consequently a relatively high incidence of preventable disease. Since the last edition of this book, the author has seen severe and

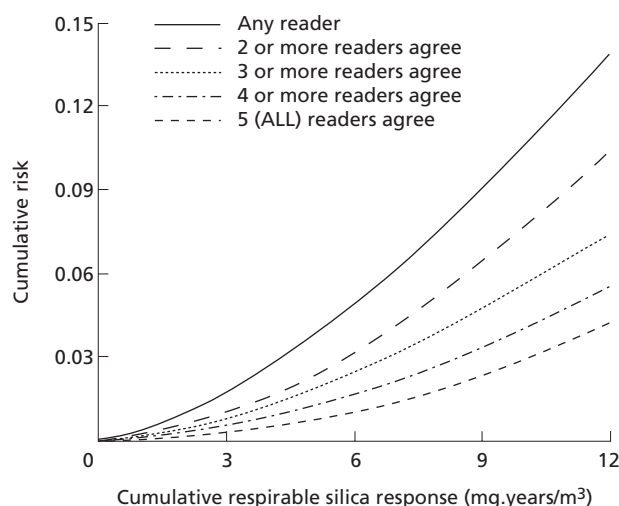
sometimes fatal silicosis in the UK among sandstone masons [99], 'limestone' crushers, barytes miners [100] and foundry workers, and this has also been reported in American sandblasters [101,102], bentonite miners [103] and silica flour workers [104], Indian slate pencil workers [105,106] and British slate-workers [107]. Finally, the expansion of mining and quarrying into economically poorer countries is likely to be attended by increasing numbers of victims of silicosis (Fig. 54.11), while the persistence of traditional stonemasonry in some such countries ensures that a steady number of people continue to get the disease from this occupation [108].

### Relationship of exposure to risk of silicosis

While it is obvious that greater risks of silicosis attend heavier exposures, the number of studies that have attempted to relate exposure to risk in numerical terms is surprisingly small. Very heavy exposures, in industries such as sandblasting, may lead to acute silicosis and moderately heavy exposures to subacute disease. Studies of classical nodular silicosis in the Vermont granite industry have suggested that the risk of clinically important silicosis was virtually eliminated by the introduction of a dust standard of approximately  $100\mu\text{g}/\text{m}^3$  [95]. More recent follow-up of this population has supported this conclusion [109]. Similar results have been obtained from a study of quartz-exposed workers in North Carolina [110], while a small but well-executed study of British gypsum workers has suggested an approximately 50% risk of developing small rounded opacities in workers exposed to  $100\mu\text{g}/\text{m}^3$  for 20 years or more [111]. An important study of Canadian gold and uranium miners has estimated the risks of radiological change in relation to careful estimates of cumulative quartz exposure [112] (Fig. 54.12).



**Fig 54.11** A typical roadside stonecrushing operation in India. Note the absence of any methods to prevent dust exposure.



**Fig 54.12** Risks of category 1 simple silicosis in Canadian hardrock miners in relation to exposure to respirable silica expressed as concentration vs. time. The different curves represent different levels of agreement between readers. (From Muir *et al.* [112] with permission.)

For category 1 pneumoconiosis to have been read by a majority of the five readers in about 3% of miners, average exposures of approximately 7 mg-year/m<sup>3</sup> are required, i.e. an exposure equivalent to 200 µg/m<sup>3</sup> for 45 years. As far as it can be interpreted, the evidence at present thus appears to show that adherence to a quartz standard of 100 µg/m<sup>3</sup> would prevent most serious silicosis but would not prevent the development of minor radiological opacities in a proportion of the workforce. The real challenge is to ensure adherence to such a standard. In the UK, the maximum allowable concentration for quartz is 0.3 mg/m<sup>3</sup>, implying a maximum cumulative exposure over a 40-year working life of 20 mg-years/m<sup>3</sup> and therefore an approximately 6% risk of radiological change in someone exposed regularly to half that concentration, using the estimates illustrated in Fig. 54.12. Rather than regular exposures to low concentrations, in real life most workers are now probably exposed to intermittent peak concentrations, sometimes well in excess of standards, and such peaks may be more relevant to the development of serious silicosis; this was almost certainly the explanation of the outbreak described in Scottish coal-miners [44].

Recent calculation of the likely exposures to quartz of two stonemasons who worked alongside each other, one of whom died from acute silicosis while the other developed PMF some years later, suggested that in the fatal case earlier prolonged exposure to low concentrations had caused fibrosis of the hilar nodes and that this was responsible for the different reactions in the two men [83]. Thus it is proposed that exposure to low concentrations over pro-

longed periods may influence the clearance of dust inhaled subsequently, and that changes for the worse in dust concentrations late in a worker's career may be particularly dangerous.

### Clinical features

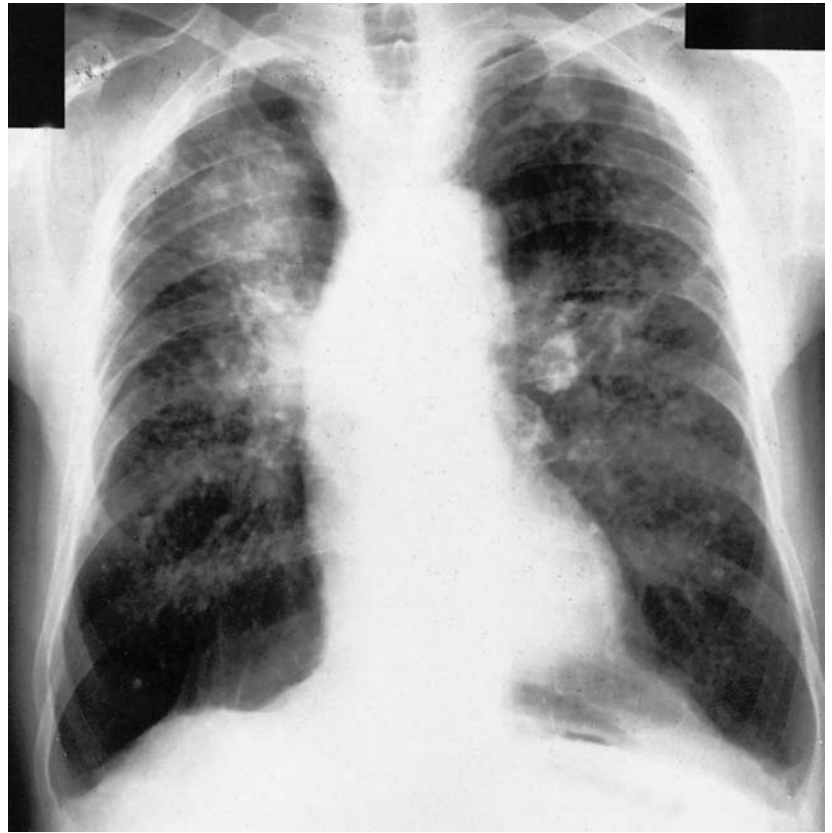
It is convenient for the purposes of description to categorize silicosis as chronic, accelerated and acute, though it must be borne in mind that such subdivision is not necessarily clear-cut; these terms are used in the descriptions that follow.

### Chest radiography

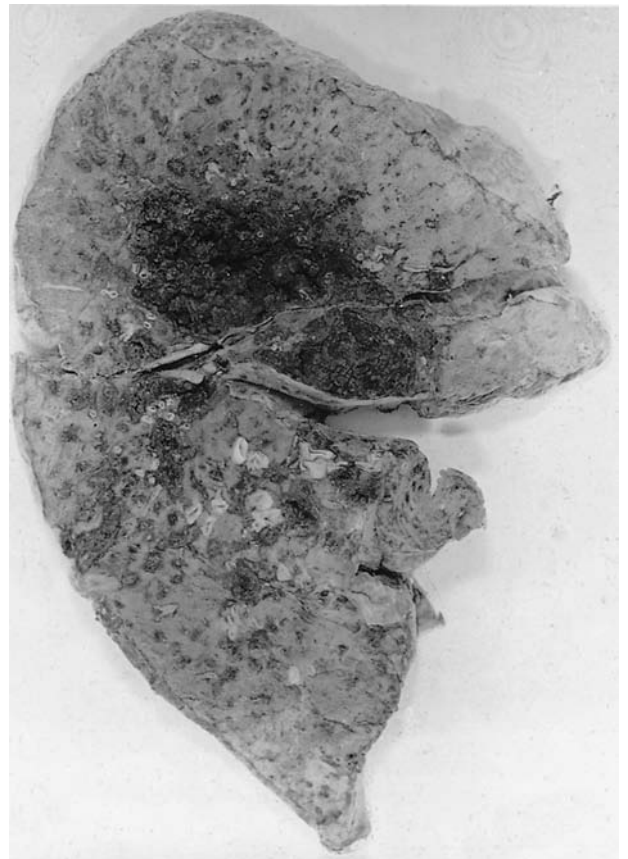
The earliest sign of classical chronic silicosis is the appearance of small nodules, particularly in the mid and upper zones of the lungs. These are characteristically somewhat more dense than those in coal-workers' pneumoconiosis. They also have a tendency to increase in size gradually and are often of the r type (see Fig. 54.5) [44]. Calcification of small nodules sometimes occurs. There may be associated Kerley B lines at the bases and pleural thickening. Eggshell calcification of the hilar nodes is an almost pathognomonic feature, occurring only otherwise in sarcoidosis (Fig. 54.13).

Once silicosis has appeared on the chest film it tends to increase, both in profusion and in size of the nodules. This occurs even after exposure has ceased [94,113,114]. However, in this respect care should be taken to distinguish between true silicosis and mixed-dust pneumoconiosis, which may be seen in welders and some foundry workers for example and which runs a much more benign course, tending not to progress or evolve into PMF [114]. True silicosis frequently shows agglomeration of nodules to form the large masses of PMF [113] (Fig. 54.14). These typically have a multinodular appearance initially but later may consolidate into a contracted dense fibrotic mass, often surrounded by bullae. Cavitation may occur, and when it does evidence of mycobacterial infection should be sought. Pleural fibrosis is often extensive close to the PMF lesions.

Accelerated silicosis, associated with heavy exposures over a relatively short period of a few years, presents radiologically as progressive irregular upper zone fibrosis, sometimes with relatively sparse and indistinct nodularity [104]. The upper lobes may become replaced completely by PMF and the lower by emphysema (Fig. 54.15). Acute silicosis, which develops over months in response to exceedingly heavy exposures as in sandblasting or dry drilling [101,102,115–117], is characterized by appearances suggestive of pulmonary oedema (Fig. 54.16). Acute enlargement of the hilar nodes may occur with heavy exposure to quartz in individuals without prior exposure [83] (Fig. 54.17).



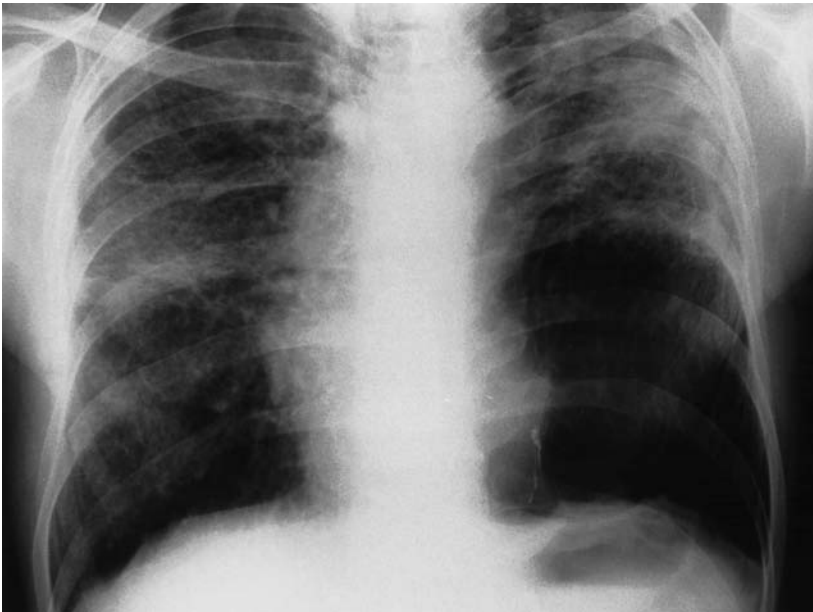
**Fig. 54.13** Chest film of hardrock miner showing eggshell calcification of hilar nodes and progressive massive fibrosis in right upper zone. The nodular, r-type lesions that formed the basis of the progressive massive fibrosis are visible, particularly in the left upper zone.



**Fig. 54.14** Silicotic lung showing grey fibrotic nodules that have coalesced in the upper and middle lobes to form massive fibrosis.

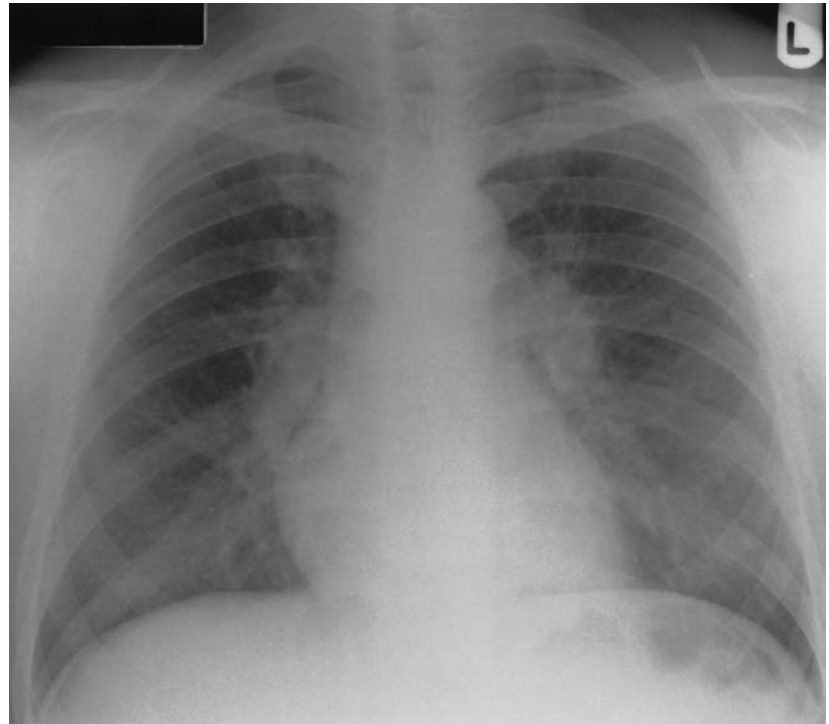


**Fig. 54.15** Chest film of patient with accelerated silicosis showing irregular upper lobe fibrosis and lower zone emphysema.



**Fig 54.16** Chest film of stonemason with 6 years of exposure to  $1 \text{ mg/m}^3$  respirable quartz following 30 years of exposure to low concentrations showing diffuse finely nodular bilateral shadowing of acute silicosis shortly before his death.





**Fig. 54.17** Chest film of 25-year-old stonemason (who worked alongside the patient shown in Fig 54.16) with 6 years of exposure to respirable quartz at  $1 \text{ mg/m}^3$  showing an acute enlargement of the hilar nodes. These later calcified and progressive massive fibrosis developed in the upper zones. The difference in the reactions to their recent very high exposures is likely to be due to prior fibrosis of hilar nodes in the patient in Fig. 54.16.

### *Symptoms and signs*

In chronic silicosis the development of small nodular opacities is not associated with symptoms or signs. However, as the disease progresses to PMF, the patient may complain of shortness of breath in proportion to the size of the lesions and the extent of emphysema. A dry cough is also often present. The condition may progress with increasing disability and ultimately cor pulmonale, although this stage is now rarely reached in chronic silicosis in most of the industries classically associated with the disease. Finger clubbing and auscultatory crackles are not a feature even of late chronic silicosis. Accelerated silicosis similarly causes no abnormal signs, but differs from chronic silicosis in that breathlessness is a relatively early feature. The very rare acute silicosis presents with rapidly increasing shortness of breath and crackles may be heard in the lungs. It progresses to death in hypoxic respiratory failure within a year or two of presentation [99].

There should not be great difficulty in making the diagnosis of chronic silicosis if an occupational history is taken. However, the radiographic appearances of accelerated disease are less familiar to physicians and chronic tuberculosis, sarcoidosis or allergic alveolitis may be considered in the differential diagnosis. However, a history of a few years of heavy dust exposure should be sufficient to prevent misdiagnosis. It is important not to be misled by a patient's understanding of the nature of the dust expo-

sure. The author has seen silicosis of severe degree in workers crushing what they believed was limestone but which clearly contained high proportions of quartz. Acute silicosis may present initially mimicking bilateral bronchopneumonia or pulmonary oedema radiographically, although the history of increasing dyspnoea over a few months together with intense exposure to stone dust should make the diagnosis easy. Again, it is important not to be deterred from the diagnosis by atypical radiographic or even pathological features and to take serious account of the occupational history [99].

### **Lung function**

Several studies have suggested that simple silicosis is not normally associated with abnormalities of lung function except in the most advanced stage (category 3) [118–121]. However, these studies have often been unable to distinguish between the effects of silicosis and possible independent effects of the dust on lung function separate from its effect in causing nodular change. Thus it may be that the functional abnormalities found are due to dust exposure, analogous to the situation in coal-miners, rather than to the development of silicosis. When abnormalities are found they are usually those of a mild mixed restrictive and obstructive pattern.

In silicotic PMF the functional changes are the same as in coal-workers' PMF, the relative amounts of obstruction and restriction depending upon the differing contribu-

tions of fibrosis and emphysema pathologically. Similar abnormalities occur in accelerated silicosis [122], while a restrictive pattern with severe hypoxaemia is to be expected in the acute disease.

### Complications

Tuberculosis and other mycobacterial infections are the most important complications of silicosis, presumably largely related to reactivation of previously quiescent lesions [94,123,124]. As tuberculous infection in childhood becomes less common so the disease in silicosis will also become rarer, although it still remains a problem in societies where tuberculosis remains endemic. As tuberculosis declines, there appears to be an increase in the incidence of infections with *Mycobacterium kansasii* and *M. avium-intracellulare*, and these organisms are recognized as important pathogens of patients with silicosis in the south-eastern USA [125]. The onset of mycobacterial infection in silicosis may be insidious, but unexpected radiological change, cavitation of PMF and the development of soft patchy opacities should alert the physician to the possibility. Fever and loss of weight, though usually only occurring with advanced tuberculosis, should not be attributed to silicosis (except of the acute type). Regular sputum examination in people with silicosis is the safest method of catching the infection early.

Other complications of silicosis include pneumothorax, associated with the combination of fibrosis and bullae [123], an increased frequency of scleroderma [126], and a tendency to renal failure due to focal damage to glomeruli and proximal tubules [127–129]. Silicotic subjects have an increased prevalence of antinuclear antibodies, and it is speculated that these, and consequent tissue damage, may be related to the damage to cells and their nuclei by quartz [130].

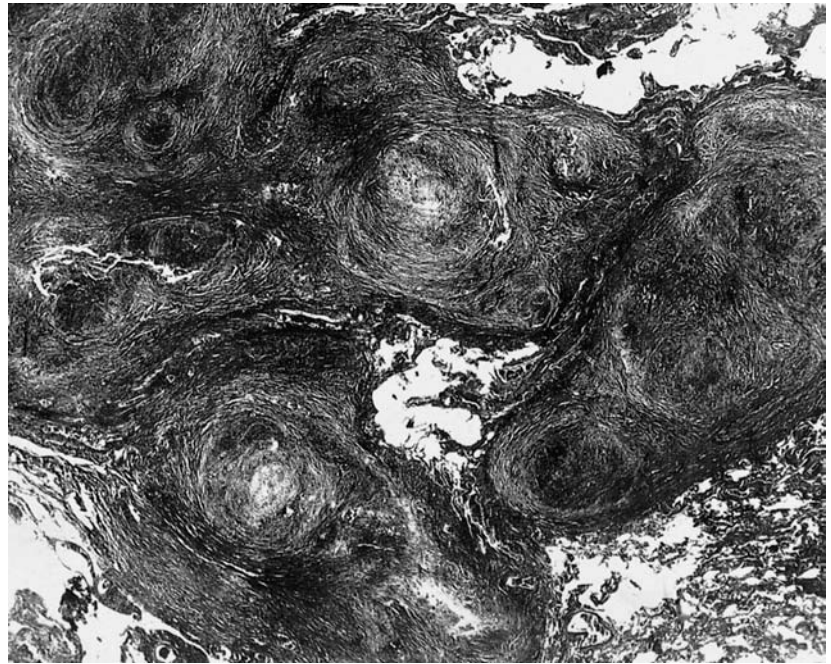
It is possible that workers exposed to silica have an increased risk of chronic bronchitis and airflow obstruction as a consequence of non-specific effects of dust [121,131], although recent studies of the Vermont granite worker cohort suggest that this association is not universal [132]. However, this is not as clearly established as in coal-miners, and it seems that non-smokers exposed to concentrations of quartz around 0.1 mg/m<sup>3</sup> do not run a significant additional risk of developing emphysema [133]. There have also been suggestions that quartz may be carcinogenic, especially from a Swedish study of workers in mining, quarrying, tunnelling and iron and steel trades and from studies of North Carolina dusty trades workers, of diatomaceous earth workers and of Ontario miners [94,134–136]. This controversial subject has been investigated by the International Agency for Cancer Research in a series of specially commissioned studies intended to take account of confounding factors such as exposure to other carcinogens and cigarette smoke [137]. The results

suggest that the presence of silicosis increases the risk of a worker developing lung cancer, although the evidence associating quartz exposure without silicosis and cancer is inconsistent. Recent evidence has been reviewed with the same conclusion [138]. It seems likely to the author that any carcinogenic effect is relatively weak compared to that of asbestos for example, and that control of dust exposures sufficient to prevent silicosis is likely to prevent an excess of lung cancer also. The UK Industrial Injuries Advisory Council has included lung cancer in association with silicosis in its list of prescribed diseases.

### Pathology

On macroscopic examination, the surface of silicotic lungs often shows fibrotic plaques and adhesions between visceral and parietal pleura. The lungs are pigmented and the hilar nodes are enlarged and contain fibrotic nodules that are often calcified. The cut surface of the lung is clothed with hard fibrotic nodules of varying sizes and with a characteristic whorled appearance. Emphysema is not usually as conspicuous a feature of simple silicosis as it is of coal-workers' pneumoconiosis. Where PMF has developed, it can usually be seen to have been formed by aggregation of several large simple lesions (Fig. 54.18). Cavitation of PMF may be present. Accelerated silicosis shows in addition a more irregular fibrosis in the upper zones, often with bullous emphysema in other parts of the lung. In contrast, acute silicosis looks quite different, the lungs being heavy and voluminous, without much nodular change [101].

Microscopically, the silicotic nodule arises around the respiratory bronchiole, around arterioles and in paraseptal and subpleural tissues, as well as in lymph nodes [139]. The centre of the nodule is collagen, while peripherally it shows reticulin, fibroblasts, macrophages and mononuclear cells. Dust, which may be seen to be doubly refractile using polarized light, is usually most profuse round the periphery of the nodule. However, this appearance should not be relied upon, since very fine particles of quartz may be too small to refract light and may be present in very high concentration with very little dust apparent on polarized microscopy [99]. In accelerated silicosis, in addition to nodular change, diffuse alveolar wall thickening and proliferation of type II alveolar epithelial cells may be seen [140]. In acute silicosis the alveolar walls are infiltrated by plasma cells, lymphocytes and fibroblasts, while the alveoli are filled with eosinophilic oedema fluid that is positive to periodic acid–Schiff staining [101,141]. PMF in chronic and accelerated silicosis can be seen to comprise smaller silicotic nodules at the periphery, though the centre loses this architecture and appears as a hard mass of fibrosis. Elastic ghosts of vessels may be seen within the PMF lesion and central ischaemic necrosis may occur.



**Fig. 54.18** Low-power view of silicotic nodules showing onion-skin appearance and aggregation.

### Pathogenesis

The damage caused by quartz occurs at the lung acinus and in the pulmonary, hilar and mediastinal nodes. As discussed above, physical factors determine the likelihood of dust gaining access to the acinus; once there, the particles are engulfed by macrophages. It seems likely that they are then transported to the nodes where they initiate fibrosis as discussed below. With relatively low exposures, fibrosis of nodes is the only pathological consequence; however, once fibrosis has occurred the route of egress is blocked and pulmonary fibrosis starts in the acinar regions [83]. With high initial exposures, acute enlargement of hilar nodes mimicking sarcoidosis may occur, to be followed by acinar disease once the nodes have fibrosed.

It seems likely that the crystal structure and the surface properties of quartz are important in determining its toxicity. Quartz and coesite, which have tetrahedral structures, are fibrogenic experimentally whereas stishovite, which has an octohedral structure, is not [142]. Alteration of the surface of the quartz crystal by coating it with aluminium hydroxide or iron oxide reduces its toxicity, while chemical cleaning of the surface increases toxicity [143–145]. Whether the toxic effects of quartz are due to the presence of a soluble layer of silicic acid, negative ionization of its surface, piezoelectric charging or some other factor is not clear from experimental work.

Whatever the reason for the toxicity of quartz, it seems to be mediated by macrophage phagocytosis, predominantly in the interstitial space [139,146]. Large amounts of quartz ingested by macrophages cause rupture of

phagosomal membranes, perhaps by peroxidation of lipids, escape of enzymes, and disruption and death of the cell [147]. However, smaller amounts of quartz do not necessarily cause rapid cell death, making it possible for macrophages to survive long enough to transport the dust within the lung, for example to hilar nodes, and to secrete bioactive materials. Among these may be reactive oxygen species and a wide range of cytokines [148–150]. One of these is probably interleukin 1, a substance that stimulates the proliferation of thymus-derived lymphocytes probably leading to transformation of B lymphocytes into plasma cells; this may also play some part in the propensity of patients with silicosis to produce autoantibodies.

### Management and prevention

Once a worker has silicosis there is no treatment that affects the course of the disease. Its rate of progression varies from case to case, and the prognosis is not necessarily bad. For example, a man who develops category 1 nodular change after 30 years' work in tunnelling or quarrying is unlikely to show much progression over the next 20 years, unless his disease is due to a relatively recent high exposure. Conversely, someone who develops accelerated silicosis after a year's heavy exposure is likely to deteriorate rapidly over a few more years, and patients with acute silicosis usually die within months of presentation. Attempts to find a treatment that interferes with the toxicity of silica to phagosomal membranes, although successful to some extent *in vitro*, have not produced a drug suitable for trial in humans [151,152].

The complications of silicosis should be treated according to standard therapeutic guidelines. Evidence from the 1950s and 1960s suggests that tuberculosis responded almost as well to adequate chemotherapy in silicotics as non-silicotics [123]. The newer regimens, including rifampicin, ethambutol, isoniazid and pyrazinamide, have not been tested in a controlled manner in patients with silico-tuberculosis, although they have been shown to be successful in coal-workers' pneumoconiosis complicated by tuberculosis [153,154]. Personal experience suggests that the infection can usually be cured by modern chemotherapy but that the prognosis depends on the severity of the silicosis and the extent to which this disease is accelerated by the tuberculosis. The author's practice is to treat for 12 rather than 6 months in the belief that macrophage function in such patients may be impaired. Opportunistic mycobacterial infections should be treated along the lines suggested in Chapter 20. The patient with silicosis may be eligible for disablement benefit if symptoms and pulmonary dysfunction are present and in the UK should apply to the Department of Social Security. Civil action against a negligent employer might also be justified in individuals with disability or handicapped from pursuing their trade.

Prevention of silicosis depends on preventing exposure to respirable silica dust, which presupposes that the risk has been recognized; regrettably this is not always the case. Most countries now recognize a silica dust standard aimed at preventing exposure of the workforce to more than  $100\mu\text{g}/\text{m}^3$  of respirable quartz. Whether this is adequate to prevent all cases is dubious, as discussed above, but, if enforced, at least prevents the most severe and rapidly developing cases [112,155]. Ideally, the use of quartz should be avoided if a safer substitute material is available. There is some evidence that inhalation of quartz mixed with other dusts leads to a less severe and progressive disease; this seems to be the case in coal-miners and foundrymen when the quartz levels, though above  $100\mu\text{g}/\text{m}^3$ , only represent a low percentage of the total dust inhaled. In such industries, a less tight standard, if based on appropriate epidemiological evidence, could be argued for. When high levels of quartz occur despite the best ventilation and water suppression that can be provided, respirators provide additional protection. In these high concentrations, the workers should be isolated from the environment by a complete helmet and suit with its own positive-pressure air supply [156].

Workers exposed to a risk of silicosis should be offered chest radiography at regular intervals, probably at least every 4 years, in order that the earliest signs of disease are detected and the worker protected from further exposure.

### Asbestosis

The naturally occurring fibrous minerals known as

asbestos have the common property of resistance to destruction by chemical and physical means, and have therefore acquired great usefulness to humans. There is archaeological evidence that asbestos was used in making clay pots in 2500 BC and for funeral shrouds and lamp wicks in classical times. However, widespread use of the minerals in industrial society dates back to the exploitation of the Quebec chrysotile deposits in the 1860s and the South African deposits in the 1890s. The first evidence of pulmonary fibrosis in association with asbestos use was reported at the turn of the century [157,158], and by 1930 the hazard was so well known that legislation was introduced in the UK to control the exposure of workers in asbestos factories [8]. Shortly after this, the association of asbestosis and lung cancer was reported [159], and the increased risk of this disease run by asbestos workers was confirmed epidemiologically by the 1950s [9,160]. Although it had been described as a form of lung cancer among shipyard workers in Scotland in 1947 [161], it was not until 1960 that the hitherto rare tumour, pleural mesothelioma, was shown to occur relatively frequently in South African asbestos workers [10]. Many subsequent studies have confirmed the relationship of this tumour, and of peritoneal mesothelioma, to asbestos exposure [162–165]. Thus, over the last 70 years society has been confronted with the problem of what action to take when faced with a highly dangerous but also extremely useful industrial material.

### Epidemiology

#### *Asbestos and its uses*

The minerals known as asbestos, a name derived from the Greek work for unquenchable, belong to one of two mineralogical groups, the serpentines and the amphiboles. Chrysotile, or white asbestos, is the only asbestos that is a serpentine; it is a magnesium silicate with a curly configuration and is able to shear into many smaller fibrils. All the other forms of asbestos are amphiboles, straight fibres that do not shear into shorter fibrils. They include crocidolite (blue asbestos), an iron–magnesium–sodium silicate; amosite (brown asbestos) and anthophyllite, iron–magnesium silicates; and tremolite and actinolite, calcium–iron–magnesium silicates.

Chrysotile is the most widely used form of asbestos, some 4 million tonnes being produced annually by the two major producers, Russia and Quebec Province in Canada. Amosite and crocidolite are produced mainly by South Africa, about 250 000 tonnes annually reaching the world markets. Little if any tremolite, anthophyllite or actinolite is now produced commercially, although anthophyllite has been exploited in Finland in the past. Asbestos is found naturally bound into rock and is obtained largely by underground mining. The rock is crushed and the

released fibres carded as in the wool industry; transport of asbestos from producer to user is now exclusively in impermeable plastic bags. The mineral has many uses, and its replacement by safer material has been a major problem for many industries. In particular, it imparts strength to cement, building materials and plastics, is an effective insulator and a durable friction material, is important in fireproofing and is useful as a filler in paints. It may be woven into fire-resistant materials. Thus people may be exposed to asbestos anywhere in the chain from the mine and crusher, the site of production of materials, to the place where the materials are used, deteriorate and are removed. Indeed, exposure to waste asbestos material at dumps is another area of concern. Of particular importance as situations where workers have been, and in some cases still are, exposed to asbestos are asbestos mills, thermal insulation, construction work and demolition, electrical repair work, railway engineering workshops, shipbuilding, ship repair and breaking, gas mask manufacture, boiler repair, and cement and friction product manufacture. Probably the most important occupation in developed countries is asbestos removal and abatement. Important exposures may also have been received by people living close to sources of heavy environmental asbestos pollution and by wives and families of asbestos workers as a result of their dusty clothes. There is little doubt also that careless disposal of asbestos waste has led to exposure of children playing on spoil heaps [166].

### Prevalence

It is not possible to know how many people are suffering the harmful effects of asbestos exposure. However, some idea may be obtained from statistics published by the British Government, which indicate the number of people certified by the Pneumoconiosis Boards as having asbestosis and mesothelioma and the number of death certificates mentioning these conditions [167]. Approximately 1000 people per annum die of mesothelioma in the UK and this figure is still rising (see Fig. 43.15). About 300–400 are diagnosed as having asbestosis, most being retired from work. This figure has been static for several years. While these figures largely reflect a pathogenic response to industrial conditions in the two decades after the Second World War, amphibole forms of asbestos were imported into the UK until 1980 and chrysotile imports only started to decline about that date, so that the maximum exposures in terms of numbers of people probably occurred around 1970 [168]. The incidence of asbestos-related lung cancer is not known, since it is almost never possible in individuals to be sure whether the disease was due to asbestos, cigarettes or both. However, there is no doubt that some workers develop lung cancer who would not have done so had they not been exposed regularly to asbestos; studies of

cohorts of heavily exposed asbestos workers have consistently shown lung cancer excesses as great as the numbers of mesothelioma cases. Thus in the UK although only some 50 people with asbestosis die of lung cancer each year, the numbers of patients in whom asbestos exposure may have contributed to the development of the disease may be considerably greater.

Clearly the incidence of these diseases reflects the numbers at risk of exposure and the cumulative amounts of asbestos to which they have been exposed. Incidence figures in individual countries cannot therefore be applied to other countries, where the workforce and industrial conditions may differ considerably. However, they do give some idea of the order of magnitude of the problem, for example in the UK there are 1000–2000 deaths annually from asbestos-related disease in a working population of approximately 20 million compared with about 30 000 deaths from lung cancer, largely due to cigarettes. This has been recognized as a serious public health problem, though not one that affects the general public but those members of it who work in jobs where exposure to asbestos occurs. The jobs most at risk of such exposure, as estimated from the mesothelioma statistics for England and Wales, are shown in Table 54.3.

### Relationships between exposure to asbestos and disease

There are considerable difficulties in determining the relationships between exposure and response with respect to the asbestos diseases [169]. Firstly, assessment of exposure depends on reliable measurements of airborne asbestos

**Table 54.3** Proportional mortality from mesothelioma in different jobs 1979–80. (from Peto *et al.* [168].)

	Proportional mortality ratio (all mean = 100) and numbers of deaths ( <i>n</i> )
Metal plate work (including shipyards)	700 (110)
Vehicle body builders	619 (35)
Plumbers, gas fitters	443 (201)
Carpenters	356 (254)
Electricians	291 (161)
Upholsterers	283 (19)
Construction workers	256 (187)
Boiler operators	254 (39)
Sheet metal workers	233 (48)
Production fitters	216 (304)
Engineers	211 (105)
Plasterers	203 (27)
Welders	203 (70)
Dockers	195 (69)
Builders and handymen	164 (98)
Machine tool operators	133 (179)
Painters and decorators	131 (100)

having been made for a prolonged period of the working lives of an industrial population. The measurement of asbestos is not a simple matter, depending as it does upon counting fibres of appropriate size under the microscope, and considerable variability between different counters may occur [170]. Secondly, the response is not always easily determined. With respect to mesothelioma, the response is fairly obvious but for asbestosis it may not be; for example, early radiological change or auscultatory crackles may also be subject to considerable interobserver and intraobserver error, as well as being able to be caused by other conditions. With respect to lung cancer, the confounding factor of cigarette smoking has to be taken into account.

Despite these problems, several studies have cast light on this important matter and therefore measures to prevent the diseases are somewhat more securely based now than before. A study of Quebec miners and millers has suggested that a 1% risk of significant functional or radiological abnormalities was associated with exposures estimated to be about 200 fibre-years/mL, i.e. equivalent to 4 fibres/mL for 50 years [171]. In an American asbestos cement factory, similar results were obtained [172]; in a British asbestos textiles factory it was calculated that in order to reduce the risks so that fewer than 1% of workers would develop early signs of asbestosis (defined by the authors as 'possible asbestosis', as diagnosed by the factory doctor) over a 40-year working life the fibre concentration should be between 1.1 and 0.3 fibres/mL [173]. In the UK, regulations to cover workers in jobs with recognized exposure to asbestos were introduced in 1969 and thereafter such workers were exposed to concentrations that should not have exceeded 2 fibres/mL. One study has shown a halving of the prevalence of small radiological opacities and pleural shadows in those exposed only under the regulations [174].

These results indicate that risks are different in different industries, and it seems likely that they are indeed lower in mining, milling and cement production than in textile and insulation work. However, as shown in Table 54.3, those occupations in which mesothelioma is most likely to be found are those in which the largest numbers of people are potentially exposed to asbestos; however, these are not the industries classically recognized as being at risk during production and manufacture of asbestos products but rather those in which the risks arise from secondary exposure [168]. Thus the greatest numbers of cases occur in fitters, carpenters, plumbers and machine tool operators. It seems likely that different types of asbestos have different magnitudes of effect, crocidolite being the most dangerous, followed by amosite then chrysotile. This also becomes particularly obvious when mesothelioma is considered, although in this disease measurements of exposure have rarely been available because of the long time between exposure and development of the tumour.

Studies of workers in the Quebec industry exposed only to chrysotile have shown a very low incidence of mesothelioma [175], whereas workers exposed to amosite alone and crocidolite alone seem to have suffered higher death rates from this disease, up to 4 and 16% respectively of all deaths over about 35 years [176,177]. In particular, studies of gas mask manufacturers, who used crocidolite intensively for periods of up to 5 years during the Second World War, have shown a high mortality from mesothelioma [177,178]. While this suggests that very short exposures may be risky, there is no evidence that this is so unless the exposure is likely to have been very intense. Indeed, there is evidence that risk decreases in proportion to reduction in duration of exposure [179,180]. Careful estimates of likely rates of death among a large cohort of crocidolite workers at Wittenoom, Western Australia have predicted a likely overall mortality around 14% from mesothelioma and 10% from lung cancer, together with some 7% having asbestosis at the time of death [181].

With respect to excess risk of lung cancer, a similar gradient between asbestos types seems to exist. Prolonged exposure to chrysotile seems to increase the risk by a factor of between two and three [171,182], while exposures to amosite of more than 2 years may increase it six times [176]. In crocidolite gas mask workers, exposures of several months doubled the risk of lung cancer [177], while in the Wittenoom study it was estimated that almost half of the 10% death rate from lung cancer was attributable to the asbestos exposure [181]. With respect to lung cancer it is notable that an interaction occurs between cigarettes and asbestos such that the effects of the two probably multiply the risk [183–185]. Thus if a smoker has a risk of lung cancer 10 times that of a non-smoker and someone exposed to high levels of asbestos five times the risk of someone not exposed to asbestos, then someone who both smokes and is exposed may have up to 50 times the risk of a non-exposed non-smoker.

Several studies have suggested a relationship between asbestos exposure and other malignant diseases [186,187]. Of these, the most plausible is laryngeal carcinoma, and it seems quite likely that heavily exposed asbestos workers had an increased risk of this tumour in the past [188–190]. Some have expressed scepticism about this relationship, preferring to attribute it to failure to correct for confounding effects of smoking and alcohol [191]. However, a more likely explanation is that the risks under more recent, better regulated exposures have been much reduced. It is doubtful if the early reports of excess risk of gastrointestinal cancer were valid and it may be that they represented misdiagnosis of peritoneal mesothelioma, a condition well known to be associated with heavy asbestos exposure. There is a suspicion from a case-control study that large-cell lymphoma of the oral cavity and gastrointestinal tract, a very uncommon tumour, may be associated with asbestos [192].

## Clinical features

### *Chest radiography*

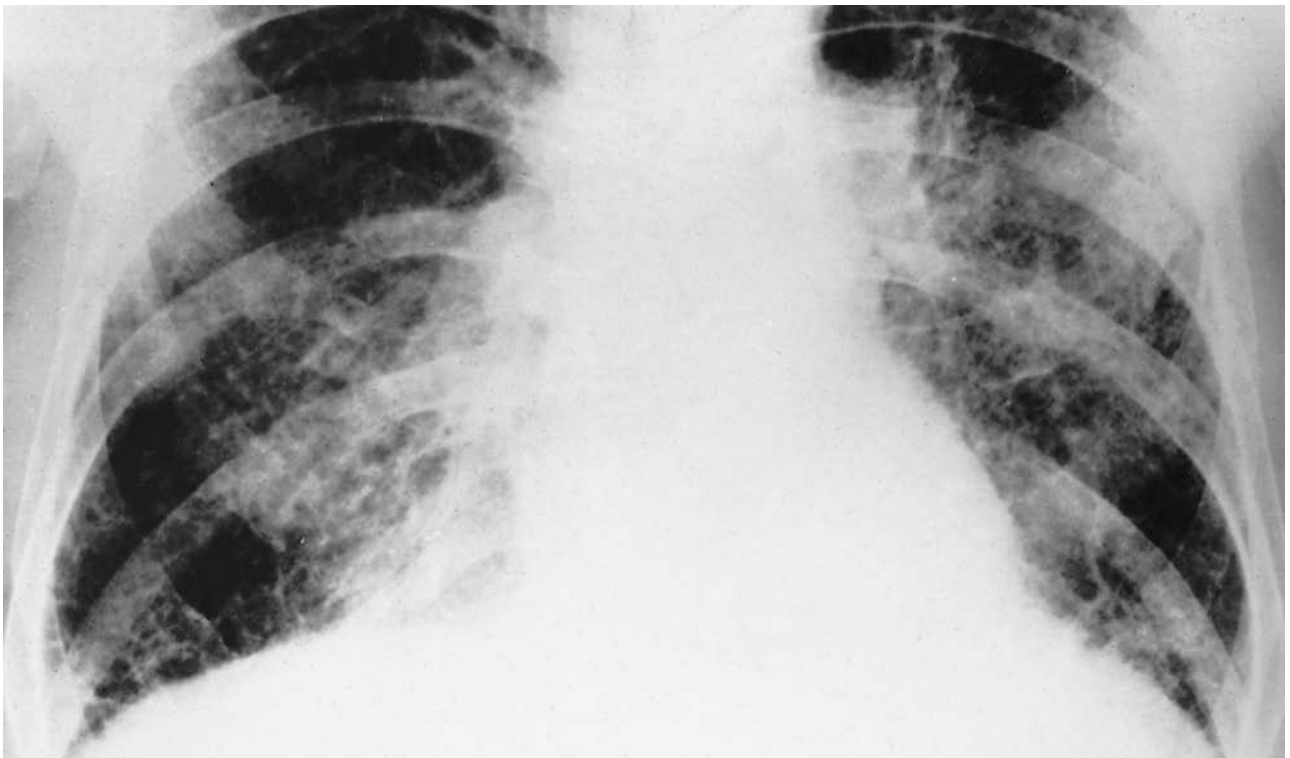
The earliest sign of asbestosis is the appearance of short linear shadows about 1–3 mm thick, predominantly in the lower lung zones. These shadows, classified as category 1s or t (see Chapter 3 for details of the ILO classification), are identical to those seen in the early stages of idiopathic pulmonary fibrosis. Moreover, they cannot be distinguished from what are probably the normal appearances of the ageing lung nor from the radiological effects associated with cigarette smoking [193]. They should not therefore be regarded as in any way diagnostic of asbestosis. As the disease progresses, these shadows become more profuse and gradually obscure the vascular pattern of the lower zones (Fig. 54.19). The individual shadows also often become thicker and take on a more irregular, sometimes stellate or blotchy, appearance. Eventually the appearance of diffuse honeycombing may become apparent. Asbestosis does not occur as a result of occasional or incidental exposure. Once the lesions have appeared they usually progress, although the rate of progression may be slow and sometimes the disease, if caught early and exposure is stopped, appears to arrest [194–196]. However, it is well

recognized that the first signs of asbestosis may occur after asbestos exposure has ceased [197,198]; in these circumstances, progression tends to be comparatively slow. When the radiological appearances of asbestosis appear for the first time after exposure to asbestos has ceased, there is almost always a prolonged history of exposure to the material, usually at relatively low concentrations.

The radiological effects of ageing and cigarette smoke do not usually extend beyond category 1 on the ILO scale of profusion, so that irregular shadows more profuse than this can be taken to indicate pulmonary fibrosis. Whether this fibrosis is due to asbestosis depends on the history of exposure, although radiological evidence may also be helpful in that the presence of pleural plaques, obliteration of costophrenic angles or diffuse pleural fibrosis is indicative of asbestos exposure. Calcified pleural plaques are indeed diagnostic of this, and if they are associated with interstitial fibrosis it is usually difficult to deny that any associated lung fibrosis is due to asbestosis. These pleural lesions are described in Chapter 43.

High-resolution CT is more sensitive than standard chest films for the detection of early interstitial fibrosis in workers exposed to asbestos and nicely demonstrates the peripheral and basal accentuation of the fibrosis. CT also shows calcified and non-calcified pleural disease and the presence of these features helps to tip the diagnostic scales in favour of an asbestos aetiology for the fibrosis in cases of clinical doubt. However, the absence of plaques on CT

**Fig. 54.19** Lower part of chest film of a patient with asbestosis showing well-marked irregular fibrosis and honeycombing.





should not be taken to exclude the presence of asbestosis if there is an adequate history of exposure, since not all plaques are visible on the scan. In the author's opinion, in the absence of pleural disease it is not possible to differentiate between early asbestosis and early cryptogenic fibrosis from the CT features alone; equally pathologists are reluctant to diagnose the cause of fibrosis from macroscopic inspection of the lung! However, a few features help to increase the confidence with which a diagnosis of asbestosis can be made [199]. Pleural fibrosis with bands extending into peripheral lung are common in asbestosis (Fig. 54.20) and rare in the cryptogenic disease, while fibrosis extending into upper lobes is uncommon in asbestosis. It should be noted that reports showing clear differences between these two diseases are at serious risk of bias from selection of the relatively few 'typical' subjects studied.

### *Symptoms and signs*

The patient always gives a history of working either directly with asbestos or adjacent to others working with the material, usually in very dusty conditions and over a prolonged period. It is most unusual nowadays in the West to see the disease in anyone who has been exposed to asbestos for less than 20 years. As mentioned above, the condition may present after exposure has ceased. The symptoms are exertional dyspnoea and, often, dry cough. The dyspnoea gradually becomes more severe and eventually may be completely disabling, the patient dying of cardiorespiratory failure. This course is uncommon, most patients developing the disease relatively late in life and their disability being moderate rather than severe. The

most common presentation in the western world is a patient who has been found to have minor radiological changes (usually pleural) on a coincidental chest radiograph, has no symptoms, but has crackles audible at the bases and minimal interstitial fibrosis on CT. However death from one of the malignant complications of asbestos exposure, bronchial carcinoma or mesothelioma, is of much more frequent occurrence. Although dependent to some extent on individual susceptibility, prognosis is also related to the amount of asbestos to which the worker has been exposed; thus heavy exposures resulting in early development of disease may be expected to result in more rapid progression, whereas asbestosis developing only after 30 years of work with the material may be expected to progress very slowly and does not usually itself influence life expectancy.

The earliest sign of asbestosis is the presence of repetitive end-inspiratory crackles, heard at the lung bases posteriorly or in the axillae [200,201]. These signs are not specific to asbestosis but in the presence of a convincing history of exposure are strong evidence of the disease. As the disease progresses, the crackles become more profuse and are heard earlier in inspiration, in early expiration and further up the lung. Only at this relatively late stage in the natural history of the disease is clubbing of the digits usually present [202]. As the disease reaches its terminal stage, diminished chest wall movements, tachypnoea and evidence of cor pulmonale may be detected, with cyanosis, tall jugular *a* waves, right ventricular heave and gallop rhythm. Gross oedematous right heart failure is uncommon, the patient usually dying of hypoxic respiratory failure.



**Fig. 54.20** High-resolution CT of patient with pleural fibrosis showing early interstitial fibrosis and marked pleural thickening with calcification and bands passing into the peripheral lung.

### Lung function

The functional abnormalities associated with asbestosis are progressive reduction in carbon monoxide diffusing capacity, vital capacity and total lung capacity, with normal residual volume [203–205]. Compliance is decreased and lung recoil pressure increased. Hyperventilation and arterial oxygen desaturation may occur on exercise in the more advanced stages. These changes are not of course diagnostic of asbestosis but characteristic of any form of chronic pulmonary fibrosis.

Some authors, taking cognizance of the fact that the earliest pathological change involves respiratory bronchioles, have shown early changes in expiratory flow rates in subjects with relatively short but heavy exposures [206,207]. From a practical clinical point of view the most useful test for detection of significant asbestosis is the *DLCO*, and deterioration in this closely mirrors disease progression. Only as the disease reaches an advanced, and usually clinically very obvious, stage do lung volumes deviate sufficiently from the predicted range to be unequivocally abnormal. In keeping with this, the transfer coefficient (*Kco*) is usually low. However, this index of lung function may be paradoxically increased in patients with extensive pleural fibrosis [208], so the combination of pleural and pulmonary fibrosis in an asbestos worker may be associated with low *DLCO* and alveolar volume and a relatively normal *Kco*.

### Pathology

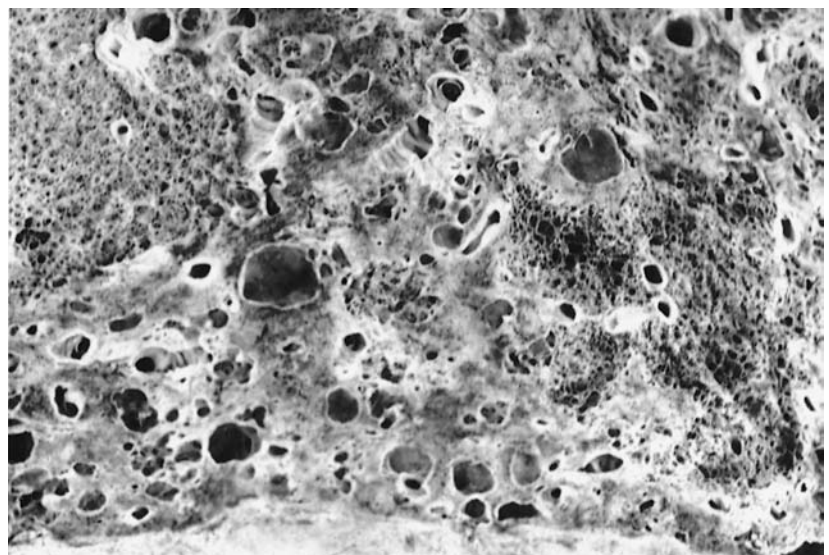
The macroscopic appearances of asbestosis are of grey-white fibrosis, most marked in the lower zones. If the disease is advanced, honeycomb changes may be apparent (Fig. 54.21). Parietal pleural plaques are usually

present and diffuse fibrosis involving both layers of pleura and extending into the surface of the lung may also be seen. These pleural changes are described in Chapter 43.

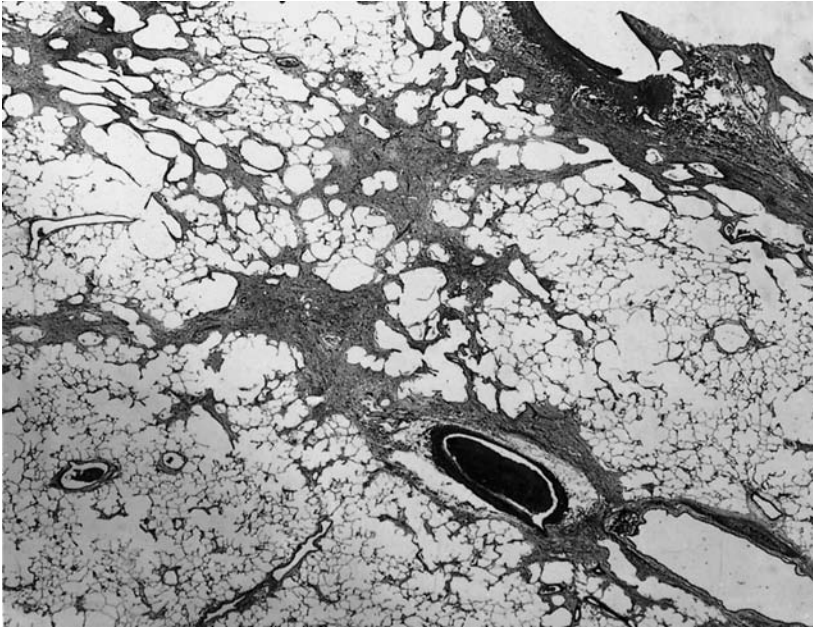
Microscopically, the earliest change is an alveolitis around asbestos fibres in the respiratory bronchioles [209–211]. In experimental lesions the first response to asbestos deposition in the acinus can be seen to be an influx of macrophages, some of which disintegrate and become surrounded by fibrin and subsequently collagen [212]. The most peripheral airspaces and the interstitium are initially free of fibrosis but as the lesion develops it can be seen to spread into alveolar walls and along the respiratory bronchioles to the distal alveoli, resulting in widespread diffuse fibrosis (Fig. 54.22). The appearances of honeycombing result from a dilatation of small bronchi and bronchioles in uninvolved parts of the lung due to their retraction by surrounding fibrosis [213]. Massive areas of fibrosis have been described but are different from PMF in other pneumoconioses in that they represent confluent areas of irregular fibrosis. Caplan lesions have also been described very rarely [214].

Asbestosis may be complicated by silicosis in asbestos miners, as has been described in South Africa; when this occurs the distribution of the diffuse fibrosis may be predominantly in the upper zones of the lung. There is not thought to be an increased frequency of tuberculosis in patients with asbestosis, although workers with concomitant silicosis may develop this complication, especially if, as in South Africa, the disease is endemic in the area. As mentioned previously, the most important complication of asbestosis is bronchial carcinoma.

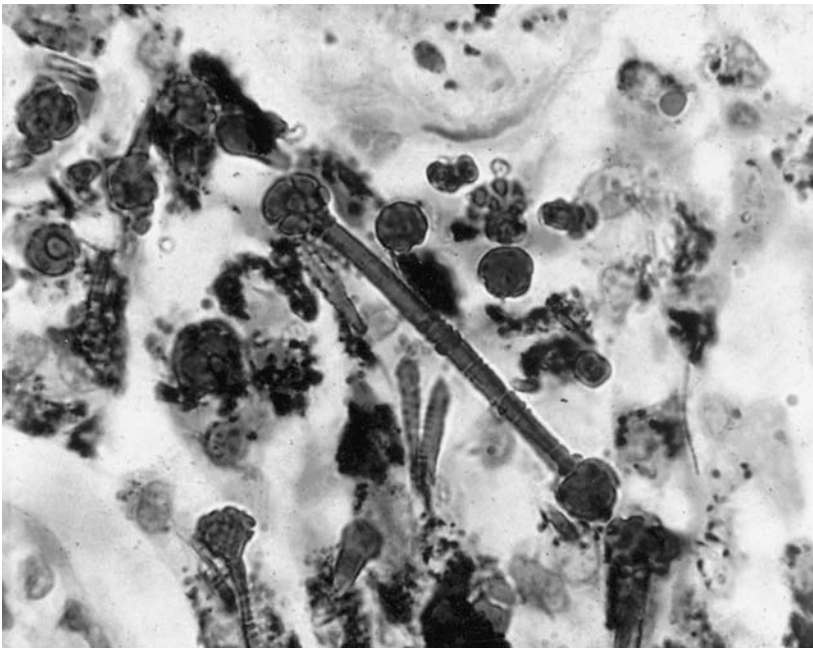
The feature that differentiates asbestosis from other forms of pulmonary fibrosis is the presence of asbestos in the lungs. On light microscopy, asbestos fibres are generally too fine to be seen and the clue comes from the



**Fig. 54.21** Lung slice showing lower zone fibrosis of asbestosis. Two areas of relatively normal lung, to left and right, are separated by coarse irregular fibrosis.



**Fig. 54.22** Low-power view of early asbestosis showing peribronchiolar fibrosis.



**Fig. 54.23** Asbestos bodies in human lung. A few small uncoated fibres are also visible.

presence of ferruginous bodies. These are yellow-brown structures, about 2–5  $\mu\text{m}$  in width and up to 150  $\mu\text{m}$  in length. They have a beaded appearance and clubbed ends (Fig. 54.23) and probably derive from deposition of ferritin and protein onto the asbestos fibre within the body of macrophages. Electron microscopy shows the asbestos body to be formed around a single fibre of asbestos, usually an amphibole, though it may occasionally form around other fibrous particles [215–217]. Such structures also form around other mineral fibres, most of which do not have the same pathogenic significance of asbestos, so

care should be taken before concluding that they are indeed due to asbestos exposure. Electron microscopy with energy-dispersive X-ray spectroscopic analysis is the only sure means of identifying the minerals present in the tissue [218]. This expensive technique is not necessary for clinical purposes but is useful in research on mineral-induced lung disease and is increasingly being used in civil litigation in efforts to strengthen evidence of exposure to asbestos.

Often relatively few asbestos bodies may be seen, even in advanced asbestosis. This is because only a very small

proportion of inhaled asbestos fibres are dealt with in this way by the lung's defences. Most fibres remain uncoated but are often less than  $0.5\mu\text{m}$  in diameter and therefore invisible on light microscopy. Special techniques of lung ashing and examination of residues by phase-contrast optical microscopy or electron microscopy allow an assessment to be made of the numbers of fibres that may be present in the lung. Using optical microscopy, such studies have shown up to 30 000 fibres/g of dried lung in apparently unexposed individuals, counts of 100 000 fibres/g or more in asbestos workers and over 3 million fibres/g in subjects with asbestosis [219,220]. Use of electron microscopy allows these figures to be multiplied by one or two orders of magnitude but also shows that many of the fibres in unexposed people are minerals other than asbestos [221].

### Pathogenesis

In order for asbestosis to develop, sufficient numbers of fibres must penetrate to the acinar parts of the lung. The aerodynamic characteristics of fibres are such that their diameter must be less than about  $3\mu\text{m}$  in order for them to remain suspended in the inspired air to acinar level. Fibres are arbitrarily defined as structures three times as long as they are wide; thus a fibre may be of almost any length if sufficiently narrow and indeed many crocidolite fibres are only  $0.1\mu\text{m}$  in diameter. However, there is increasing evidence that in order to have a pathogenic effect fibres must be too long to be engulfed completely by macrophages and therefore fibres of less than  $10\mu\text{m}$  are probably of little

pathological significance [139,222] (Fig. 54.24). Furthermore, the shape of the fibre is probably important, such that chrysotile, with its curly configuration, is more liable to be intercepted by contact with bronchial walls than are the straight amphibole fibres [223]. Once the fibre has penetrated to acinar level, another factor of pathogenic importance is its durability [224]. This may prove to be of overriding importance in assessing the possible health effects of new fibrous substitutes for asbestos, such as glass and other synthetic fibres. A fibre that remains intact despite the attack of the lung's macrophages and the physical and chemical trauma of residence within a constantly moving organ is the one with the greatest potential harmfulness.

The mechanisms of fibrogenesis are not fully understood. *In vitro* studies show asbestos not to be very toxic to macrophages, though some studies have indicated that release of cytokines and reactive oxygen species may play a part [139]. Lavage studies in rats have shown only a moderate immediate cellular response to asbestos inhalation, in contrast to the rapid recruitment of polymorphonuclear cells that occurs with coal and quartz inhalation [225]. Nevertheless, like the human lung, the rat lung responds by production of diffuse fibrosis and bronchial carcinomas. Even more strikingly, as discussed in Chapter 43, injection of asbestos of any type into the pleura or peritoneum of a rat produces a dose-dependent incidence of mesothelioma; with appropriate doses almost 100% of rats die of this disease [226].

The epidemiological differences between the effects of chrysotile and of the amphiboles (i.e. the former seems to

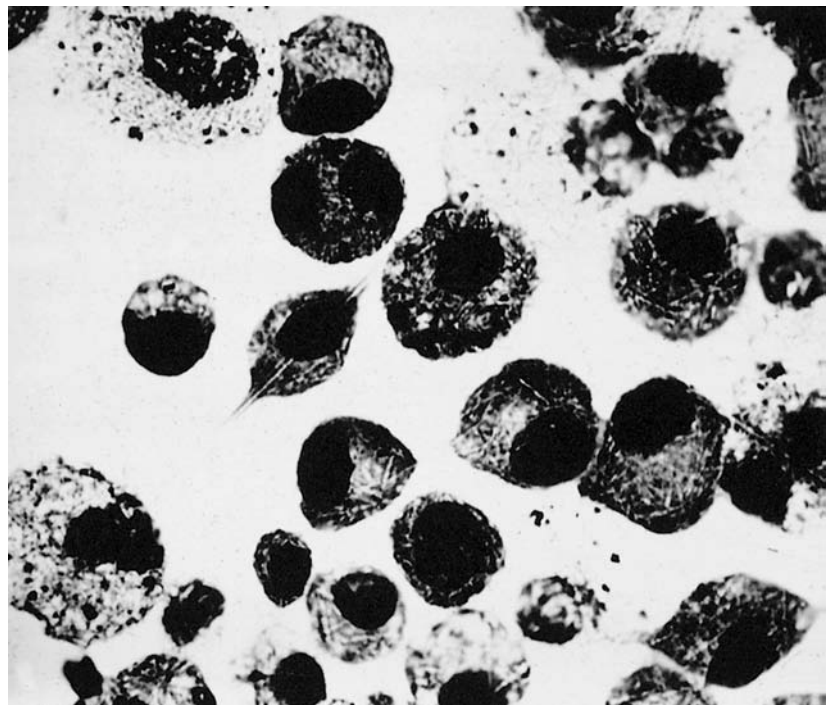


Fig. 54.24 Macrophages in culture with asbestos: several have engulfed short fibres but in two cases the fibres are too long and protrude through the cell membrane.

cause less disease dose for dose than the latter) may be explicable on the basis of two factors: (i) chrysotile is filtered out more efficiently by the airways because of its shape and its tendency to clump into groups of fibres and (ii) once inhaled, chrysotile is gradually broken up into tiny fibrils that because of their size are gradually removed by macrophages. This hypothesis explains why mesothelioma is so much less common in workers exposed to chrysotile than in those exposed to amphiboles, since in the long time period required for sufficient asbestos to migrate to the pleura chrysotile is broken up. However, it still has time to initiate the processes of fibrogenesis and bronchial carcinogenesis. In support of this hypothesis, studies of the lungs of workers exposed to a mixture of asbestos types have in general shown unexpectedly high proportions of amphiboles in relation to the amounts to which they were exposed during life [224,227].

### Management

People exposed to asbestos may present to their doctors for a number of different reasons, and it is more usual to see such individuals before they develop disease than after. The usual reasons for presentation are discussed below.

1 A well person with no radiological abnormality has found that he or she has been or is currently exposed to asbestos. This is often due to the discovery of fixed asbestos materials in the house or workplace rather than to actual work with the material. Such people should be reassured that the risks of such incidental exposure are of no account. However, the physician should give general advice on future avoidance of exposure to airborne asbestos. If the workplace is the suspected source of exposure, the employer should be encouraged to seek the opinion of an occupational hygienist, and if thought necessary the regulatory authority, in the UK the Health and Safety Executive, should be contacted.

2 A fit person has been found to have pleural plaques on chest radiography. Again, the individual should be reassured once it has been established that current exposure to asbestos has ceased. Advice against smoking should be given but follow-up in clinics should not be arranged, since it serves no purpose other than to increase the subject's anxiety. There is no evidence that pleural plaques increase risks of any other disease, and any risks of lung cancer and mesothelioma relate to the history of asbestos exposure and, in the case of lung cancer, to smoking.

3 An asbestos worker presents with early irregular basal X-ray shadows and no symptoms. The diagnosis is made on the occupational history, radiological findings and presence of repetitive inspiratory crackles. Further exposure to asbestos should be discouraged, since detection at

an early stage may be associated with only very slow progression unless more asbestos is added to the load in the lungs. In the UK, if the worker has been employed, as opposed to self-employed, he or she should be encouraged to apply for pneumoconiosis benefit, which is awarded in proportion to the disability as assessed by the doctors of the Medical Board for Respiratory Diseases of the Department of Social Security. Since the risk of lung cancer is much increased, the individual should be discouraged from smoking. Such patients commonly sue their previous employers.

4 Patients presenting with late-stage, previously undiagnosed, asbestosis should be encouraged to apply for pneumoconiosis benefit. Treatment should be along routine lines for patients with respiratory failure, with provision of domestic aids, oxygen for symptomatic relief of breathlessness, diuretics for right heart failure and antibiotics for acute infections. Corticosteroids are of no value and should be avoided. In a patient of appropriate age and general health who does not smoke, transplantation would be an option (see Chapter 59).

### Prevention

In taking steps to prevent asbestos-related diseases, two important points need to be borne in mind. Firstly, mesothelioma is almost always due to exposure to amphiboles and therefore avoidance of all use of these types of asbestos will eventually largely eliminate the disease. In the UK, crocidolite has effectively been excluded (by the imposition of very strict hygiene standards) since 1970 and amosite use has been restricted in the same way since 1980. Furthermore, tight regulation of asbestos removal since 1970, especially where amphiboles are concerned, should have ensured that mesothelioma would soon become a rare condition once again. However, it has now become apparent that most cases of mesothelioma occur in people working in effectively unregulated industries, with exposure to asbestos that has been *in situ* for many years, and that the epidemic of this disease is therefore likely to peak around the year 2020 and only decline to current levels some decade or two after that [168]. Secondly, asbestosis and lung cancer develop in relation to the dose of asbestos to which people are exposed. Therefore, occasional and incidental domestic or workplace exposures are likely to be of no significance. Such risks of death have been calculated to be considerably less than those associated with driving daily to work or living in a house with a smoker for example [169]. However, the risks that are run by someone working with asbestos on a regular basis are more easily imagined. While it is probable that risks of clinically significant asbestosis may be eliminated by preventing workplace exposure to more than 0.5 fibres/mL over a lifetime, these exposure levels may still entail a risk of developing lung

cancer, dependent partly on the smoking habits of the workforce, rising to perhaps 6 per 1000 for men exposed to the mineral for 35 years from the age of 20. For a discussion of these risks and the assumptions made in calculating them, the reader is referred to the monograph of Doll and Peto [169].

Thus the prevention of asbestos-related disease depends on reduction or elimination of exposure to the mineral. This should be achieved by the enforcement of a strict code of practice in handling the material, by increased public awareness of its hazards (thus ensuring it is handled with respect) and by the setting of appropriate hygiene standards. Currently in the UK the maximum allowable concentration of chrysotile is 0.5 fibres/mL, while the use of crocidolite and amosite is effectively prevented by a standard of 0.2 fibres/mL. Regulations also enforce the wearing of protective clothing and full-face respirators by workers removing asbestos, effective sealing off and vacuuming of such areas and safe disposal of the waste material. Other countries have their own regulations, which range from a complete ban on the use of asbestos to none at all.

### **Disease due to other silicate materials**

Although coal, quartz and asbestos are the three minerals containing silicon to which humans are most frequently exposed, there are other compound silicates that either occur naturally or are synthetic which may expose the lungs to hazard. In general, their toxic effects are likely to be similar to those of coal if they produce amorphous airborne dusts or similar to those of asbestos if they produce fibrous dusts. The most important such minerals are kaolin, fuller's earth, mica and cement, which are all amorphous; talc, which has a plate-like shape; and mullite, erionite, attapulgite, sepiolite and wollastonite, which are fibrous. Synthetic fibres are also considered here, as is oil-shale, which contains a complex mixture of clay minerals.

### **Non-fibrous silicates**

#### ***Talc***

Talc is a hydrated magnesium silicate with multiple uses as a lubricant and filler in cosmetics, paper and rubber manufacture, paints and building materials. It is mined in Canada, the USA, Russia, Italy and the Pyrenees, and in some of these places is associated geologically with tremolite asbestos. Cosmetic talc should be free of asbestos [228,229], but industrial grades may contain it as well as other minerals such as quartz and accordingly should be carefully handled.

The coincidence of talc and fibrous tremolite in the mineral deposits has caused some difficulty in deciding

what the true effects of talc are on the lung. Talc miners have been shown to have an increased risk of pleural plaques, diffuse pulmonary fibrosis and lung cancer [230–232]. However, these effects were probably due to the tremolite (though this is of little consequence when it comes to protecting the miners and millers, who continue to be exposed to both minerals). In places where exposure has been to pure talc, the disease described is a nodular pneumoconiosis with a tendency for the small nodules to aggregate and form PMF, similar to silicosis [232]. There is no evidence that exposure to talc is carcinogenic unless associated with fibrous tremolite. A follow-up survey of people who had previously been treated for pneumothorax with insufflation of medicinal grade talc into the pleural space showed no excess mortality and no cases of mesothelioma [233].

Some rather more bizarre hazards of talc have been described. One man has been recorded as giving himself pneumoconiosis by obsessive overuse of talcum powder [234], another by enthusiastic work as a talc aerosol inspector [235] and a third by inhaling (illegally) the contents of medicinal capsules prior to performing as a punk-rock drummer [236]. Talc may also initiate bronchoconstrictive episodes when inhaled by babies [237] and is of course one of the means by which intravenous drug abusers accidentally kill themselves [238].

#### ***Kaolin and other clays***

Kaolin consists mainly of the mineral kaolinite, a hydrated aluminium silicate, and is produced in south-west England, the USA, Japan, Egypt, Czechoslovakia and Germany. It is quarried by washing it out of the deposits with water and is then dried and milled for use in ceramics, paints, paper, soap and pharmaceuticals. Both simple and complicated pneumoconiosis have been described in workers in the milling and bagging plants, the pathological and radiological appearances being very similar to those of coal-workers' pneumoconiosis [239,240]. In particular, kaolin does not produce the highly collagenous lesions seen with quartz inhalation, unless the worker has been exposed to a mixed silica-containing dust. Studies of lung function in patients with kaolin pneumoconiosis have shown results similar to those described in coal-workers, with impairment associated with PMF and a possible dust-related obstructive and restrictive component in subjects with simple pneumoconiosis [241–243].

Fuller's earth is an absorbent clay that was named after its early use in fulling, the removal of grease from wool. It usually contains calcium montmorillonite, an aluminium silicate, and is obtained by quarrying in the UK, the USA and Germany. It is used as a filter, filler and binder for foundry moulds. A relatively benign simple pneumoconiosis, occasionally progressing to PMF and very similar

to kaolin pneumoconiosis, has been described in production workers [244,245].

Oil-shale was mined in Scotland until 1962 for the production of mineral oil. Other deposits have been mined in France and Estonia, while enormous amounts wait to be exploited in the Rocky Mountains in the USA. The rock is crushed and heated in retorts to produce the oil which is then refined. Skin cancer is a well-known hazard of workers exposed to the oil [246], although pneumoconiosis has been described in the miners and dust-exposed surface workers [247,248]. The disease appears relatively benign, although PMF has occurred occasionally and a mixed restrictive and obstructive dysfunction has been described in the simple disease [249]. It is probably due largely to the kaolin component of the shale. Epidemiological studies have shown no associated lung cancer hazard [250].

It should be remembered that mining or quarrying and production of clays may expose workers to a risk of silicosis if the clay deposit contains substantial amounts of quartz. This may be the case with ball clays, used in earthenware and bricks, and bentonite, which is used in the same applications as fuller's earth [103,251,252]. In addition, some clay minerals such as palygorskite, attapulgite and sepiolite have a fibrous habit and are mentioned below.

### *Mica*

There are two commercially important forms of mica: muscovite, a potassium–aluminium silicate, and phlogopite, a magnesium–aluminium silicate. The former is transparent and both are resistant to heat and electricity. They are mined in North America and India and used in furnace windows, as fillers in papers and paints, and in insulating materials in the electricity industry. There have been occasional reports of pneumoconiosis among workers exposed to ground mica, usually of a nodular type but diffuse interstitial fibrosis has been described [253–256]. However, such episodes seem to be rare.

Vermiculite is another form of mica mined mainly in the USA and South Africa and used predominantly as an insulation material. Some of the mineral deposits are contaminated with fibrous amphiboles and it is likely that the reports of radiological disease and increased cancer mortality in these workers have been largely due to this contamination [257–259].

### *Cement*

Cement is produced by heating a crushed mixture of limestone and clay or shale in a long rotary kiln. The clinker produced is mixed with gypsum and slag, crushed, and ground in ball mills. The product consists largely of

calcium silicates and aluminates. There is some evidence that cement workers may develop simple pneumoconiosis and decrement in ventilatory capacity, although adequate studies need to be carried out [260,261]. Workers handling and producing asbestos cement are at risk from exposure to the asbestos.

### **Fibrous silicates**

Enough is now known about the nature of tissue damage from fibrous minerals to be able to generalize about risks to health from exploitation of any such new material. It is stressed that this is a generalization and that there may be exceptions; nevertheless, this information may be used as a guide to manufacturers and as a means of designing preventive measures in industry [262]. The factors that determine toxicity, in terms of both fibrogenicity and pleural carcinogenicity, are the length and diameter of the fibres to which workers are likely to be exposed and the solubility of the fibres. Fibres longer than about 10 µm are likely to be retained in the lung, while shorter fibres are likely to be removed. Thus short fibres act like amorphous dusts and are generally harmless unless inhaled in very high concentrations. Fibres wider than 3 µm are unable to reach the respiratory epithelium in sufficient numbers, and can also therefore be regarded as relatively benign. Once in the acinus, the factor that primarily determines toxicity is the solubility of the fibre and therefore its ability to remain in the tissue [263,264]. Relatively soluble fibres such as most glass fibres will dissolve quickly and cause no disease whereas insoluble fibres such as some ceramic and carbon fibres might be expected to persist much longer and ultimately lead to fibrosis and sometimes neoplasia.

### *Erionite*

Erionite is a naturally occurring fibrous aluminium silicate found in volcanic rocks. It is not used commercially but may be the cause of disease in people who are digging through the rock. In particular, it occurs in parts of Turkey where villagers have been in the habit of cutting into the rock to make their homes and to produce building materials and stucco [265–267]. The inhabitants of these villages have been shown to have a very high rate of pleural plaques, pulmonary fibrosis, lung cancer and mesothelioma. In other words, the mineral behaves in the body like asbestos, which it resembles physically but not mineralogically. These observations have been important in supporting the hypothesis that the effects of asbestos are due to its size and shape rather than its chemical and mineralogical characteristics. They imply therefore that other minerals of similar shape and size may have similar effects and should therefore be handled with care.



Deposits of erionite occur in other parts of the world, particularly in desert areas of Nevada and Utah in the USA. There is a potential for human exposure, for example in digging missile silos, and one patient who lived and worked in such an area has been described as having pulmonary and pleural fibrosis associated with erionite in his lung [268].

### *Synthetic fibres*

The realization that the fibrous shape of asbestos is likely to be important in the pathogenesis of disease has led to anxiety about the production and use of synthetic glass wool, rock wool, carbon and ceramic fibres, which are widely used as asbestos substitutes. Experimentally, some of these fibres have been shown to cause mesothelioma if they are introduced into the rat pleura and are sufficiently fine and long [269,270]. Studies of human workforces exposed to them have not so far shown any significant degree of hazard from mesothelioma or non-malignant respiratory disease, although there is some evidence from very large epidemiological studies in Europe and the USA of a slight increase in risk of lung cancer in workers with prolonged exposure to rock/slag wool [271,272]. Some of this risk may have been a consequence of exposure to other carcinogens in the early stages of the industry, but an open mind should be kept, especially with respect to the use of relatively insoluble fibres. Moreover, the apparently low incidence of disease may be due to the relatively low exposure of workers to fine respirable fibres and should not be taken as an indication of harmlessness if finer fibres are to be used in future applications.

### *Other fibrous silicates*

Mullite, another aluminium silicate, occurs as a result of combustion of coal and is a component of fly ash, the ash residue from power stations. It has a fibrous shape, though the fibres tend to be short. It is commonly identified in human lungs when their mineral content is being measured by electron microscopy, although whether it is harmful has not been established. Interstitial lung disease has been described in men using it in the production of cat litter [273]. Attapulgite, palygorskite and sepiolite are fibrous clay minerals that have commercial applications as absorbents and filter materials. Again, there have been occasional reports of pulmonary fibrosis in those working with attapulgite and it seems possible that there may be a hazard with high exposures [274]. There is also a suspicion that attapulgite miners may have an excess risk of lung cancer, though this cannot be said to be firmly established [275]. In general the fibres are rather short and therefore likely to be less harmful than asbestos. Wollastonite, a fibrous calcium silicate, is used in ceramics and as an asbestos substitute. These fibres are also short but there

has been one report of possible pulmonary fibrosis and pleural plaques in exposed workers [276].

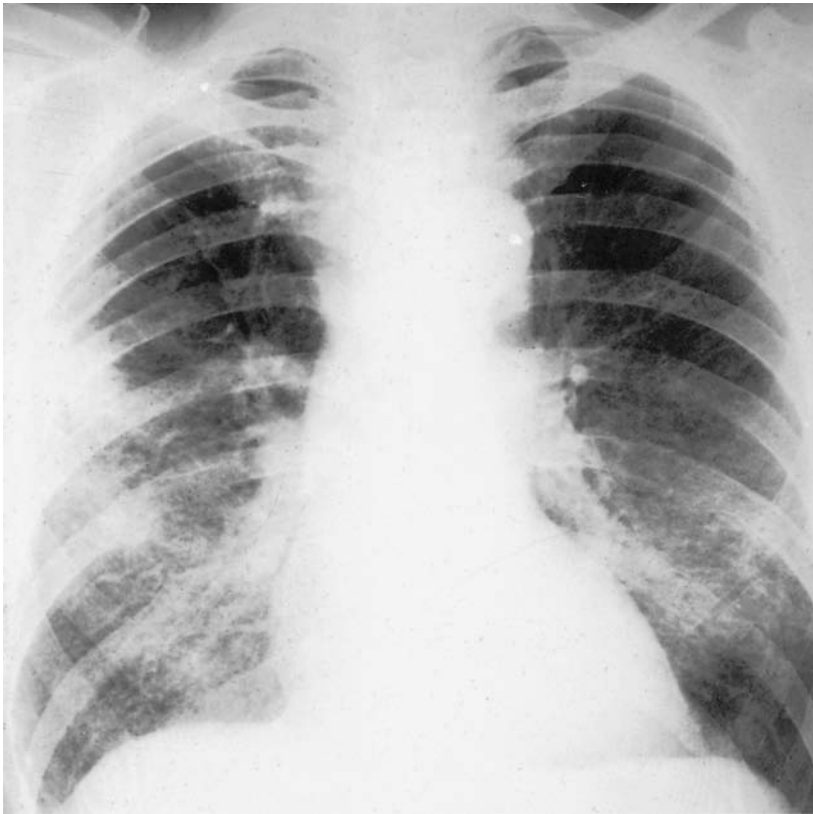
## **Siderosis and mixed-dust pneumoconioses**

### **Siderosis**

Pure siderosis is due to deposition of iron oxides in the lung, where they are taken up by macrophages in both the alveoli and interstitial tissue. No fibrous reaction occurs but the chest radiograph shows multiple radiodense nodules due to the presence of the iron (Fig. 54.25). The condition occurs in arc welders and oxyacetylene cutters due to the presence of iron oxides in the fume from the heated metal [277]; it should be noted that welders and cutters may also be exposed to other metals and carbon in the fume and that pneumoconiosis in such workers cannot always be assumed to be pure siderosis. Siderosis also occurs in silver polishers, who use iron oxide (jeweller's rouge) to polish the metal [278]. The radiological changes of siderosis tend to regress after exposure ceases and the condition in its pure form is not associated with abnormality of lung function [279]. There has been debate about the possible carcinogenicity of inhaled iron, based on the known increased hazard in haematite miners (see next section) and an excessive death rate from lung cancer noted by the British Registrar General. However, it seems likely that iron itself is not carcinogenic and that when cancer occurs it is probably due to concomitant exposure to other carcinogens in either cigarettes or the occupational environment.

### **Mixed-dust pneumoconioses**

Mixed-dust pneumoconiosis is a convenient term covering pneumoconioses occurring in a variety of trades in which the inhaled dust is a mixture of silica and other substances. Strictly speaking, coal-workers' and shale-miners' pneumoconioses are mixed-dust pneumoconioses. The pathological reaction and its physiological consequences depend on the constituents of the dust though, in general, the higher the proportion of silica, the more closely the disease resembles silicosis. Haematite miners' lung is an example of this. The iron ore, haematite, was mined in Cumbria where it was noted that miners developed pneumoconiosis often after many years of exposure underground [280,281]. Both simple pneumoconiosis and PMF occurred and at postmortem the lungs were noted to be brick-red in colour [282]. Pathologically, the appearances are those of silicosis with the additional feature of accumulation of iron pigmentation. Haematite miners in the UK were shown to have an increased risk of lung cancer, although this was almost certainly related to exposure to radon daughters in the mine atmosphere [283].



**Fig 54.25** Welders' siderosis showing diffuse pin-point opacities. The peripheral lesion in the right mid zone was removed at thoracotomy and proved to be a carcinoma.

Other workers who may develop pneumoconiosis related to inhalation of a mixture of iron oxides and silica are foundry workers, especially fettlers, welders and burners, boiler scalers and ochre miners. Any worker exposed to a mixed dust containing more than about 10% quartz is liable to develop silicosis.

### **Berylliosis**

Beryllium ore (beryl or beryllium aluminium silicate) is mined predominantly in South America. The metal is extracted from the crushed ore by heating and treatment with sulphuric acid or fluoride and is used as an alloy in the manufacture of components in X-ray equipment, atomic reactors, the aerospace industry, armaments and heat-resistant ceramics. These alloys have the properties of tensile strength, resistance to corrosion, metal fatigue and heat, as well as being non-magnetic, transparent to X-rays and of high electrical conductivity.

### **Effects of exposure to beryllium**

Exposure to beryllium fume or salts may occur in extraction, refining or production of alloys. In the UK a few cases of berylliosis have occurred in workers producing and breaking fluorescent lights, which used to be coated with the metal, and in refinery workers [284]. The greatest

experience of the harmful effects of beryllium comes from the USA, where a registry of cases has been kept at the Massachusetts General Hospital since 1952 following a postwar epidemic of the disease [285–287].

Exposure to high concentrations of beryllium fume may cause an acute toxic pneumonitis, with oedema of mucous membranes from pharynx to small airways together with pulmonary oedema [285]. The radiograph shows evidence of the pulmonary oedema and the clinical signs are tachypnoea, cyanosis and diffuse inspiratory crackles. Mild cases of the condition are usually self-limiting but severe cases may need treatment with oxygen and corticosteroids to prevent a fatal outcome. Approximately 10% of patients with acute berylliosis have progressed to the chronic form of the disease.

Chronic berylliosis was first described in 1946 [286]. It is different from other mineral pneumoconioses in that it is a systemic hypersensitivity disease, with principal effects on the lung and skin. Sensitization usually occurs by inhalation of dust or fume of the metal or its salts but may occur by introduction of beryllium into the skin through an abrasion. Only a small proportion of those exposed have developed the disease, often after a prolonged latent period and sometimes after a relatively light exposure. Cases have occurred in wives of workers, presumably from beryllium carried on clothing, and in people living close to beryllium refineries.

### Clinical features

The disease may present years after exposure to beryllium has ceased [288,289]. It should be a routine in patients presenting with apparent sarcoidosis to ask about possible exposure to the metal in the past, as in ceramics, metal alloying, the nuclear industry or even dental prosthetics [290]. It has also been described in wives of such workers who have been exposed to their husbands' contaminated clothes [291]. The symptoms are cough and dyspnoea and the course of the untreated disease is usually progressive. However, an apparently self-limiting variant has been described in people exposed to beryllium in rather low concentrations [292], in whom minor radiological changes appeared and subsequently disappeared without treatment. Finger clubbing only occurs rarely and inspiratory crackles are not a feature of the early disease, although they may appear as fibrosis becomes established. Hepatosplenomegaly may occur, as may macular skin lesions, although generalized lymphadenopathy and uveitis are not features. Pneumothorax and cor pulmonale are complications of advanced disease. As in sarcoidosis, hypercalcaemia, hypercalciuria and nephrocalcinosis may also occur, but the other less common manifestations of sarcoidosis such as cardiac and neurological involvement have not been described.

The radiographic changes are initially a diffuse fine granularity that evolves into a reticulonodular pattern and finally irregular fibrosis, often of a coarse generalized type as in chronic sarcoidosis [293] (Fig. 54.26). Bilateral hilar adenopathy may occur but only when there is also evidence of interstitial lung infiltration. As would be expected, the functional changes are those associated with

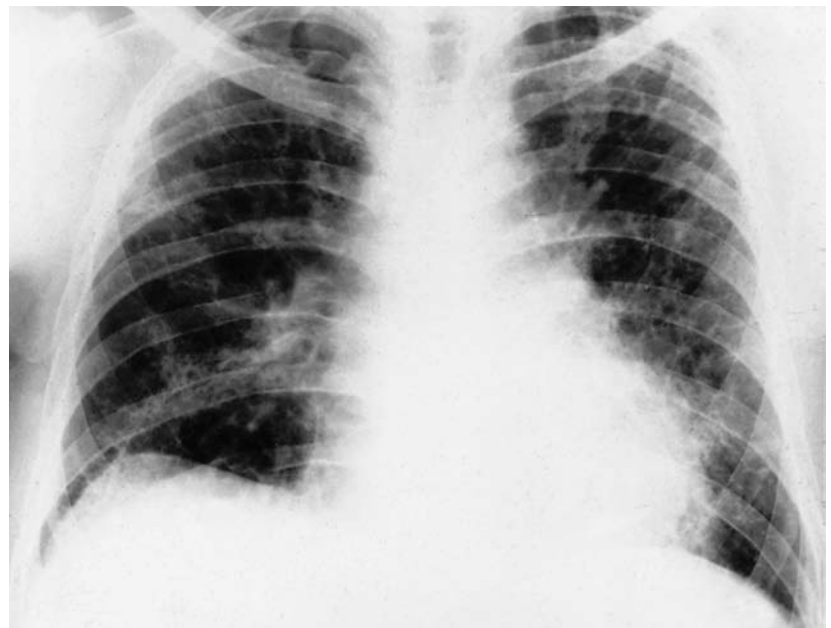
diffuse interstitial disease, with reduced *DLCO* and progressive reduction in lung volumes and compliance as fibrosis increases [294].

### Pathology

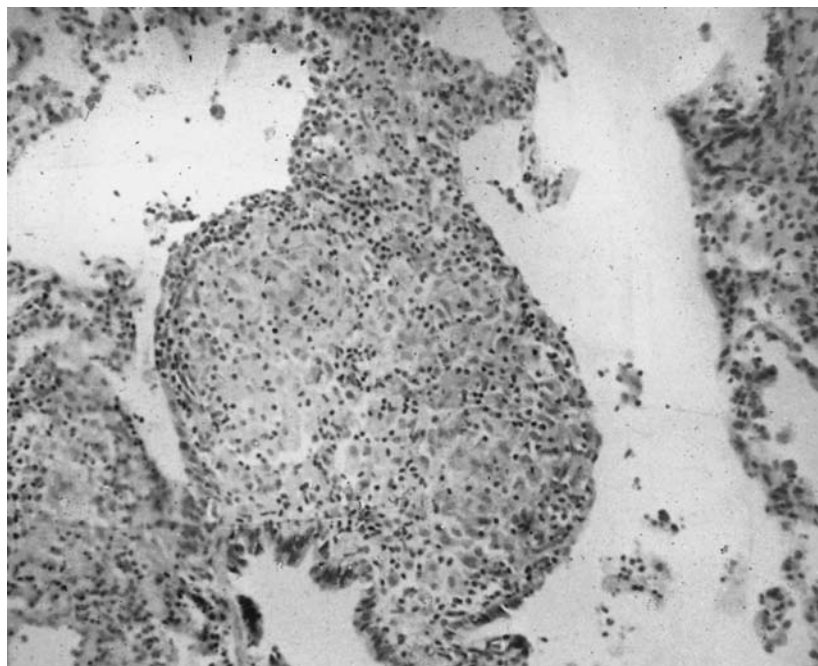
The gross appearances of chronic berylliosis at an advanced stage are of irregular fibrosis with bullae and cyst formation. The important microscopic feature is the non-caseating granuloma. At an early stage, discrete follicles of epithelioid cells surrounded by lymphocytes and plasma cells are seen in the interstitial tissues and alveolar walls. Similar appearances are found in lymph nodes, skin lesions, liver and spleen. Langhans' giant cells develop by fusion of the epithelioid cells, and sarcoid-type inclusion bodies may be seen. These pathological features are indistinguishable from those of sarcoidosis (Fig. 54.27). As the disease progresses, interstitial pulmonary fibrosis occurs, which may proceed to widespread acinar destruction and dilatation of small airways, to produce honeycombing.

### Pathogenesis

The characteristic immunological features of beryllium disease are cutaneous anergy to tuberculin, delayed skin reactivity to beryllium, and *in vitro* stimulation of lymphocytes by beryllium salts so that they transform into lymphoblasts and produce lymphokines such as a factor that inhibits macrophage migration [295]. In addition, the pathological features of mononuclear cells and giant cells lend weight to the concept that berylliosis is due to a delayed hypersensitivity reaction to the metal and its salts.



**Fig. 54.26** Chronic berylliosis in ex-beryllium refiner showing diffuse irregular pulmonary fibrosis.



**Fig. 54.27** Sarcoid-like granuloma in the lung of patient with berylliosis.

Bronchoalveolar lavage studies in patients with chronic berylliosis have shown increased cell numbers, almost 80% being lymphocytes, most of the T subtype [296]. These cells have been shown to react to beryllium more rapidly than blood lymphocytes, suggesting that a high proportion are sensitized to the metal.

It seems likely therefore that certain individuals react to inhaled or absorbed beryllium, coupled to protein as a hapten, via a cellular immune response. Perhaps ingestion of the antigen by macrophages allows persistent stimulation of the immune system, activation of T lymphocytes and production of lymphokines, which in turn stimulate further recruitment of mononuclear phagocytes leading to granuloma formation. Further discussion of the immunopathology of granulomatous disease may be found in Chapter 39.

### Diagnosis and management

The disease should be suspected when someone who has worked with (or whose spouse has worked with) beryllium presents features of interstitial lung disease with histological findings suggestive of sarcoidosis [297]. There is no absolutely reliable test for berylliosis, although features that distinguish it from sarcoidosis include a negative Kveim test and absence of erythema nodosum, hilar adenopathy without lung changes, or uveitis. The beryllium patch test is not now recommended since it may itself lead to sensitization. The test for lymphocyte proliferation in response to beryllium sulphate using blood or bronchoalveolar lavage cells is the most reliable

test of sensitization and may also reflect severity of the disease [298–301]. Studies of tissue or urine levels of beryllium have proved disappointing, since high level may be found in beryllium workers with other disease and low levels in ex-beryllium workers with berylliosis [302]. However, the use of laser microprobe mass spectrometry to analyse the content of granulomas rather than of general lung tissue has enabled the demonstration of beryllium in the granulomas and not in those of sarcoidosis [303]. Where this highly specialized chemical test is available, it is therefore possible to increase diagnostic confidence appreciably.

Since the disease usually progresses, treatment with corticosteroids is normally advised. The dose should initially be of the order of 40mg daily and subsequent reductions guided by measurements of lung function, diffusing capacity being the most useful test. Most patients improve but few show full functional recovery and the treatment therefore needs to be continued indefinitely.

Prevention of sensitization depends on reducing the exposure of workers to as little beryllium as possible by careful occupational hygiene. A workplace hygiene standard of  $2\mu\text{g}/\text{m}^3$  is enforced in the UK and the USA, and adherence to this may prevent most cases occurring in future. However, its efficacy requires further study by surveillance of exposed workforces and it should be remembered that hypersensitivity diseases may not be dose-related, so that a single excursion above a relatively safe limit may produce sensitization in a susceptible worker.

## Other pneumoconioses

### Aluminium

Aluminium is mostly open-cast mined as bauxite ( $\text{Al}_2\text{O}_3 \cdot 2\text{H}_2\text{O}$ ), particularly in Jamaica. The ore is crushed, washed and treated with caustic soda to produce alumina,  $\text{Al}_2\text{O}_3$ , which is then reduced electrolytically after dissolution in cryolite,  $\text{Na}_2\text{AlF}_6$ . Fumes from this process, which is carried out in large vessels called pots, are responsible for pot-room asthma; this is probably due to fluoride rather than aluminium [304].

A diffuse interstitial fibrosis has been described in workers manufacturing alumina abrasives (corundum) composed of bauxite. The bauxite is ground, mixed with iron coke and melted at high temperatures, causing fumes containing both silica, mostly cristobalite, and aluminium oxide to be given off. The disease, characterized by honeycombing and a high risk of pneumothorax, has been called Shaver's disease after one of the physicians who first described it in 1947 [305]. It is possible that the condition was a variant of silicosis, probably of the accelerated type, rather than an effect of aluminium, the fumes having contained up to 30% silica. Fibrosis of the lungs has also been described in workers producing flake powder of metallic aluminium for the manufacture of fireworks, paints and armaments [306,307]. In this process, a coating of stearin was used to prevent oxide formation; when the metal was covered with either oxide or stearin it was relatively non-reactive. However, a change of process during the Second World War substituted mineral oil for stearin and this apparently allowed the reactive surface of metallic aluminium, when inhaled, to come into contact with alveolar walls and to initiate fibrosis. The doses that caused this disease were clearly very high and it seems unlikely that workers are at risk nowadays.

A report in 1962 [308] of a patient who worked in an aluminium powder-ball mill and who developed pulmonary fibrosis and progressive encephalopathy is of interest in view of the association of aluminium with the plaques in the brains of people dying with Alzheimer's disease [309]. The aluminium worker had very high levels of aluminium in his brain at death. It would seem that studies of neurological function in aluminium workers would be of interest. There has also been a report of a patient who developed alveolar proteinosis after 6 years' work as an aluminium grinder and whose lungs contained vast numbers of submicrometre-sized particles of aluminium [310], in keeping with more recent work suggesting that ultrafine particles may cause lung inflammation. The author has seen a patient who developed severe diffuse pulmonary fibrosis and died of a complicating alveolar cell carcinoma and who had a history of heavy and prolonged exposure to fume in a refinery producing aluminium from scrap. The lungs showed bronchiolitis as

well as alveolitis, suggesting an inhaled cause, although aluminium was not detectable. The cause of these episodes of disease remain unclear but arouse suspicion that exposure to substances in fume generated by the processes may sometimes have toxic effects.

In contrast to the uncertainty surrounding fibrogenic effects of aluminium, there is clear evidence of an increased risk of lung cancer in workers involved in the pot room and manufacture of the anodes in aluminium refineries. The evidence strongly suggests that this relates to heavy exposure to polycyclic aromatic hydrocarbons [311].

### Antimony

Antimony is mined as ores containing oxide and sulphide radicals and is used in metallic alloys, paints and pharmaceuticals. An apparently benign, non-fibrosing pneumoconiosis has been described in workers crushing the ore [312,313].

### Barium

Barium is mined mostly as barytes, barium sulphate, and may be used in the production of paints, rubber and glass, and as a drilling mud in the oil industry. Miners may be exposed to quartz dust and are at risk of silicosis [100]. In contrast, workers grinding barium salts develop strikingly dense micronodular radiological shadows without any functional abnormalities (Fig. 54.28). This benign, non-fibrosing pneumoconiosis is called baritosis [314,315]. The radiographic changes tend to disappear when exposure ceases and there is no functional abnormality associated with them [316].

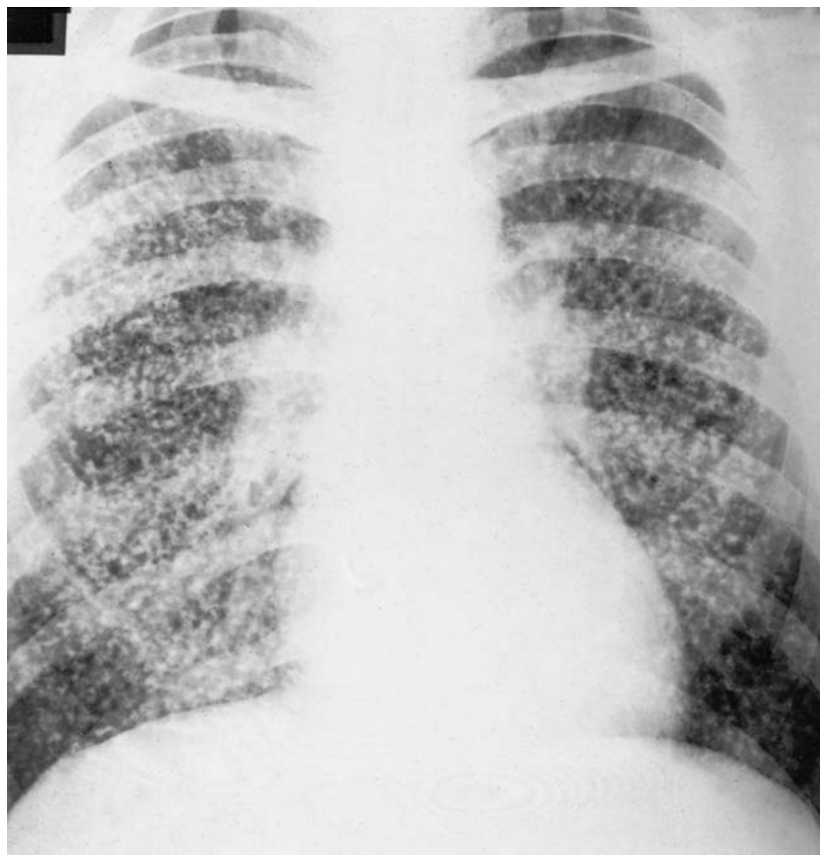
### Carbon

Workers exposed to dust from graphite and carbon pigment may develop a form of pneumoconiosis indistinguishable from that afflicting miners of high-rank coal. Simple nodular changes and PMF have been described [317,318], and there is also evidence of some impairment of lung function in relation to exposure to carbon black [319].

Carbon fibres are now finding wide applications in industry and may be very fine and durable. While no problems have been described in workers, as with all such fibres care should be exercised in their use.

### Polyvinyl chloride

The best-known hazards of polyvinyl chloride (PVC) manufacture are acro-osteolysis of the fingers and angiosarcoma of the liver due to exposure to vinyl chloride monomer [320,321]. However, a low category of



**Fig. 54.28** Dense micronodular shadows of baritosis in a barium grinder.

radiological pneumoconiosis has been described in some workers and lung macules containing PVC have been demonstrated pathologically and experimentally [322–324]. It seems likely that this is a non-progressive and benign condition. Lung function changes, particularly a low  $DLCO$ , that have been described in some workers with normal radiographs were probably due to high exposures to the monomer before controls were introduced rather than to the polymer [325].

#### **Silicon carbide**

Silicon carbide is of historical interest as Carborundum, an early US invention that saved many lives because of its use as a substitute for sandstone in knife grinding. It is widely used as an abrasive and now also used in the manufacture of synthetic fibres, known as silicon carbide whiskers. There has been a report of the development of what seems to have been a benign pneumoconiosis in two workers exposed to silicon carbide dust in refractory brick works [326]. Perhaps of more concern is the demonstration in rats injected with the fibres intrapleurally of a possible neoplastic risk [270]. A study of a cohort of silicon carbide production workers exposed *inter alia* to fibres has shown a significant increase in risk of non-malignant respiratory disease and a possible increase in risk of lung cancer [327].

#### **Tin**

Tin miners are at risk of silicosis and, if exposed to radon daughters, lung cancer [328]. Tin refiners may inhale the fume from the smelting process and develop a highly radiodense but entirely benign fine nodular pneumoconiosis. The condition has been called stannosis [329,330].

#### **Tungsten carbide (hard metal) and cobalt**

Tungsten carbide is produced, usually alloyed with cobalt and other metals, for materials requiring great hardness and resistance to heat. Pulmonary fibrosis, airways obstruction and granulomatous (giant cell) interstitial pneumonitis have been described in tungsten carbide workers [331,332]. It is probable that all these reactions are the result of inhaling the cobalt, which dissolves in coolants used in the process of grinding the hard metal [333,334]. The same syndrome has been described in diamond polishers exposed to a cobalt aerosol [335]. Ionized cobalt combines with proteins to form a hapten and has long been known as a cause of skin sensitization.

The disease presents with dry cough and breathlessness and appears to be more common in non-smokers. Inspiratory crackles may be heard and diffuse fine reticulonodu-

lar infiltrates may be seen radiographically. Detected early, the condition may remit either on cessation of exposure or following a course of corticosteroids. If exposure continues, progression to diffuse interstitial fibrosis and cor pulmonale may occur. There has been a report of a patient in whom fatal giant cell pneumonitis recurred in the transplanted lung even though exposure to hard metal had ceased [336].

In some subjects a syndrome of reversible airflow obstruction may occur. This seems to be an asthmatic response to cobalt (and sometimes also nickel) and has been reproduced by challenge testing [337,338]. Mixed patterns of asthma and interstitial disease may occur.

### **Occupational bronchitis**

The interrelationships of occupational dust and fume exposure and clinical evidence of bronchial disease and airways obstruction have been the subject of some controversy. While it is rarely possible to recognize a distinct disease in individuals that can be called occupational bronchitis, exposures to dust and fume may increase the risk of these conditions occurring in exposed workers, whether they smoke or not. For example, an increased prevalence of chronic productive cough and of impaired expiratory flow rates has been recorded in coal-miners [40,46,47], gold-miners [121], foundry workers [339], cement workers [261], grain workers [340,341], asbestos miners [207] and coke oven workers [342]. Evidence that the reduction in lung function is related to cumulative dust exposure has been obtained from studies of South African gold-miners [121] and British coal-miners [56], while a relationship between dust exposure and prevalence of pathological emphysema in coal-miners suggests one possible mechanism [48]. There is some evidence of somewhat different patterns of response to dust inhalation in smokers and non-smokers; smokers develop classical airflow obstruction, with relatively greater reduction in FEV<sub>1</sub>, while non-smokers tend to develop a reduction in both FEV<sub>1</sub> and FVC, suggesting a restrictive component [343].

Although these effects have been studied in greatest detail in coal-miners, it seems likely that the effect of dust on lung function may be a general one, possibly mediated through an alveolitic and elastolytic response of macrophages and polymorphs to the dust. It is not surprising to the author, who has visited many workplaces, that prolonged exposure to dust and fume could cause, via either bronchial irritation or alveolar inflammation, chronic sputum production and airflow obstruction, resulting in an increased prevalence of such conditions in a population. In such circumstances, as with cigarette smoking, the average effect is small but the distribution of responses in the population as a result of differences in both susceptibility and exposure may result in a few

people developing clinical disease. If, as is likely, susceptibility to the irritants inhaled from cigarettes is the same as that to other irritants, it would be expected that this effect would show mainly in smokers, especially when one considers that such effects are likely to be additive. Therefore in any dust-exposed population, one might expect to see an excess of people with disease compared with a non-dust-exposed population while in individual cases being unable to point firmly to dust as a cause. In addition, if exposures to industrial dust or fume are generally controlled, it would nowadays be unusual to see non-smoking individuals with purely dust-induced disease. This gives great opportunities for sceptics to deny that prolonged inhalation of such substances is in any way harmful, an attitude usually coloured by a need to be dogmatic in front of a judge or jury who prefer to hear that diseases have only one cause. However, a more important consideration is that such an attitude leads to a denial of the need for employers to take preventive action. Application of a precautionary principle should lead one to conclude that exposure to dust and fumes generally in industry has the potential to harm the lungs and that the exposures of workers should be minimized.

## **Organic dust diseases**

### **Occupational asthma and allergic alveolitis**

These conditions are considered in detail in Chapters 34 and 37 respectively.

### **Byssinosis**

Byssinosis is a term applied to a complex of symptoms associated with the manufacture of cotton, flax and hemp [344–347]. Cotton, after picking, is cleaned and the lint separated from the seed by a process known as ginning. The lint is compressed into bales, which are then opened out by machines in a blowing room. Cleaning these machines is a very dusty job. The cotton fibres are then combed out, or carded, twisted into threads and woven. Carding and stripping the carding machine is also very dusty work. Flax is separated from the plant stems by retting (rotting, by bacterial or fungal action) followed by beating. The fibres are then carded and drawn through gills prior to spinning and weaving. Similar processes are used in the production of hemp and jute, though there is little evidence that the latter fibre is associated with byssinosis.

### **Acute effects of cotton exposure**

Up to one-third of people exposed to cotton dust for the first time develop an acute airway reaction with often



substantial fall in FEV<sub>1</sub> [348]. This is more likely to occur in atopic subjects and people with asthma and is associated with increased bronchial reactivity. It probably means that workers who develop this syndrome tend to leave the industry and that those who remain, some of whom later develop byssinosis, contain a relatively smaller proportion of atopic subjects [345].

The classical description of byssinosis is of a worker in a dusty area developing, usually after at least 10 years in the industry, a sensation of oppression in the chest or difficulty in breathing on the first day of the working week. A slight rise in temperature may also occur, as may cough and wheeze. The symptoms usually occur after about 2–4 h of exposure and clear some time after going home. No radiological changes occur. As the condition progresses, the symptoms may arise on subsequent working days, ultimately becoming permanent. However, longitudinal studies have shown that this progression from first day through to more persistent symptoms is not invariable, and that some workers start with symptoms on a daily basis while some even show remission despite continuing exposure [349]. For epidemiological purposes these symptoms have been used in the following classification of the disease.

- Grade 0: no byssinosis.
- Grade 0.5: occasional chest tightness on the first day of the working week.
- Grade 1: chest tightness on the first day of every working week.
- Grade 2: chest tightness on the first and following days of every working week.
- Grade 3: grade 2 symptoms accompanied by evidence of permanent incapacity from diminished exercise tolerance and/or reduced ventilatory capacity.

Lung function studies have shown declines in FEV<sub>1</sub> both throughout a shift and throughout the week, the change over a shift being greatest on the first day [350,351]. Longitudinal decline in FEV<sub>1</sub> has been suggested by finding lower levels of lung function than predicted in cotton workers [352], although how far these are due to smoking and how far to cotton dust remains undecided. There is evidence that those workers who show declines in lung function over a shift are most likely to show a progressive change over several years [353]. Bronchial reactivity is increased in most workers with byssinosis and falls in indices of small airways disease have been taken to suggest that the physiological response may begin in peripheral airways and that byssinosis may be regarded as a form of occupational asthma [354,355].

In the light of newer studies of the natural history and functional effects of byssinosis, the World Health Organization has proposed a new grading system for the disease (Table 54.4).

**Table 54.4** The World Health Organization grading system for byssinosis.

Grade 0	No symptoms
<i>Byssinosis</i>	
Grade B1	Chest tightness and/or shortness of breath on most of first day back at work
Grade B2	Chest tightness and/or shortness of breath on the first and other days of the working week
<i>Respiratory tract irritation</i>	
Grade RTI1	Cough associated with dust exposure
Grade RTI2	Persistent phlegm initiated or exacerbated by dust exposure
Grade RTI3	Persistent phlegm initiated or made worse by dust exposure, either with exacerbations of chest illness or persisting for 2 years or more
<i>Lung function</i>	
<i>Acute changes</i>	
No effect	A consistent decline of <5% (or an increase) in FEV <sub>1</sub> over a work shift
Mild effect	A consistent decline of 5–10% over the work shift
Moderate effect	A consistent decline of 10–20% over the work shift
Severe effect	A decline of 20% or more over the work shift
<i>Chronic changes</i>	
No effect	FEV <sub>1</sub> at least 80% of predicted
Mild to moderate	FEV <sub>1</sub> 60–79% of predicted
Severe	FEV <sub>1</sub> <60% of predicted

FEV<sub>1</sub>, forced expiratory volume in 1 s.

### Chronic effects of cotton exposure

This subject remains controversial. It is certainly the belief of many doctors in cotton and flax milling areas that some workers become permanently disabled by byssinosis. Cough and sputum are found more frequently among cotton workers than among controls [356] and ventilatory function tends to be impaired [357]. Several studies have shown a progressive decline in workers' FEV<sub>1</sub> in relation to exposure to cotton dust, in some cases of a dramatic degree [358,359]. Some of these declines are such that one would anticipate a very poor survival rate among these workers. However, mortality studies have shown either no or only small effects on mortality from chronic respiratory disease [360–362], suggesting that they may be flawed.

Necropsy studies of cotton workers with byssinosis have failed to show any distinctive pathological features [363]. There is some evidence that cotton workers have mucous gland hypertrophy and increased bronchial

smooth muscle but nothing to suggest that they suffer an excess of emphysema, either pathologically or physiologically [364,365].

### Pathogenesis

The prevalence of byssinosis varies from mill to mill, although the condition occurs in many different countries, including the UK, the USA, Indonesia, Sudan and India, being more prevalent in developing than developed countries [366,367]. The common factor seems to be the raw fibres, this material always being contaminated by fungi and Gram-negative bacteria. Fungal overgrowth may be responsible for weavers' cough and Gram-negative bacterial endotoxin for mill fever. Some types of cotton appear to be worse than others, while the earlier and dustier parts of the production process tend to cause more disease [368]. Washing of cotton reduces its effects in experimental studies [369].

The effects of inhalation of extract of cotton dust, namely chest tightness, cough, some fever and fall in FEV<sub>1</sub>, have some of the features of asthma and allergic alveolitis without being typical of either. The delayed onset after challenge is similar to that of allergic alveolitis, although the functional change differs. The symptoms and reduced response on subsequent days are similar to those described in some episodes of humidifier fever [370]. It seems likely that some component of cotton bract or its fungal and bacterial contaminants is responsible, though the mechanism of this has been much debated. Early suggestions that the action is a direct one on mast cells, causing release of histamine and other mediators of smooth muscle constriction, now seem too simplistic [371]. Similarly, evidence for an antigen-antibody reaction is unconvincing, although atopic subjects do seem at slightly greater risk [372]. Inhalation of cotton dust has been shown to lead to a neutrophil response in airways, probably due to a lipid fraction of bacterial cell walls, and it may be that release of leukotrienes and platelet-activating factor by these cells plays a part in causing the disease [373]. Similar mechanisms have been invoked in the causation of asthma, pulmonary fibrosis and emphysema, diseases with very different clinical features, so this apparent explanation of the disease is really only a framework for further research. It is probable that the reaction in byssinosis is confined to the airways and is due to larger, non-respirable dust particles. Perhaps the electrostatic charge on cotton dust is also important in determining the site of action. Much more work, in both epidemiology and the study of basic mechanisms of bronchial inflammation, is necessary before byssinosis is fully understood.

### Prevention and management

In the absence of knowledge of the precise cause, most

attempts at control of the problem have concentrated on reducing the dust exposure of workers by enclosing machinery, ventilation and, where necessary, use of respirators. Attempts have been made to reduce the hazard by removing the soluble fraction of raw cotton by washing or steam treatment [374], although these have proved either impracticable or ineffective. In the case of steam treatment, the hazard appeared to be transferred to workers in the later stages of the process. Exclusion of very sensitive workers at an early stage is necessary and transfer of workers developing early symptoms to less dusty work is desirable. Exclusion of atopic subjects is probably of little importance, although increased susceptibility of such people to the early acute bronchoconstrictive reaction results in most leaving the industry before developing classical byssinosis. Primary prevention therefore depends on the difficult process of dust control, in accordance with national legislation on dust standards. Since byssinosis is primarily a bronchial disease, it is logical that such standards should be based on inhalable rather than respirable dust measurements and the present standard in the UK and USA takes account of this (0.5 mg/m<sup>3</sup> measured as inhalable dust, less the coarse component known as 'fly').

Once the condition has developed, some symptomatic relief may be obtained by the use of inhaled bronchodilators and steroids if removal from the workplace proves impracticable. In the UK, industrial injuries benefits are available to victims of the disease.

### Humidifier fever and related syndromes

A variety of patterns of illness has been described in people working or living in buildings with humidifiers and air conditioners. The original descriptions from the USA were of typical extrinsic allergic alveolitis, and thermophilic actinomycetes were isolated from the systems [375,376]. Since then, typical allergic alveolitis and asthma have also been described in a few individuals in British offices [377,378] and cases of allergic alveolitis due to various bacterial contaminants of nebulizers and humidifiers continue to be reported [379,380]. More characteristically, British outbreaks have consisted of episodes of malaise, fever and sometimes breathlessness, often associated with non-specific aches, occurring predominantly on the first day of the working week [381-384]. Occasionally, falls in diffusing capacity or peak flow rate have been described and the syndrome clearly has overlaps with both allergic alveolitis and occupational asthma. Usually the chest radiograph is normal and physical signs are absent from the lungs.

The common factor in all these outbreaks is the presence of profuse microbiological contamination of the humidifier system. Water and air entering the system convey microorganisms that then recirculate in the water and

reproduce in sumps and on baffle plates. In such circumstances it is commonplace to find a thick jelly-like deposit on baffle plates; culture of this and of the water in the sump reveals many bacteria and fungi, together with more complex organisms such as amoebae, *Paramecium* and worms. Precipitating antibodies to the jelly and to extracts of the water are commonly present in exposed workers, whether affected or not, although recent evidence suggests that the presence of high levels of IgG antibody to humidifier water are associated with the more severe symptoms of fever, headache and chest tightness [385]. There has been much debate as to which organisms are responsible and what mechanisms are involved; amoebae, or the Gram-negative bacteria on which they feed and whose antigens they contain, have been thought to be important [386,387]. However, it seems likely that different syndromes may be related to different organisms or combinations of organisms. The mechanisms remain unresolved, though the striking similarity of humidifier fever to byssinosis has been noted [370]. It is of interest that the air conditioner was actually invented to control the temperature and humidity in cotton mills in the USA.

As far as is known, typical humidifier fever does not progress to a disabling type of lung disease and is often regarded by its victims as a 'Monday morning feeling'. Nevertheless while some of those exposed are unaffected, others may suffer more severe malaise and breathlessness. Diagnosis is made from the typical history and from the finding of a source of contaminated aerosol. Control of the problem usually requires very frequent cleaning of the systems or, preferably, change to either steam injection or the use of fresh unrecirculating water. Biocides and the use of ultraviolet light have so far proved disappointing. The efficacy of control measures may be tested by measuring antibody in the blood of exposed people or, in some outbreaks, by measurement of peak flow rates in sensitized workers.

Similar syndromes to humidifier fever have been described in cotton mills (mill fever), grain silos (grain fever) [388], piggeries (swine confinement fever) [389] and sewage works (sewage sludge fever) [390]. It is possible that Gram-negative bacterial endotoxin is responsible for these reactions. Cotton and grain workers are also at risk of the more typical features of byssinosis and occupational asthma.

Apart from the more dramatic features of humidifier fever, workers in modern offices may complain of non-specific symptoms such as headache, nasal stuffiness and general malaise. Such outbreaks have been given the rather unsatisfactory name of 'sick building syndrome' [391]. They seem to be related to a design of building intended to save energy, with little natural ventilation and much recirculation of air. Occasionally, complaints from workers have reached such a pitch that buildings have

had to be closed until their ventilation systems have been redesigned.

Finally, it should be noted that water droplets from humidifiers and cooling towers may occasionally be a source of *Legionella* infection in people working in or even visiting offices and other buildings. This disease is discussed in Chapter 13.

## Toxic gases and fumes

A wide range of gases and nanometre-sized particles (fumes) may cause toxic effects on the lung and other organs if inhaled. In general their effects may be mediated by asphyxiation, local irritation, toxic absorption and allergy. All save the last are discussed here and the most common of these substances are shown in Table 54.5.

### Asphyxiant gases

Asphyxiation may occur as a result of exclusion of oxygen from the air by physiologically relatively inert gases or by interference with oxygen transport within the body by inhalation of metabolic poisons. The important simple asphyxiants are carbon dioxide, nitrogen and methane, which may all be encountered in unventilated mine workings and after fires. Carbon dioxide causes hyperventilation, sweating, headache and vasodilatation, with loss of consciousness, a syndrome familiar to chest physicians used to dealing with patients with chronic airways obstruction. Unconsciousness occurs rapidly and often unexpectedly when breathing nitrogen as the oxygen concentration falls to about 10%. Methane has a similar effect. It is an important problem in mines, where it may accumulate as a result of decaying vegetable matter and is released spontaneously from the coal seam. Unlike carbon dioxide, it is lighter than air and loss of consciousness may occasionally save a worker's life. Explosion is the other serious hazard associated with methane.

Management of asphyxiation depends on removal of the victim and administration of oxygen. Unfortunately, industrial accidents often produce multiple casualties, as would-be rescuers are themselves overcome by hypoxia. Self-contained breathing apparatus should be available to all workers at risk of such accidents; in most countries all miners are issued with simple oxygen-generating apparatus (self-rescuers) for use in an emergency.

The important toxic asphyxiants are carbon monoxide, phosphine, cyanides and hydrogen sulphide. Carbon monoxide is a product of incomplete combustion and is encountered classically in fires, around blast furnaces and in underground mines. It is colourless, odourless and lighter than air. It combines not only with haemoglobin (with an affinity some 200 times that of oxygen) but also with myoglobin and cytochrome oxidase, as well as shifting the oxyhaemoglobin dissociation curve to the left and

**Table 54.5** Toxic fumes and gases.

Agent	Main occupations	Occupational exposure standard*
<i>Asphyxiants</i>		
Acrylonitrile (vinyl cyanide)	Plastics, rubber	2 ppm (MEL)
Carbon dioxide	Mining, tunnelling	5000 ppm
Carbon monoxide	Mining, foundry	50 ppm
Hydrogen cyanide	Plating, fumigation	10 ppm (MEL)
Hydrogen sulphide	Sewage, tanning, gas making	10 ppm
Methane	Mining, tunnelling	O <sub>2</sub> > 17%
Nitrogen	Mining, tunnelling	O <sub>2</sub> > 17%
Phosphine	Fumigation	0.3 ppm (STEL)
<i>Irritants</i>		
Acrolein	Plastics, rubber	0.1 ppm
Ammonia	Fertilizer, refrigeration	25 ppm
Cadmium fume	Alloying, welding	0.025 mg/m <sup>3</sup> (MEL)
Chlorine	Bleaching, chemicals, disinfecting	0.5 ppm
Formaldehyde	Paper, photography, preserving	2 ppm (MEL)
Hydrogen chloride	Chemicals, dyes	5 ppm (STEL)
Hydrogen fluoride	Etching, oil refinery	3 ppm (STEL)
Nitrogen dioxide	Welding, farming	3 ppm
Osmium tetroxide	Alloys	0.0002 ppm
Ozone	Welding	0.2 ppm (STEL)
Phosgene	Dyes, chemicals	0.2 ppm
Sulphur dioxide	Bleaching, smelting	2 ppm
Vanadium pentoxide	Chemicals, alloys	0.05 mg/m <sup>3</sup>
<i>Toxic absorption</i>		
Arsine	Smelting, refining, scrap metal work	0.05 ppm
Copper fume	Welding	0.2 mg/m <sup>3</sup>
Lead fume	Refining, batteries	0.05 mg/m <sup>3</sup>
Mercury fume	Electrolysis	0.025 mg/m <sup>3</sup>
Zinc oxide fume	Welding	5 mg/m <sup>3</sup>

\*Occupational exposure standard in UK, expressed as 8-h time-weighted average except where indicated. These values are subject to regular revision and should be taken as a general guideline only.

MEL, maximum exposure limit, measured over 10 min, that must not be exceeded.

STEL, short-term exposure limit, measured over 10 min.

impairing oxygen uptake into mitochondria [392]. The first symptom of carbon monoxide poisoning is usually headache and general malaise, which occurs with carboxyhaemoglobin concentrations around 10%. Such symptoms may persist for prolonged periods in people exposed to low concentrations of the gas from defective gas apparatus and are frequently disregarded or misdiagnosed by doctors. Higher concentrations lead to dizziness, nausea, weakness in the limbs and, at about 30%, clouding

of consciousness. Death in fit people occurs at carboxyhaemoglobin concentrations of about 50%, though lower levels may be fatal in people with coronary artery disease or if oxygen demands are higher, as during exercise. Long-term sequelae may include myocardial and cerebral infarction; in about 10% of survivors, a neuropsychiatric syndrome occurs that may include extrapyramidal signs due to damage to basal ganglia, amnesia and psychotic symptoms [393–395]. Management of carbon monoxide poisoning depends upon removal of the victim and administration of 100% oxygen. Use of a hyperbaric chamber is desirable if one is available and is advisable if the patient has been unconscious, even if recovery has occurred, in order to prevent the neurological complications.

Cyanides act by blocking the cytochrome oxidase enzyme system, preventing access of oxygen to the tricarboxylic acid cycle. They may be encountered in industry as hydrogen cyanide gas or as inorganic cyanates in metal refining, plating, laboratories and fumigation. In addition, vinyl cyanide (acrylonitrile) is a gas used in the production of synthetic rubbers. Exposure to these gases causes rapid onset of dizziness, nausea and tachypnoea; these symptoms usually serve as a warning so that the worker can escape, but if ignored unconsciousness and death ensue very rapidly. Treatment should be available in any sites where exposure may occur; the traditional kit consists of amyl nitrite for immediate inhalation and sodium nitrite with sodium thiosulphate for intravenous injection. The nitrites combine with haemoglobin to form methaemoglobin, which in turn reacts with cyanide to form cyanmethaemoglobin; this then combines with thiosulphate to form harmless thiocyanate. This reaction reduces the oxygen-carrying power of the blood because of the formation of methaemoglobin and is also less effective for treatment of vinyl cyanide poisoning. Thus the preferred treatment is usually to neutralize the cyanide by intravenous injection of dicobalt edetate, 150 mg of which contains sufficient cobalt to deal with 40% of an LD<sub>50</sub> of cyanide. Up to 600 mg may be given slowly, each 300 mg being followed by 50 mL of 50% dextrose to reduce risks of the anaphylactoid side-effects of the cobalt [396]. Clearly the patients should be removed from exposure by rescuers wearing self-contained breathing apparatus and given oxygen in high concentrations.

Hydrogen sulphide is also an inhibitor of the cytochrome oxidase system and is as rapidly fatal as cyanides. It is heavier than air and has the characteristic smell of rotten eggs, although olfactory accommodation occurs rapidly so that high concentrations may not be noticed. Fatal exposures have occurred in industry, in tanning, fish processing, chemical waste disposal and natural gas production [397–399]. Survivors may develop pulmonary oedema several days after exposure. Low-level exposures are associated with conjunctivitis and

keratitis and various neurological syndromes. Treatment of hydrogen sulphide poisoning requires removal from exposure, administration of oxygen and of amyl nitrite and intravenous sodium nitrite, which combine with sulphide to form sulphmethaemoglobin. Ventilatory support may be necessary for delayed pulmonary oedema and hyperbaric oxygen may help to prevent long-term neurological sequelae.

Phosphine ( $\text{PH}_3$ ) is a gas used mainly in the fumigation of grain; it is introduced into cargoes in the form of tablets of aluminium phosphide, which react with water to produce the gas. Accidental poisoning of workers, particularly grain inspectors, has been described as a result of entering the holds of ships or rail freighters holding fumigated grain [400,401]. The gas poisons intracellular oxygen transport mechanisms and manifests effects particularly on heart and liver. Cardiac failure and dysrhythmias are common complications of poisoning. There is no antidote, treatment being symptomatic.

### Irritant gases and fumes

Irritant gases injure the respiratory tract by causing acute inflammation when inhaled in high concentration. The main site of injury depends on the solubility of the gas, the more soluble gases exerting maximal effects more proximally. It is probable that the consequences of inhalation of irritant gases are non-specific to the particular chemical and that any one or more of a spectrum of adverse effects may follow exposure to any such gas when inhaled in sufficient concentration. Short-term reactions include cough, wheeze, acute bronchoconstriction, tracheobronchitis and laryngeal or pulmonary oedema. These may be followed by temporary or persistent bronchial hyperreactivity with a syndrome indistinguishable from bronchial asthma, often called the reactive airways dysfunction syndrome (see Chapter 36). In some subjects, airways obstruction is much less reversible and resistant to antiasthma treatment, suggesting the development of obliterative bronchiolitis.

Although this alarming array of consequences may follow acute exposure to toxic gases, fortunately in most cases complete recovery is the rule. Such episodes of gassing are not rare, and represent one of the more common causes of reports to the UK SWORD project, 1180 having been reported between 1990 and 1994 [402]. The most common agents in this series were chlorine, nitrogen oxides, phosphine, perchloroethylene, sulphur dioxide and trichloroethylene. In a further study of these data, some 70% of patients with acute exposure to irritant gases had recovered and were back at work within a week but 12% still had symptoms 1 month later, of whom about one-quarter had symptoms of asthma/reactive airways disease. It is intuitively obvious but not clearly established that the greater the exposure in terms of duration and con-

centration to a given irritant, the more likely the occurrence of longer-term sequelae. However, the nature of these episodes, which are always accidental and sporadic, means that only rarely have appropriate studies been carried out to observe the natural history of the condition. In the author's experience, which like all experience may be misleading, sometimes quite minor exposures may lead to persistent asthmatic or other respiratory symptoms [403], while in other cases major exposures with severe immediate reactions lead to full recovery. All such episodes should therefore be treated seriously and the use of corticosteroids to suppress persistent inflammation at least considered.

### Ammonia

Ammonia ( $\text{NH}_3$ ) is a highly irritant, soluble alkaline gas with many uses in industry. Much is used in the production of fertilizers, as well as in manufacture of synthetic fibres and plastics, explosives, nitric acid, refrigerants, pharmaceuticals and oil refining. Accidental exposure to high concentrations results in intense irritation of eyes, nose and throat with stridor due to laryngeal oedema [404]. The soluble nature of the gas results in direct damage to proximal mucous membranes rather than to more distal parts of the lung. Death may occur through asphyxia. Management involves removal of the victim and maintenance of oxygenation for the 2–3 days until laryngeal oedema settles; this may require tracheostomy. Weakly acidic eye and mouth washes may give some symptomatic relief initially. Full recovery usually ensues, although persistent cough, bronchiolitis obliterans and bronchiectasis have been described as sequelae [405].

### Chlorine

Chlorine is a heavy gas, less soluble than ammonia, used in the manufacture of alkalis, bleaches, plastics and solvents, as well as being used as a sterilizing agent. Many industrial accidents following spillages and crashes of transporters have been described [406,407]. The acute effects of inhalation are choking, chest pain and dyspnoea. Pulmonary oedema may occur immediately or after a delay of several hours, with inspiratory crackles, frothy pink sputum and radiographic changes. Management is that of non-cardiogenic pulmonary oedema; the role of corticosteroids is not established but most clinicians would probably use them. Follow-up studies of survivors of chlorine inhalation have shown equivocal results, usually confounded by ignorance of previous respiratory health and by high prevalences of smoking [408–411], but which are probably partly related to the observation made above that only a small proportion of people exposed actually develop long-term effects. Exposures to low levels of chlo-

rine might be expected to provoke attacks of asthma in those with bronchial hyperreactivity [412].

### Oxides of nitrogen

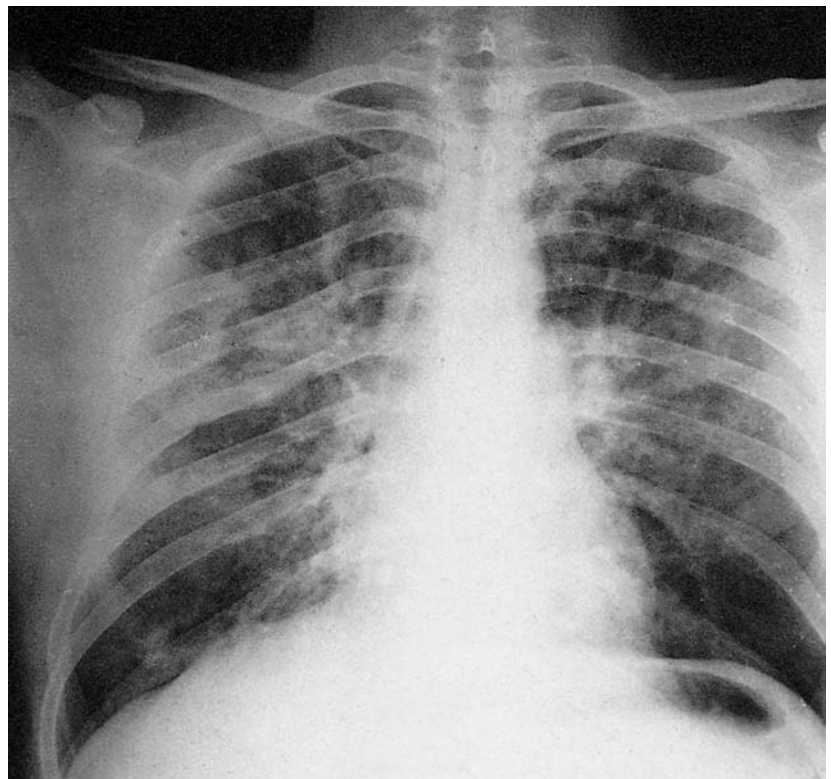
Nitrogen dioxide exists in two forms in equilibrium,  $\text{NO}_2$  and  $\text{N}_2\text{O}_4$ , a relatively insoluble, brown, mildly irritating gas. Toxic exposures have occurred particularly in four circumstances: exposure to silo gases, arc welding, combustion of nitrogen-containing material and spills of nitric acid [413–415]. Silofillers' disease occurs when farm workers enter the top of a silo, usually shortly after ensilage has begun. Nitrogen dioxide may accumulate in this situation as a result of oxidation of nitrates in the silage; being heavier than air, the gas lies on the top and in pits. Arc welders may produce the gas by combination of nitrogen and oxygen in the heat of the arc. Exposure as a result of fires occurs when dynamite burns; this has caused accidents in mines [415]. A notorious episode occurred at the Cleveland Clinic in Ohio, when nitrocellulose X-ray film caught fire and caused over 100 deaths, many of which were thought to have been due to nitrogen dioxide [416]. Exposures in the chemical industry occur when nitric acid spills and reacts with organic material such as wood or paper.

The person exposed to nitrogen dioxide may only notice relatively mild nasal and throat irritation, though with heavy exposures cough and choking may occur. Such

exposures may then lead to the progressive development of pulmonary oedema over an hour or two (Fig. 54.29), which may prove fatal. Moreover, apparent recovery may be followed 2–3 weeks later by progressive breathlessness associated with fever and diffuse lung crackles. This late reaction, which may occasionally occur after a relatively minor initial episode, is due to progressive bronchiolitis obliterans, and it also may prove fatal [417,418]. The radiograph shows diffuse punctate opacities and the lung function a predominantly restrictive pattern.

There has been much debate about the effects of prolonged low-level exposure to nitrogen dioxide, such as occur in workers exposed to diesel exhausts, people living in cities with heavy traffic pollution or in people exposed to gas cookers in their homes. Experimental chamber studies have shown that effects on airways resistance and reactivity may occur in healthy people exposed over about 2 h at concentrations of up to 10 parts per million and that similar changes occur in people with asthma exposed to concentrations down to about 0.2 ppm [419]. There is some evidence that children and women living in houses with gas cookers may show increased susceptibility to pulmonary infections, increased respiratory symptoms and some reduction in ventilatory capacity [420–422].

Exposure to high levels of nitrogen dioxide should largely be prevented by appropriate education of workers. Farmers in particular should be aware of the hazards of



**Fig. 54.29** Acute toxic pneumonitis in welder exposed to oxides of nitrogen.

silos. Management of the acute attack is as for other irritant gases, and there is anecdotal evidence that early use of corticosteroids may be of benefit both in the acute stage and in preventing bronchiolitis obliterans.

### Sulphur dioxide

Sulphur dioxide ( $\text{SO}_2$ ) is a heavy irritating gas. Its solubility causes it to provoke eye, throat, laryngeal and bronchial oedema, together with pulmonary oedema in severe exposures [423]. Such industrial accidents are rare but may occur in bleaching, preservation of foods, refrigeration and chemical industries. The gas is a general atmospheric pollutant, produced by combustion of fossil fuel, and is of importance in causing deterioration of limestone buildings and contributing to acid rain. Low-level exposures may contribute to the burden of chronic airflow obstruction and bronchial symptoms in exposed workers, though the evidence for this is controversial [424,425]. Experimental chamber studies of volunteers have shown subtle effects on lung function to occur at concentrations above 1–2 ppm in normal subjects and above about 0.2 ppm in those with asthma [426–428]; the role of sulphur dioxide in ambient air pollution is discussed in Chapter 11.

### Ozone

Ozone ( $\text{O}_3$ ) is a relatively insoluble but reactive gas that may be encountered in inert gas-shielded arc welding, the chemical industry, bleaching and industrial waste treatment. It is a respiratory irritant although severe or fatal exposures do not seem to have occurred. Occupational health interest has centred upon its long-term effects, particularly on the crews of high-flying aircraft and spacecraft, who seem to suffer an excess of symptoms attributable to respiratory irritation [429]. As discussed in Chapter 11, it is an important contributor to summer air pollution episodes and there is evidence of irritant effects in experimental studies on airways in terms of provoking changes in lung function and airway inflammation at exposures over about 0.1 ppm for several hours [427,430]. Epidemiological studies have shown relationships between rises in ambient ozone concentrations, measures of respiratory illness, and even mortality from respiratory and cardiovascular diseases [431,432].

### Phosgene

Phosgene ( $\text{COCl}_2$ ) is a heavy gas that was used as a chemical weapon in the First World War. It is now used in the production of isocyanates, pesticides, dyes and pharmaceuticals. Occasional cases of acute toxicity have been described in the chemical industry and in using carbon tetrachloride fire extinguishers. It is only mildly irritant

but acts directly on the alveolar wall, causing acute pulmonary oedema [433].

## Toxic fumes and vapours

### Metal fumes

Metal fume fever is a condition characterized by a metallic taste followed by rigors, high fever, muscle aches and headache [434,435]. It follows a few hours after acute exposure to metal fumes, particularly zinc, copper and magnesium, and settles spontaneously, without sequelae, in 24 h. It occurs in welding, smelting and galvanizing. Episodes usually occur on first exposure to fumes after a break, tolerance then developing, and in this respect bears some resemblance to byssinosis and other causes of 'Monday fever'. It is probably due to chemotaxis within the lung of neutrophil leucocytes damaged by the very small ( $<1\mu\text{m}$ ) particles of metal. Recent studies of experimental zinc oxide fume inhalation have shown evidence of alveolar inflammation and release of cytokine mediators over a 24-h period following exposure [436,437], while bronchoalveolar lavage in a worker suffering from inhalation of zinc fumes has shown a lymphocytic alveolitis [438].

Metal fume may also cause direct toxic damage to the lungs and, by absorption, to other organs. A characteristic of fumes is the very small particle size, the majority being less than  $0.1\mu\text{m}$  in diameter with a high rate of alveolar deposition. Exposure to high concentrations even of relatively non-toxic substances of this size range causes an alveolitis and may lead to pulmonary oedema. This has occurred after deliberate exposure of fire-fighters and military personnel to zinc chloride fumes during training exercises [439,440]. Mercury causes a toxic pneumonitis together with neuropsychiatric symptoms [441]. Cadmium may also cause acute pulmonary oedema and renal cortical necrosis [442]. There has been debate about whether high-level or long-term low-level cadmium exposure causes fibrosis or emphysema [443,444]. There is experimental evidence that it may cause either, depending on the conditions [445], and a detailed follow-up of workers in a copper-cadmium alloy plant has shown greater physiological and radiological changes consistent with emphysema in those exposed to cadmium than in controls [446]. A mortality study has also shown a high incidence of death from chronic airways disease in such workers [447]. One unusual episode of rapidly developing emphysema after several years of exposure to cadmium at concentrations of  $150\text{--}1000\mu\text{g}/\text{m}^3$  has also been reported [448]. Vanadium exposure, encountered in cleaning oil-fired boilers and in the use of the catalyst vanadium pentoxide, is associated with an increased risk of upper respiratory and asthmatic symptoms [449,450]. A green tongue is a characteristic of acute exposure to this chemi-



cal. Manganese workers have been shown to be at increased risk of bronchitis and pneumonia [451,452] as well as extrapyramidal disorders. Osmium tetroxide is an acute respiratory irritant [453], while chromium salts may cause nasal perforation and lung cancer.

### Other fumes

The exhaust gases of diesel engines contain a complex mixture of substances, including oxides of nitrogen, aldehydes and sulphur dioxide. They are undoubtedly irritant and cause cough in exposed workers, especially if the concentrations are high because the engine is labouring or working in an enclosed space such as a mine. Studies of long-term effects on lung function have proved negative [454,455] but it would be surprising if exposure to high concentrations for prolonged periods did not have some deleterious effects.

A condition similar to metal fume fever has been described in workers exposed to fumes of heated polytetrafluorethylene (Teflon) [456], while a reaction that is probably primarily an irritant bronchoconstriction may occur in workers exposed to heated PVC [457]. This condition has been called meat-wrappers' asthma. It is not clear whether it is provoked by PVC fumes or by heated adhesives from the label being affixed to the wrapping material [458]. Trimellitic anhydride, an epoxy resin hardening agent, is a known cause of occupational asthma [459]. In addition, haemorrhagic pneumonitis and haemolytic anaemia have been described in subjects exposed to its fumes [460]. Other organic substance, such as isocyanates, may be irritant in the high concentrations that occur with chemical spills and fires. While most isocyanates used in industry are diisocyanates, the notorious episode at Bhopal in Central India, in which several thousand people died of either acute asphyxiation or chemical pneumonitis, was probably caused by the highly irritant methyl isocyanate gas [14].

### Smoke inhalation

Acute smoke inhalation is a not uncommon emergency in non-occupational settings, as well as being an occupational hazard of fire-fighters. Smoke may contain a wide range of chemicals, especially now that plastics and synthetic foams are so widely used in furnishings. Those exposed to smoke may asphyxiate due to lack of oxygen or carbon monoxide inhalation, or suffer acute tracheitis and pneumonitis due to irritant chemicals such as hydrogen chloride or isocyanates in the smoke. Acute falls in ventilatory capacity have been recorded in fire-fighters after smoke inhalation and the inhalation of smoke has been shown to cause an influx of neutrophils into the lung with subsequent impairment of macrophage chemotaxis [461]. While short-term effects are obvious, long-term effects of

smoke inhalation are less clear; although it is reasonable to suppose that repeated exposures would increase a person's risk of chronic airways obstruction, this has not yet been demonstrated convincingly [462]. A mortality study of fire-fighters in the USA has shown the expected 'healthy worker effect', but a somewhat increased mortality from non-malignant lung disease [463]. Long-term exposure in Nepal to wood smoke in huts also seems to lead to an increased likelihood of cough and sputum production [464].

### Occupational neoplasms

Mesothelioma is discussed in Chapter 43 and asbestos carcinogenicity earlier in this chapter. Occupational lung cancer was first described in the metal miners of Schneeberg [7], and subsequently in uranium miners in Joachimstal and Colorado [465,466]. The common factor in metal mining is exposure to radon daughters, which are suspended in water droplets and inhaled by the miners. Similar increased risks of lung cancer were run by tin miners in Cornwall [328], by haematite miners in Cumbria [283] and by fluorspar miners in Newfoundland [467]. The radiomimetic, mustard gas, has been shown to have a similar effect on workers producing it [468]. Lung cancer has also been shown to occur to excess in workers exposed to arsenic [469], nickel carbonyl [470], hexavalent chromates [471], bischloromethyl ether [472,473], oils in the production of isopropyl alcohol [474], fumes in aluminium refineries and coke ovens [475,476] and printing ink [477].

In almost all patients with lung cancer, smoking is the most important aetiological factor. However, there is evidence that non-smokers exposed to these carcinogens may nevertheless develop the disease and that the two risk factors at least add up and, in the case of asbestos and cigarettes, may even multiply. It has been estimated that as many as 15% of men with lung cancer might not have developed the disease had they not also had occupational or environmental exposure to a carcinogen [478]. To the clinician, this seems an overestimate but is based on a careful review of the epidemiological literature.

Other aspects of lung cancer are discussed in Chapter 41.

### Management

The diagnosis of an occupational lung disease should lead to consideration of three separate but related aspects of management: (i) the management of the patient and the condition; (ii) rehabilitation and re-employment of the patient; and (iii) prevention of the same disease in other workers [479].

The first of these involves the general principles of disease management and has been mentioned where

applicable above. The acute conditions such as asthma, allergic alveolitis and inhalation injury may respond to routine therapy but are likely to recur if steps are not taken to prevent re-exposure to the causative agent. In the diseases caused by chronic exposure, such as the pneumoconioses, specific therapy is usually not available although supportive treatment may be of help. In all such patients consideration should be given to the availability of compensation (see Chapter 61). Rehabilitation of the patient if still of employable age should include consideration of return to the previous job. Since this often implies recurrence of the condition if exposures to the offending agent are not prevented, it is necessary for steps to be taken to ensure that the management of the company are aware of the hazard to their employees and have taken appropriate steps to reduce risks. In the UK, this can be achieved by an approach to the Health and Safety Executive, who will visit the workplace and ensure that the Health and Safety

at Work Act and relevant regulations are enforced. Taking this step also ensures that other workers are protected from the same hazard.

If the patient's condition is such that employment in the same job is undesirable, the management, or the company's occupational health service if one is available, may be approached to seek redeployment. In doing this it is necessary to observe the ethical principle of not revealing confidential medical information without the written consent of the patient. Only if redeployment proves impracticable or if attempted re-employment causes recurrence should retirement on the grounds of ill-health be considered. In these circumstances the patient should be advised about the benefits available, including industrial injuries benefit. In the UK, the Department of Employment runs a scheme for advising and limited retraining of disabled people. These matters are considered in more detail elsewhere [479].

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# DRUG-INDUCED LUNG DISEASE, OXYGEN TOXICITY AND RELATED SYNDROMES

ANTHONY SEATON

Until the widespread application of cytotoxic chemotherapy to patients with neoplastic disease, pulmonary drug reactions were relatively uncommon, usually occurring as occasional bronchospasm in response to aspirin or pulmonary infiltrates following nitrofurantoin. The introduction of cytotoxic drugs in particular has increased both the range of mechanisms and the frequency of pulmonary drug reactions, so that in some hospitals they are an important component of the differential diagnosis of pulmonary disease. The range of reactions is wide, from familiar simple pharmacological effects (e.g. opiates causing respiratory depression or  $\beta$ -blocking drugs causing bronchoconstriction), through less well-understood reactions (e.g. aspirin-induced asthma, eosinophilic reactions due to sulphonamides or fibrosis due to busulphan) to the infective complications of immune suppression.

Drug reactions present to the clinician as a syndrome that may be due to a number of different causes, the patient's treatment being one possibility. This chapter therefore is organized under headings denoting the main types of reaction. However, several drugs may produce different syndromes in different subjects and appear in more than one section. Table 55.1 lists the important known adverse effects on the lung of drugs grouped according to their broad therapeutic actions. For convenience, this chapter also includes some discussion of the harmful effects on the lung of oxygen and of three syndromes in which oxygen toxicity is believed to be an important component: radiation pneumonitis, paraquat poisoning and the toxic oil syndrome.

## Types of reaction

### Bronchoconstriction

#### Mechanisms

Drugs may cause bronchoconstriction in a number of different ways. The most easily understood is a direct

pharmacological effect on airway smooth muscle, as when  $\beta$ -blockers are used for the treatment of angina or as eyedrops for glaucoma [1,2]. Similar effects have been reported following anticholinergic therapy for glaucoma [3]. The best-known pharmacological cause of asthma, aspirin, probably acts through its inhibitory action on cyclooxygenase, diverting arachidonic acid metabolism from the formation of prostaglandins to the production of leukotrienes; a genetic basis for this effect has been described that involves a leukotriene (LT) $C_4$  synthase promoter polymorphism [4,5]. Other non-steroidal anti-inflammatory drugs have a similar mechanism of action, indometacin (indomethacin) being particularly potent in this respect [6]. *In vitro* studies have shown conflicting results when considering the effects of aspirin on the cyclooxygenase of platelets [7,8] but there is some evidence of an inhibitory effect, which can be blocked by sodium salicylate and which correlates with increased respiratory burst and increased killing of *Schistosoma mansoni* [9]. Interestingly, no such effect has been found with basophils or monocytes. This raises the possibility of a role for platelets in the aetiology of aspirin-induced asthma via production of arachidonic acid metabolites.

Direct irritation of airways leading to bronchoconstriction presumably via a vagal reflex may be a mechanism in the case of asthma worsening paradoxically after inhalation of sodium cromoglicate (cromoglycate) [10] or of hypotonic nebulized solutions of ipratropium bromide [11,12]. A direct action on mast cells causing release of bronchoconstrictor substances has been suggested as a cause of wheeze following administration of morphine and codeine [13], while classical type I hypersensitivity mediated by IgE is probably the mechanism of asthma and anaphylaxis following penicillin and other antibiotics [14–16]. It should be noted that a number of drugs contain the yellow dye tartrazine, which may cause exacerbation of asthma; the mechanism of this is not known [17]. Finally, the antituberculosis drug rifampicin has important effects on the enzymatic degradation of other drugs in the liver. Of particular note is its ability to reduce the effi-

**Table 55.1** Main groups of drugs having adverse effects on the lung.

Pharmacological action	Effects	Examples
Antibiotic	Bronchoconstriction Alveolitis	Penicillin Nitrofurantoin
Anti-inflammatory	Bronchoconstriction Alveolitis Bronchiolitis Pulmonary oedema	Aspirin Sulfasalazine Penicillamine Aspirin
Cardiac	Cough Bronchoconstriction Alveolitis Pulmonary oedema Pleural fibrosis Lupus syndrome	ACE inhibitors $\beta$ -blockers Amiodarone Thiazides Practolol Hydralazine
Anticonvulsant	Alveolitis, lupus syndrome	Phenytoin
Psychotropic	Alveolitis Pulmonary oedema	Amitriptyline Phenothiazines
Cytotoxic	Alveolitis  Opportunist infection	Busulfan, bleomycin Most combinations
Analgesic	Bronchoconstriction, respiratory depression, pulmonary oedema	Opiates
Contraceptives	Pulmonary embolism	High-oestrogen pill

ACE, angiotensin-converting enzyme.

cacy of corticosteroids (and the contraceptive pill) [18]. Asthmatic patients on steroids who develop tuberculosis often require their dose of steroids to be more than doubled when rifampicin therapy is introduced. Similarly, asthmatic patients on regular xanthine therapy may require a higher dose if they need treatment with rifampicin [19].

### Drugs causing bronchoconstriction

The more important drugs causing bronchoconstriction are listed in Table 55.2. The most significant of these from a clinical point of view are the  $\beta$ -blockers and the non-steroidal anti-inflammatory drugs. Although most of the newer  $\beta$ -blockers have been promoted as being cardioselective, this can only be regarded as a relative advantage; subjects with asthma or airflow obstruction are quite liable to suffer exacerbations when treated with effective doses [1,20] and it is wiser to avoid the use of these drugs altogether. There is some evidence that atenolol is a less potent bronchoconstrictor than other drugs of this class.

**Table 55.2** Drugs causing bronchoconstriction.

<i>Autonomic system modulators</i>
$\beta$ -Blockers
Propranolol
Timolol
Oxprenolol
Metoprolol
Anticholinesterase
Ecothiopate
<i>Analgesics and anti-inflammatory drugs</i>
Opiates
Morphine
Non-steroidal anti-inflammatory agents
Aspirin
Indometacin
Naproxen
Ibuprofen
Mefenamic acid
<i>Antibiotics</i>
Penicillins
Penicillin
Amoxicillin
Ampicillin
Tetracyclines
Cephalosporins
Rifampicin*
<i>Others</i>
Cromoglicate
Hydrocortisone sodium succinate
Tartrazine
Pancreatic extract
Iron dextran
Iodinated contrast media

\*By interfering with antiasthma drugs.

The usual pattern of response to  $\beta$ -blockers is a gradual worsening of the patient's breathlessness and a failure to respond in the normal way to treatment with  $\beta$ -agonist drugs. The subjects usually have pre-existing asthma or airflow obstruction, although it is not uncommon for symptoms to be provoked for the first time by the use of  $\beta$ -blockers. Sometimes the adverse effect of the drug persists for some months after it has been discontinued [20].

Asthmatic and anaphylactic reactions to aspirin were first described not long after its introduction to therapeutics [21,22], and a syndrome comprising asthma, nasal polyps and aspirin sensitivity has been recognized since the 1920s [23,24]. Typically, the patients are middle-aged and non-atopic; the condition may be familial and occurs in 2–4% of all asthmatic subjects [25–28]. When it occurs in children, atopic features are usually absent [26]. The order in which the three features of the syndrome occur is variable, though aspirin sensitivity usually appears after the asthma and the polyps [29]. Urticaria and anaphylaxis may sometimes occur. The syndrome appears to be related

to release of products of arachidonic acid metabolism via the 5-lipoxygenase pathway, notably  $\text{LTE}_4$  [30].

Asthmatic subjects sensitive to aspirin are often found to respond similarly or to a greater degree to other non-steroidal anti-inflammatory drugs [31] and may show increased sensitivity to histamine provocation [32]. This may cause problems in the management of pain and rheumatic conditions in asthmatic subjects. As far as possible, analgesics with minimal or no anti-inflammatory action, such as paracetamol and dihydrocodeine, and local treatment should be used in these circumstances. Paradoxically, some asthmatic subjects find that their condition improves when they take aspirin or other anti-inflammatory drugs, such as indometacin and mefenamic acid [33–36]. In selected patients these drugs may therefore have a therapeutic role.

Other pharmacological causes of bronchoconstriction are rare. A number of antibiotics have occasionally provoked asthma or anaphylaxis. Several of these, notably ampicillin, cephalosporins, tetracyclines and spiramycin, have been described as causing occupational asthma in workers exposed to them during their manufacture [15,16,37,38]. Contrast media used in radiology that contain iodine and the iron dextran compound Imferon may provoke severe anaphylactic responses. A test dose should be administered before their use, though this may sometimes fail to predict a reaction following the full dose. Hydrocortisone used intravenously or intramuscularly may occasionally have the paradoxical effect of making asthma worse [39]. This appears to occur predominantly in aspirin-sensitive subjects; the mechanism is unknown, but in one case investigated by the author occurred with the sodium succinate but not the phosphate preparation. Cromoglicate may also occasionally cause bronchoconstriction. This has usually been attributed to irritation, although occasionally very severe episodes suggestive of an anaphylactic mechanism may occur; other rare side-effects of cromoglicate, including pulmonary infiltration, urticaria, eosinophilia and nasal congestion, support the idea that true allergies may occur [40,41].

## Cough

Any of the drugs able to provoke asthma or bronchoconstriction may cause the symptom of cough. However, one group of drugs is notable for causing cough rarely if ever accompanied by bronchoconstriction, the angiotensin-converting enzyme (ACE) inhibitors [42,43]. These drugs are widely and successfully used in the management of hypertension and cardiac failure. The cough usually starts after several months of treatment and is of a dry irritant nature. It ceases within a few days of stopping the drug, and this is therefore an appropriate diagnostic test. The symptom, which is probably related to bradykinin release, occurs in 5–20% of patients treated with the drugs and

there is little benefit to be expected from changing to another ACE inhibitor. There is some evidence that administration of cromoglicate reduces the severity and frequency of cough in such patients, experimentally attenuating the response to inhaled capsaicin [44]. However, the patients can usually be transferred successfully to an angiotensin II antagonist, which does not have the same side-effect.

## Bronchiolitis obliterans

A syndrome of progressive breathlessness associated with increasing airflow obstruction has been described in patients with rheumatoid arthritis and other collagen diseases [45,46]. A proportion, though not all, of these subjects has been treated with D-penicillamine [46,47] and it now seems possible that this drug may occasionally provoke the disease; however, it is a rare condition, in one study having occurred in only 2 of about 250 subjects with reactions to penicillamine [48]. A similar syndrome has also been described in a patient with ulcerative colitis treated with sulfasalazine (sulphasalazine) and in a patient who took an overdose of L-tryptophan [49,50]. The clinical features are difficult to distinguish from those of airflow obstruction of other causes. The breathlessness is progressive, although the rate varies from a rapid progression over weeks to a slow course over years. The airflow obstruction is irreversible and may be associated with the auscultatory signs of late inspiratory repetitive crackles and a mid-inspiratory squeak. The radiograph may show diminished peripheral markings in generalized disease or consolidation in more local disease, but is often normal.

Lung function tests show reduced forced expiratory volume in 1 s ( $\text{FEV}_1$ ) and forced vital capacity (FVC) (the former to a greater extent), raised residual volume and normal total lung capacity. Diffusing capacity is typically somewhat reduced. Pathologically there is widespread obliteration by fibrous tissue of small bronchi and bronchioles, a pattern identical to that occurring occasionally after toxic gas inhalation [51] or after adenovirus infection in children [52]. Since the condition may occur in rheumatoid disease untreated by penicillamine, it may be difficult to decide on the cause. It is wiser to assume that penicillamine is responsible if this drug is being administered and to stop it, in the hope that the condition stops progressing; reversal of the airflow obstruction in these circumstances or following treatment with corticosteroids is not common but has been reported [53].

## Alveolitis

### Clinical features

Many drugs have been described as causing diffuse alve-

olitis and the spectrum of the ensuing clinical syndrome is a broad one. The patient usually presents with slowly increasing breathlessness and, sometimes, cough. Repetitive crackles may be heard in the lung and the radiograph usually shows diffuse patchy infiltration (Fig. 55.1). A raised eosinophil count may be found in the blood, and occasionally the clinical and serological features of systemic lupus erythematosus (SLE) may be present. Lung function testing reveals a reduction in diffusing capacity, sometimes associated with diminished lung volumes. In some cases this restrictive type of abnormality is associated with an obstructive pattern as well.

These features are non-specific and may give rise to diagnostic difficulty, especially if the patient is being treated for a condition that may itself cause pulmonary infiltration. It is therefore wise to consider the possibility of drug reaction in all patients presenting with diffuse lung infiltrates. In many instances, stopping the offending drug leads to an improvement in the clinical features. Further investigation is discussed in the section on diagnosis and management.

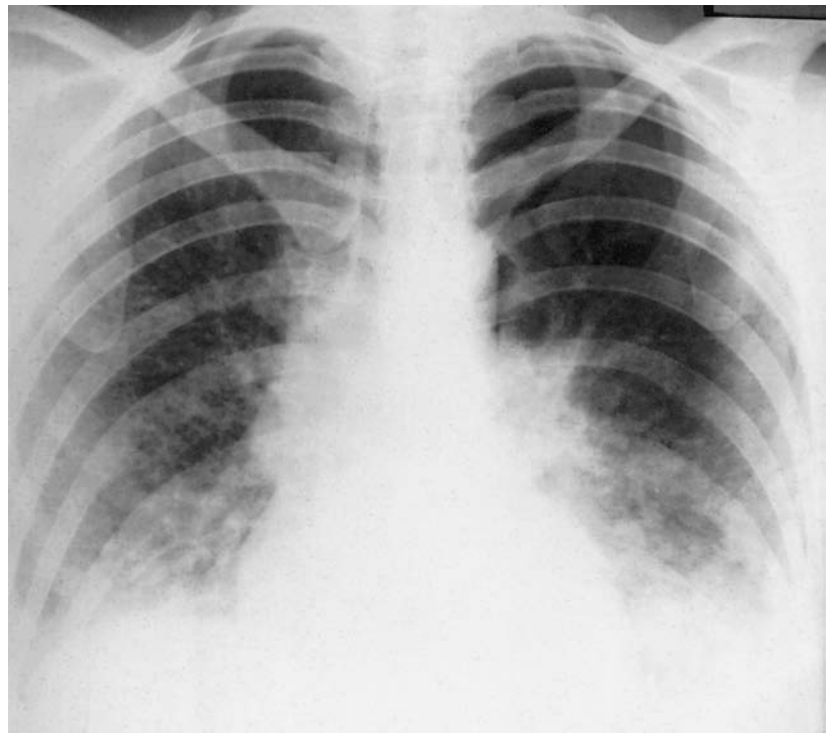
### Mechanisms

It would be misleading to imply that the mechanisms of alveolitis due to drugs were clearly understood. Different drugs may cause very different reactions, and indeed the same drug may provoke different responses in different individuals. Some reactions are clearly related to the known pharmacological effects of the drug, i.e. they are

direct toxic effects, while others are clearly the result of an idiosyncratic reaction. For the purposes of this section, the different reactions leading to alveolitis are divided into toxic, allergic and those related to drug-induced SLE.

Direct toxic effects of drugs may be mediated in several different ways. Some drugs, including bleomycin, cyclophosphamide and nitrofurantoin, have been shown to be able to cause the generation of toxic oxygen species or acrolein [54–56], with consequent lung damage. Others may act on the system whereby the lung matrix repairs itself, interfering with or increasing the formation of collagen. Again, bleomycin is known to cause proliferation of fibroblasts with increased formation of collagen [57], while penicillamine may impair collagen formation [58]; indeed this is partly responsible for its therapeutic efficacy.

Allergic reactions are the most frequently recognized mechanisms of drug-induced alveolitis. Their sporadic unpredictable occurrence, the common association with eosinophilia and, usually, lack of a relationship to dose are evidence in support of this hypothesis. Experimental and clinical studies have shown, for example, evidence of enhanced cell-mediated immunity or a T-lymphocyte alveolitis provoked by gold salts [59,60], nitrofurantoin [61], amiodarone [62] and methotrexate [63]. It is assumed that these drugs act as haptens, binding to plasma proteins in order to induce allergic reactions. However, the search for such antibodies has been singularly unsuccessful, leading to the hypothesis that the hapten may be a metabolic product rather than the drug itself [64]. It may be that differences between individuals in the ways in



**Fig. 55.1** Bilateral, predominantly lower zone, infiltrates in a patient with an acute reaction to sulphonamides.

**Table 55.3** Drugs causing systemic lupus erythematosus.

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Hypotensives: hydralazine, methyldopa, reserpine
Antituberculous drugs: isoniazid, para-aminosalicylic acid
Cardiac drugs: procainamide, thiazides, digoxin
Antibiotics: sulphonamides, tetracycline, penicillin
Anticonvulsants: phenytoin, primidone
Others: gold, carbamazepine, thiouracil, oral contraceptives

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which drugs are metabolized in the liver could thus be a partial explanation for the sporadic nature of drug reactions.

Drug-induced SLE is a rare event. Originally described in patients treated with hydralazine, it has now been recorded following treatment with many other drugs [65,66], of which the most frequently used are shown in Table 55.3. Most cases are caused by hydralazine, procainamide, isoniazid and phenytoin. The condition mimics the idiopathic disease, with joint symptoms, fever, positive antinuclear factor (but less commonly anti-DNA antibodies), malaise, together with pleuropericardial disease and pulmonary infiltrates. Renal disease and malar erythema occur uncommonly and central nervous involvement and discoid lesions are very rare. The condition resolves when the drug is stopped. The drugs presumably act on the DNA of cell nuclei, and the sporadic nature of the condition suggests that allergic factors, perhaps combined with genetically determined slow metabolism, may be responsible. However the mechanisms are unknown.

### Drugs causing alveolitis

Table 55.4 lists some of the more important drugs known to have caused alveolitic reactions. Of the antibiotics, the most frequent offender is nitrofurantoin, used primarily for long-term urinary antiseptics [67–70]. Two syndromes have been described. The more common, first reported in 1962, is an acute illness with cough, breathlessness and fever ensuing several weeks after the drug has been started. Crackles may be heard at the lung bases on inspiration, the radiograph usually shows bilateral diffuse micronodular or patchy infiltrates (sometimes with pleural effusion) and the diffusing capacity ( $DL_{CO}$ ) is reduced. There is often blood eosinophilia and lung biopsy may show infiltration with inflammatory cells and eosinophils; vasculitis may also be present. The condition usually resolves rapidly when the drug is discontinued but recurs if it is restarted. Persistence with the drug may lead to fatal pulmonary fibrosis. The more chronic syndrome presents rather insidiously with cough and dyspnoea, usually after several years of treatment. The chest film shows basal infiltrates,  $DL_{CO}$  is reduced, eosinophilia is inconstant and the course is progressive if the drug is not stopped. Other antibiotics seem to

**Table 55.4** Drugs causing alveolitis.

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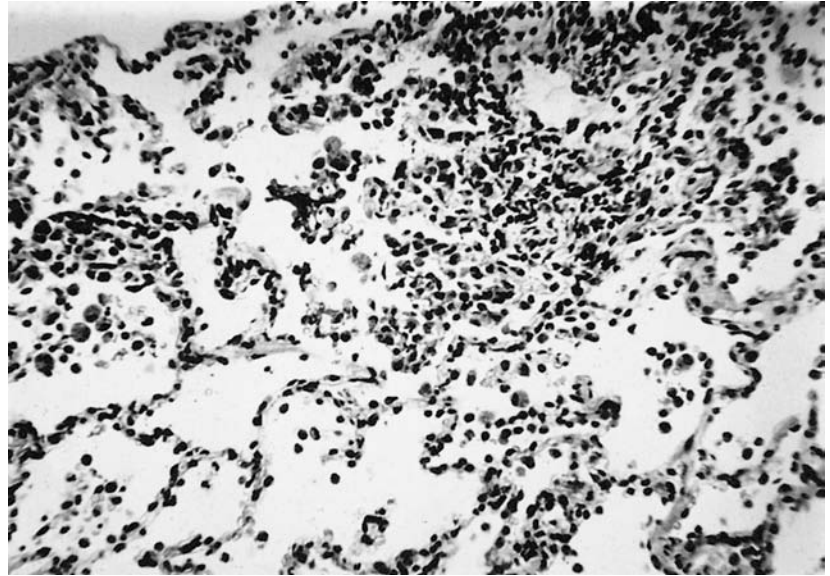
<i>Antibiotics</i>
Nitrofurantoin
Sulphonamides
Penicillins
Para-aminosalicylic acid
<i>Anti-inflammatory</i>
Sulfasalazine
Penicillamine
Gold
<i>Cardiac</i>
Antiarrhythmics
Amiodarone
Tocainide
Procainamide
Quinidine
Hypotensives
Hydralazine
Methyldopa
Hexamethonium
<i>Anticonvulsants</i>
Phenytoin
Carbamazepine
<i>Psychotropic</i>
Amitriptyline
Imipramine
<i>Cytotoxic</i>
Antibiotics
Bleomycin
Mitomycin
Alkylating agents
Busulfan
Chlorambucil
Folic acid antagonists
Cyclophosphamide
Methotrexate
Nitrosourea
Carmustine
<i>Others</i>
Chlorpropamide
Cromoglicate
Pituitary snuff
Cocaine

---

cause pulmonary allergic reactions much less frequently, perhaps partly because they are rarely administered for such prolonged courses. Sulphonamides (Fig. 55.2), penicillin, ampicillin and para-aminosalicylic acid have occasionally been associated with acute eosinophilic pneumonitis [71–76].

Of the anticonvulsant drugs, phenytoin and carbamazepine have caused pulmonary reactions. The former drug causes a number of non-pulmonary toxic effects, including gum hyperplasia, hirsutism, acne and cerebellar ataxia; rarely it has been described as causing an allergic





**Fig. 55.2** Drill lung biopsy of patient with reaction to sulphonamides showing infiltration of alveoli with predominantly eosinophil inflammatory cells.

alveolitic reaction, with fever, cough, dyspnoea and eosinophilia [77,78]. The chest film shows diffuse interstitial shadowing sometimes with marked hilar lymphadenopathy, and occasionally generalized lymph node enlargement may cause a pseudolymphomatous syndrome [79]. Lung biopsies have shown alveolar wall and small vessel infiltration with inflammatory cells [77]. The condition resolves when the drug is stopped. A similar syndrome has been described very infrequently following the use of carbamazepine [80,81].

Several drugs used in cardiac disease may cause alveolitis. Of those used to treat dysrhythmias, amiodarone seems most frequently to have this effect [82–84]. Its action is almost certainly a direct toxic one. Radiological signs of alveolitis tend to be related to the dose, occurring in some 13% of patients on high doses and 5% of those on doses of 400mg daily, and are often associated with other toxic manifestations such as corneal deposits [85,86]. A somewhat higher proportion of subjects develop abnormalities of lung function, and the likelihood of this is increased if a pre-existing abnormality was present. Indeed, side-effects are so frequent that amiodarone is generally only used for dysrhythmias resistant to other drugs. The clinical findings are fever, cough, dyspnoea and weight loss, usually after a few months of treatment, with interstitial shadowing on the radiograph. Subjects with pre-existing radiological abnormality seem to be at greater risk [85]. The histological features also suggest a toxic rather than allergic mechanism, with hyperplasia of type II pneumocytes and accumulation of foamy macrophages within the alveolar spaces [87,88]. The drug has a very prolonged action and its withdrawal is usually followed by slow resolution of the pulmonary abnormalities, although persistent interstitial fibrosis may remain [89,90]. Use of amiodarone should take account of this dangerous

side-effect; the dose should be the minimum required to control the dysrhythmia and the pulmonary effects should be monitored by regular measurement of the diffusing capacity.

Tocainide, a drug derived from lidocaine (lignocaine) and also used for suppression of ventricular dysrhythmias, has been reported to cause alveolitis in occasional patients [91,92]. Procainamide and quinidine may cause a syndrome resembling SLE, as may the hypotensive drugs methyldopa, hydralazine and hexamethonium [65,66,93,94]. In this syndrome, the clinical manifestations are pleurisy, sometimes associated with effusion, interstitial pneumonitis with fever, cough and dyspnoea, and positive antinuclear antibodies. The condition remits if the drug is stopped and usually also responds to corticosteroid treatment.

The most frequent of the anti-inflammatory drugs to be associated with alveolitis is sulfasalazine [95–98]. This is a drug that is broken down after ingestion to sulphapyridine and 5-aminosalicylic acid, and is used in the management of ulcerative colitis. It may cause the typical syndrome of fever, eosinophilia and pulmonary infiltration. Some patients may show evidence of airflow obstruction, probably due to involvement of the small airways. Challenge testing in one case has shown the reaction to be due to hypersensitivity to the sulphapyridine moiety [96]. As well as being associated with bronchiolitis obliterans, penicillamine may occasionally cause a diffuse type of alveolitis [99,100] or a rapidly progressive and often fatal alveolar and renal haemorrhage, mimicking Goodpasture's syndrome [101]. The alveolitis may be expected to improve on stopping the drug, although the pulmonary–renal syndrome has been reported to respond to plasmapheresis and immunosuppression [102]. Gold therapy has been occasionally associated with pneumoni-

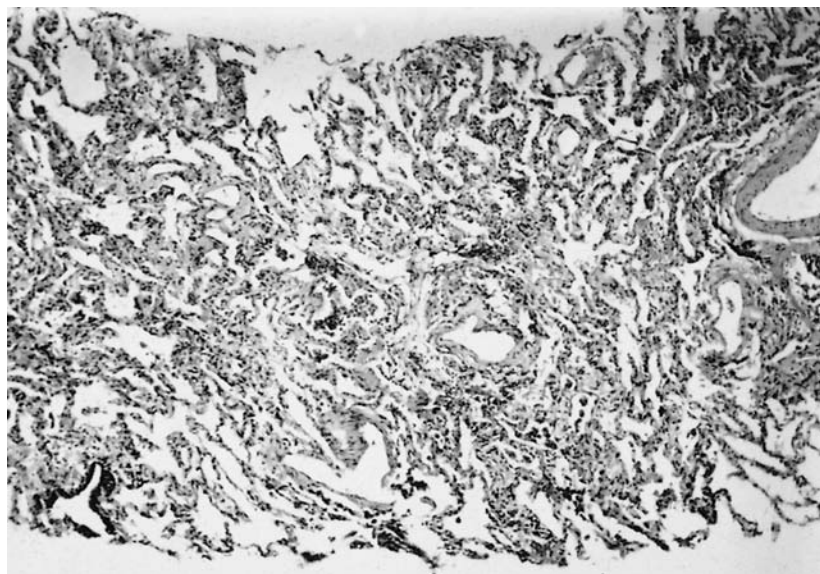
tis, rashes and eosinophilia in patients with rheumatoid disease [59,103–105]. There is some evidence to suggest that this is due to a cell-mediated immune response. It usually starts 1–3 months after initiation of treatment and has been shown to resolve on treatment with corticosteroids together with cessation of the gold therapy [104]. Gold may also provoke SLE.

The drugs most frequently associated with alveolitis are those used in the cytotoxic therapy of patients with neoplasms. In most cases it seems that they have a direct toxic effect on the lung cells, though occasionally allergic reactions may occur. Since they are often used in combination, it may not be possible to know which drug is responsible. Moreover, in some instances they may act with radiotherapy in a synergistic or additive manner to increase the likelihood of lung damage. In contrast to the non-cytotoxic drugs discussed above, the usual pulmonary injury with cytotoxic therapy is a progressive pulmonary fibrosis with relatively little of an inflammatory component and a tendency to cause irreversible lung damage.

Bleomycin and mitomycin are cytotoxic antibiotics, both of which cause progressive pulmonary fibrosis in 5–10% of patients (Fig. 55.3). Their effects generally seem to be related to age and dose and to be potentiated by radiotherapy. Bleomycin is used in the treatment of squamous carcinomas, lymphomas and testicular cancer. Lung toxicity presents as progressive breathlessness, cough and usually diffuse nodular radiographic infiltrates [106,107]. In a personally studied group of patients, half of those receiving more than 100 mg/m<sup>2</sup> showed a greater than 15% fall in DLCO, although some patients receiving less than 100 mg/m<sup>2</sup> showed an appreciable fall while others receiving more than 400 mg/m<sup>2</sup> showed none. Apart from dose, other risk factors appear to be concomitant radiation therapy or administration of high concentrations of

oxygen [108]. The histological changes are of interstitial fibrosis with metaplasia of type II pneumocytes and scanty inflammatory cells [109,110]. Bleomycin toxicity usually arrests and may regress if the drug is stopped, and there is some evidence that steroid therapy may be helpful [111,112]. Occasionally, bleomycin causes a more obviously allergic type of reaction, with fever and eosinophilia [113]. This seems more likely to be responsive to steroids. Mitomycin, which is used in treating upper alimentary tract and breast cancers, has also been described as causing pulmonary fibrosis [114,115]. The features are usually indistinguishable from those caused by bleomycin, though pleural effusions have occurred [114].

Several cytotoxic drugs that act by alkylation of DNA have been shown to cause alveolitis and pulmonary fibrosis. Busulfan (busulphan) was the first cytotoxic drug reported to have this effect [116,117]. It is used in the treatment of chronic myeloid leukaemia. The symptoms of cough, breathlessness and sometimes fever may present quite rapidly and the chest film shows bilateral infiltration [118]. Lung function shows a restrictive pattern with a low DLCO. About 5% of patients may develop this side-effect, usually after a prolonged course of treatment, often of several years. Many patients who develop lung fibrosis die, although cessation of therapy and treatment with steroids may allow recovery if the condition is detected sufficiently early [118]. The pathological changes are non-specific, with damage to type I cells, proliferation and metaplasia of type II cells and interstitial fibrosis [117,119,120]. Very similar clinical features have been described, but less frequently, following treatment with the other alkylating drugs chlorambucil [121,122], cyclophosphamide [123,124] and melphalan [125,126]. Carmustine, a nitrosourea used mainly in the manage-



**Fig. 55.3** Drill lung biopsy of patient on bleomycin therapy for end-stage lymphosarcoma showing diffuse alveolar wall fibrosis.

ment of brain tumours and lymphomas, is a more frequent cause of alveolitis and fibrosis, these effects occurring in 1–20% of patients [127,128]. The risk is related to the total dose received although, as with all these cytotoxic drugs, idiosyncratic early or acute reactions may occur [129]. In one instance, early-onset pneumonitis seems to have occurred at the site of previous lung radiotherapy, suggesting prior sensitization [130].

Pulmonary reactions leading to fibrosis have been described in association with many other cytotoxic drugs, usually when given in combination [131]. The only one of these where such reactions seem to have occurred frequently is methotrexate, a folic acid antagonist used for prolonged maintenance treatment in leukaemia and lymphomas as well as for some solid tumours. It is now used increasingly in the management of severe rheumatoid arthritis, primary biliary cirrhosis and psoriasis. The pulmonary syndrome has allergic characteristics, occurring sporadically with no obvious relation to dose. Fever, eosinophilia and pleuritis may occur in addition to the alveolitis, which usually has a granulomatous histology. Resolution usually follows cessation of therapy and institution of corticosteroid treatment [63,132–137].

Many other drugs have been described as occasional causes of a hypersensitivity type of alveolitis. Of the more commonly used, chlorpropamide, sodium cromoglicate (possibly), imipramine and amitriptyline have all caused pulmonary shadowing associated with eosinophilia [138–140]. Pituitary snuff, when produced from animal pituitaries, has been responsible for allergic alveolitis [141] and a similar syndrome has been described following recreational abuse of cocaine [142]. Aspiration of mineral oil taken as an aperient is a well-known, though uncommon, cause of patchy pulmonary fibrosis or of areas of irregular consolidation. It occurs usually in the elderly, often in association with oesophageal reflux or hiatus hernia [143]. Finally, the use of bacille Calmette–Guérin (BCG) as a tumour-suppressant drug, most notably in the treatment of bladder cancer by intravesical instillation, has resulted in disseminated disease involving lungs and other organs in a granulomatous reaction responsive to antituberculous therapy [144].

### **Pulmonary oedema**

Acute pulmonary oedema (discussed in detail in Chapter 27) may be occasionally caused by drugs, sometimes as an idiosyncratic reaction though usually in response to an excessive dose. The mechanisms are not clear but may be a direct effect on pulmonary alveolar structures or an indirect effect mediated through the central nervous system. What evidence there is suggests that the oedema is of the high-protein increased-permeability type [145,146].

The most frequent causes of drug-induced pulmonary oedema are overdoses of aspirin and opiates. Aspirin acts

to reduce prostaglandin production by inhibition of the cyclooxygenase pathway. This may have a direct effect by increasing pulmonary endothelial permeability or an indirect effect by increasing production of leukotrienes. Whatever the mechanism, patients admitted to hospital with high salicylate levels after an overdose (>40 mg/dL) are at risk of developing acute pulmonary oedema [147–149]. Fortunately the condition responds to routine management with forced alkaline diuresis, oxygen and, if necessary, assisted ventilation. Pulmonary oedema is also a frequent feature of patients admitted with an overdose of heroin or other opiates [150,151]. Again, the mechanisms are not clear and both direct and central nervous-mediated actions have been suggested. Treatment depends on the use of naloxone and assisted ventilation; recovery is to be expected in hospitalized patients.

The other drugs associated with pulmonary oedema are much less frequent causes. Sympathomimetic drugs used in high dosage for the prevention of premature labour occasionally cause the syndrome [152,153], as does hydrochlorothiazide [154,155]. The rarity of these episodes suggests an allergic mechanism. Antipsychotic drugs such as the phenothiazines and butyrophenones sometimes cause hyperpyrexia, muscle rigidity and abnormalities of the autonomic and central nervous system, the so-called neuroleptic malignant syndrome [156]; this may be associated with cardiovascular collapse and pulmonary oedema.

### **Pulmonary vascular disease**

Oestrogen-containing oral contraceptive drugs have been shown to increase the risk of pulmonary thromboembolism in women by about six to nine times [157,158], though not the risk of subsequent recurrence [159]. They may also cause an increased risk of thrombotic stroke and myocardial infarction [160]. The effects on the clotting mechanism are probably due to the oestrogen content of the pill and the risk of thromboembolism related to its dose; there is evidence of increased activity of procoagulant factors and reduction of antithrombins [161,162]. For this reason, preparations with the lowest oestrogen content consistent with efficacy are generally prescribed. It should be remembered that the increased risk of thrombosis also applies to the use of oestrogens for other purposes, such as in the treatment of prostatic carcinoma and for the suppression of lactation. There is some evidence that some cases of pulmonary hypertension may be caused by oestrogen-containing contraceptives [163]. However, the increased frequency with which this condition was recognized in central Europe in the 1950s and 1960s was probably related to the use of an appetite-suppressant drug, aminorex [164,165]. Although the drug was not shown to cause pulmonary hypertension in animals, the epidemiological evidence in humans was

strong and the drug was withdrawn. So far no other drugs have been shown to have similar effects.

### **Pleural and mediastinal fibrosis**

Fibrosis of the pleura and underlying lung is an occasional and dose-related complication of the therapy of migraine with methysergide [166,167]. The patient usually presents after several years of treatment with shortness of breath and chest pain. The erythrocyte sedimentation rate is raised and there may be loss of weight. Chest radiography shows bilateral pleural thickening, sometimes with small effusions, and biopsy shows vascularized mature collagen. The mechanism is not known, although methysergide blocks serotonin receptors. This, together with its ability to cause fibrosis of pleura, peritoneum, and cardiac valves [168], suggests an analogy with the carcinoid syndrome in which there is overproduction of serotonin and in which cardiac valve fibrosis may also occur. Interestingly, all the other drugs that have been reported to cause pleural fibrosis are blockers of neurotransmission. *Practolol* blocks  $\beta$ -adrenergic receptors and may cause pleural, mediastinal and peritoneal fibrosis, as well as involving skin, eye and joints [169,170]. *Pleuropulmonary* fibrosis may present alone, in a manner identical to that following methysergide. *Ergotamine* blocks dopamine receptors, while *bromocriptine* blocks dopamine  $D_1$  receptors and stimulates  $D_2$  receptors. Both these drugs have been shown to cause an identical syndrome of pleural fibrosis [171,172]. Hypothetically, this observation may be explained by a balance between collagen breakdown and synthesis that is controlled by messages between involved cells, whereby receptors for these messages are blocked by the drugs [173]. In the case of carcinoid syndrome, which has also been described as a cause of pleural fibrosis [174], excess production of a neurotransmitter might cause all receptors to be blocked.

With all these drugs the course of pleural fibrosis is progressive, producing a restrictive pattern of lung function. However, the condition remits when the drug is stopped and in most instances there is reduction in symptoms and some improvement in lung function, though residual fibrosis remains on the chest film (see Figs 43.12 & 43.13).

### **Other pulmonary reactions to drugs**

It should not be forgotten that drugs may cause lung disease in an indirect manner. Not infrequently hypoventilation and respiratory failure may be provoked by overdose or injudicious therapeutic use of narcotic or sedative drugs, particularly in the elderly or in those with previous airflow obstruction. On one occasion in the author's experience, the cause of a mysterious case of hypercapnic respiratory failure was discovered when the patient was found

to have been taking large doses of a traditional Edinburgh treatment for peripheral vascular disease, prescribed by a surgeon, containing narcotic doses of barbiturates and masquerading under the name of *Chief's Powder*! Respiratory failure is discussed further in Chapter 24. Drugs acting on the immune system, used in the management of cancer, transplantation and vasculitic diseases, may set the scene for opportunistic pulmonary infections; these conditions are described in Chapter 52.

## **Diagnosis and management**

The key to diagnosis of drug-induced pulmonary disease is awareness of the possibility. Most lung diseases have an external or environmental cause and it is important to exclude such possibilities in the case of alveolitis or asthma of obscure aetiology. A note should be made of all drugs taken by every patient and any drugs with unfamiliar names should be checked in reference books.

If a drug reaction seems a possibility, appropriate baseline investigations should be carried out and the drug stopped. These investigations normally include chest radiography and lung function testing, although erythrocyte sedimentation rate, temperature records and differential white cell counts may often be helpful. If several drugs are under suspicion, it is best to stop all those regarded as not essential to the patient's well-being. In the case of single drugs, cessation usually results in clinical improvement; normally this provides sufficient proof for the drug to be avoided subsequently, but if necessary when allergy is suspected a challenge test can be carried out after an interval during which the drug is not taken. This should not be performed unnecessarily as severe reactions may sometimes occur. Appropriate indications are when the drug is one of a multiple regimen and it is not clear which is responsible, or when the drug is itself a combination of two medicaments, for example *Salazopyrin* or *Rifinah*. Challenge testing should be carried out under hospital supervision and initially should use a fraction (perhaps a hundredth) of the therapeutic dose; the results should be monitored by lung function testing. It is only appropriate in suspected allergic reactions and is unlikely to be of value in diagnosing reactions due to direct toxic effects.

Lung biopsy, gallium scanning and bronchoalveolar lavage have only a small part to play in the diagnosis of these reactions, as they only show non-specific effects of a wide range of pulmonary reactions. They may of course have an important role in the differential diagnosis, by excluding other possible pathological processes. In general they are appropriately employed after drug reactions have been excluded.

Management of pulmonary drug reactions consists in stopping the offending drug and, if necessary, substituting a less harmful one. Occasionally, corticosteroid therapy

may be used though its value can only be judged by anecdotal evidence in most cases. In the management of malignant disease, pulmonary side-effects are relatively frequent occurrences and cessation of the drug may result in relapse. They are therefore an important and sometimes fatal complication of therapy. Hyposensitization, or induction of tolerance, may be tried if the drug is considered essential, all alternatives are unsatisfactory and the reaction is thought to be allergic or idiosyncratic. These circumstances must be rare with respect to drug-induced lung disease, although many older chest physicians will be familiar with the techniques for management of allergic rashes to para-aminosalicylic acid and isoniazid in treating tuberculosis. The main interest in this subject currently centres on the induction of tolerance to aspirin and non-steroidal anti-inflammatory drugs [175]. There is evidence that this may be of benefit to some patients, particularly with respect to alleviation of rhinitis. However, it should be embarked upon with great care, as serious reactions can occur [176]. There is some hope that in the future leukotriene antagonists may also have a role to play in aspirin sensitivity [177].

### Lipoid pneumonitis

Inhalation of oil is an occasional cause of lung disease. The reaction depends on the type of oil. Mineral oil remains in the lung, engulfed by macrophages, and may give rise to fibrosis; animal fats are hydrolysed by lung lipases and the resulting fatty acids cause acute inflammatory pneumonitis, while vegetable oils are relatively inert [178]. Animal and vegetable oils may enter the lungs by aspiration in subjects with hiatus hernia, oesophageal reflux or neuromuscular disease, and the former are an important cause of unresolved pneumonia in the elderly [179]. Mineral oil may be inhaled occasionally by shipwrecked mariners, but the important causes are the use of oily nasal drops or of liquid paraffin as an aperient [180–182]. The paraffin is usually taken daily over years and aspiration of small amounts regularly may cause a patchy diffuse granulomatosis leading to fibrosis [183]. A similar syndrome has been described in Guyana in people of Indian origin who smoked cigarettes made of tobacco to which mineral oils had been added as flavouring [184]. This blackfat tobacco-smokers' lung was an important cause of chronic pulmonary fibrosis, leading to much disablement and death in that country. Diffuse fibrosis at least partly due to inhaled paraffin has also been described in a fire-eating punk-rock drummer [185].

### Oxygen toxicity and related syndromes

#### Mechanisms

It may seem paradoxical that oxygen, upon which animal

life depends, has the potential to harm the lung. However, oxygen became an important component of the earth's atmosphere only after the evolution of plant life and photosynthesis, and all animals may therefore be regarded as organisms that have not only turned this gas to good effect but which have also developed mechanisms for overcoming its toxic effects. These effects depend upon the relative ease with which oxygen may be reduced by cells to produce superoxide anion ( $O_2^-$ ) and hydrogen peroxide ( $H_2O_2$ ). These radicals are toxic to cell membranes but may also react together to form hydroxyl radical ( $\cdot OH$ ) and singlet oxygen ( $^1O_2$ ), which are highly toxic and react with cellular chemicals leading to peroxidation of lipids, depolymerization of mucopolysaccharides, rupture of protein sulphhydryl bonds and damage to nucleic acids. These reactions are utilized by phagocytic cells in the destruction of invading organisms; however, when phagocytic or other metabolizing cells are damaged they may be responsible for the destruction of adjacent cells in the tissue under attack.

Clearly, the alveolar tissues are in a vulnerable position with respect to toxic damage by oxygen, since they have to provide adequate concentrations to other tissues while resisting potential harm themselves. In common with other cells, those of the lung have developed mechanisms for defending themselves against such damage; superoxide dismutase eliminates superoxide radical, catalase and peroxidases deal with hydrogen peroxide (the green colour of infected sputum is due to the presence of myeloperoxidase from leucocytes) and substances such as glutathione, uric acid, vitamin C and vitamin E mop up free radicals. Thus the normal lung is protected by a balance between production and destruction of free radicals, a balance that may be disturbed by a number of different factors.

The inhalation of high concentrations of oxygen makes more oxygen available for conversion to free radicals and this may reach the stage of overwhelming the antioxidant defences [186,187]. However, there is evidence that gradual increase of oxygen concentration may prevent this by induction of superoxide dismutase and catalase, although experimentally there appears to be a limit to the amount by which the catalase gene can be upregulated [188]. Overwhelming infection or recruitment of inflammatory cells to the lungs may similarly result in tissue damage by release of free radicals. Radiation therapy is particularly toxic to the lungs because of its ability to produce free radicals from cells in its path. Similarly, the herbicide paraquat acts by increasing production of superoxide radical in the lung.

#### Ventilator lung

Some patients requiring prolonged assisted ventilation develop a syndrome of decreasing compliance, increasing

hypoxaemia and diffuse radiological shadowing. They require increasing inspired concentrations of oxygen but with decreasing effect on  $P_{aO_2}$ . At autopsy, their lungs may present a variety of pathological appearances, including oedema, hyaline membranes, septal thickening by oedema and proliferating fibroblasts, and some interstitial fibrosis [189] (Fig. 55.4). Although in such situations it is often difficult to distinguish between the various possible causes, as there is almost always some other underlying lung disease, it is clear that hyperoxia is an important factor in the production of this damage. The condition may be reproduced in animals, where it has been shown that the sequence of pathological change consists of, firstly, an acute phase with generalized interstitial oedema, alveolar haemorrhage, capillary endothelial necrosis and damage to type I pneumocytes and, secondly, a proliferative phase in which the oedema is reabsorbed and there is hyperplasia of interstitial fibroblasts and type II pneumocytes [187]. Resolution may occur, although progressive fibrosis of the interstitial tissues is a more usual sequel in animals that survive.

Studies in humans have shown that 100% oxygen may be tolerated for up to 24h with no more than some bronchial irritation and substernal discomfort [190,191]. However, lavage studies have shown that by 18h there is early evidence of leakiness of alveoli and of liability of macrophages to release mediators of fibrogenesis [192], while physiological studies have shown falls in compliance, diffusing capacity and tracheal mucus flow rate [193–195]. It seems likely therefore that subtle changes may occur relatively early in the course of hyperoxia. However, the clinical syndrome does not usually present until after several days of exposure to high oxygen con-

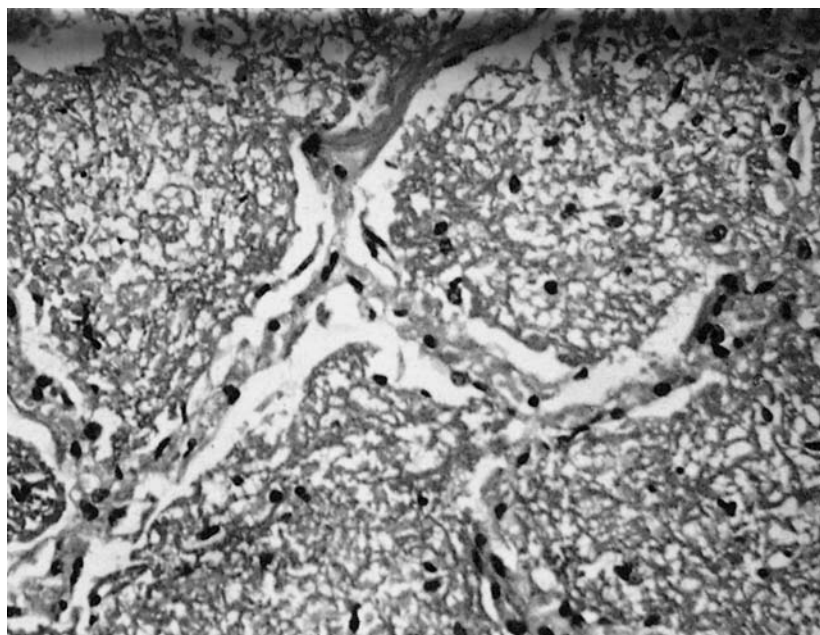
centrations, the time varying inversely with the concentration. Inspired oxygen concentrations of less than 50% seem to be tolerated indefinitely [196].

The management of oxygen toxicity presents the physician with a therapeutic dilemma. Patients at risk of this problem inevitably have serious lung disease and require tissue oxygenation. Adequate inspired concentrations of oxygen must therefore be delivered to prevent hypoxic damage to other tissues. The aim should therefore be to deliver a sufficient concentration to keep the patient's blood adequately saturated but without exceeding a  $P_{aO_2}$  of about 13 kPa (100 mmHg). If this requires inspired concentrations above 50%, then this concentration has to be given, in the knowledge that far from all such patients suffer lung damage as a result and the effects of hypoxaemia are more acutely threatening. The use of appropriate methods of ventilation, such as positive end-expiratory pressure, may allow the oxygen concentration to be kept as low as possible (see Chapter 58).

Increased understanding of the mechanisms of oxygen toxicity has given rise to hope that some pharmacological therapy may eventually be helpful in the prevention of the condition [187]. Intramuscular vitamin E has been used with some success in premature infants and superoxide dismutase has been tried in paraquat poisoning [197–199]. Small doses of endotoxin have been shown to protect rats from hyperoxia, probably by increasing production of superoxide dismutase and catalase [200].

### Paraquat poisoning

The herbicide paraquat kills plants by virtue of its ability to be reduced and oxidized very readily. It is thus able to



**Fig. 55.4** Lung of patient who died after prolonged intensive care and ventilation for pneumonia of undetermined aetiology showing intra-alveolar fibrosis and hyaline membranes.

compete with NADP for electrons, becoming reduced to a stable free radical. In humans, it is able to react with oxygen within cells to catalyse the production of superoxide radical and hydrogen peroxide.

Most cases of paraquat poisoning occur as a result of accidental ingestion of the 20% agricultural preparation called Gramoxone, usually in the belief that it is lemonade [201,202]. It has also been taken with suicidal intent and deaths have been described following subcutaneous injection and after transcutaneous absorption in men employed to spray the poison [203]. Ingestion of the 20% solution is attended by a mortality of about 60%, the risk being related to the dose taken [204]. Deaths have also followed ingestion of the 2.5% paraquat in the Weedol granules commonly used by gardeners.

### Clinical features

The patient often suffers oral and oesophageal ulceration after ingestion and may complain of abdominal pains, vomiting and diarrhoea. Toxic effects on the kidneys and liver may lead to acute renal failure and jaundice, although these conditions are self-limiting and usually resolve if the patient can be helped over them without pulmonary problems. Respiratory symptoms, with increasing breathlessness and cyanosis, commence a few days after ingestion and almost always progress remorselessly [201,205]. The chest radiograph shows diffuse opacification and there is a progressive fall in oxygen saturation. The patient usually dies of irreversible respiratory failure within 2–3 weeks of ingesting the paraquat, although occasional patients who have taken lower doses may survive despite having shown evidence of lung disease [206]. There is some evidence from studies of workers engaged in spraying paraquat, and who have absorbed it in relatively small doses through the skin, that subacute poisoning can occur which may lead to chronic interstitial fibrosis, thromboses and proliferative changes in small pulmonary arteries [203]. Similar lesions have been produced in rats by application of paraquat to the skin [203].

### Pathology

The pathological appearances in humans are confused by the presence of changes that could be related to the prolonged high  $FIO_2$  that has usually been given as treatment. However, identical changes occur in rats given paraquat and kept in normoxic conditions. In animal studies, the first sign of damage is oedema and ballooning of the type I and II pneumocytes [207,208]. Within a few days these cells have been destroyed, leaving the capillary endothelial cells intact. Cells that are progenitors of fibroblasts then fill the alveolar spaces, eventually developing into mature cells. The alveoli thus become organized into a

mass of cellular fibrous tissue surrounded by intact capillaries. In humans, two pathological appearances have been noted [204]. In patients dying acutely after paraquat ingestion, alveolar and interstitial oedema with hyaline membranes is prominent. In those dying later, either intra-alveolar fibrosis or diffuse irregular fibrosis with dilatation of bronchioles causing a honeycomb appearance is seen. It is likely that these appearances represent progression rather than different reactions, analogous to the appearances found in animals.

### Management

The essential point in management is to act early. Any unabsorbed paraquat should be removed from the gastrointestinal tract by administration of fuller's earth and by gastric or bowel lavage followed by forced diuresis, haemodialysis or charcoal haemoperfusion. Management may be guided by the plasma concentration of paraquat measured by rapid colorimetric or radioimmunoassay methods. It has been shown that if the concentration does not exceed 2.0, 0.6, 0.3, 0.16 and 0.1 mg/L at 4, 6, 10, 16 and 24 h after ingestion, survival is likely [209].

If the patient presents with evidence of jaundice, renal failure or respiratory symptoms, it is almost certainly too late for effective therapy. Unfortunately, oxygen is needed by the tissues but enhances the toxic effects of paraquat. Dialysis is unhelpful at this stage since the sequence of pulmonary damage has already begun. Corticosteroids and cyclophosphamide have their advocates [210] but are probably ineffective [211]. A logical approach would be the early use of iron chelators or superoxide dismutase to antagonize toxic oxygen radicals and D-propranolol to block paraquat receptor sites [198,212]; there is one case report of survival following vigorous treatment with desferrioxamine and acetylcysteine after bowel decontamination and haemodialysis [199]. However, almost all such patients end up on a ventilator and their chances of survival are negligible. Lung transplantation has been tried but except in one case the transplanted lung itself has succumbed to the effects of residual circulating paraquat [213,214]. The very few survivors of early pulmonary damage following paraquat ingestion or intravenous injection all probably had relatively small doses, though the fact that survival has occurred in such circumstances justifies vigorous treatment [215,216]. At present, the hopeless outlook of patients with progressive lung disease requires compassionate treatment with opiates.

### Radiation pneumonitis

Irradiation of tissues causes cell death, the most actively dividing cells being those affected most readily. The effect of radiation bombardment of atoms and molecules in cells is to remove electrons. Irradiation of the water molecules



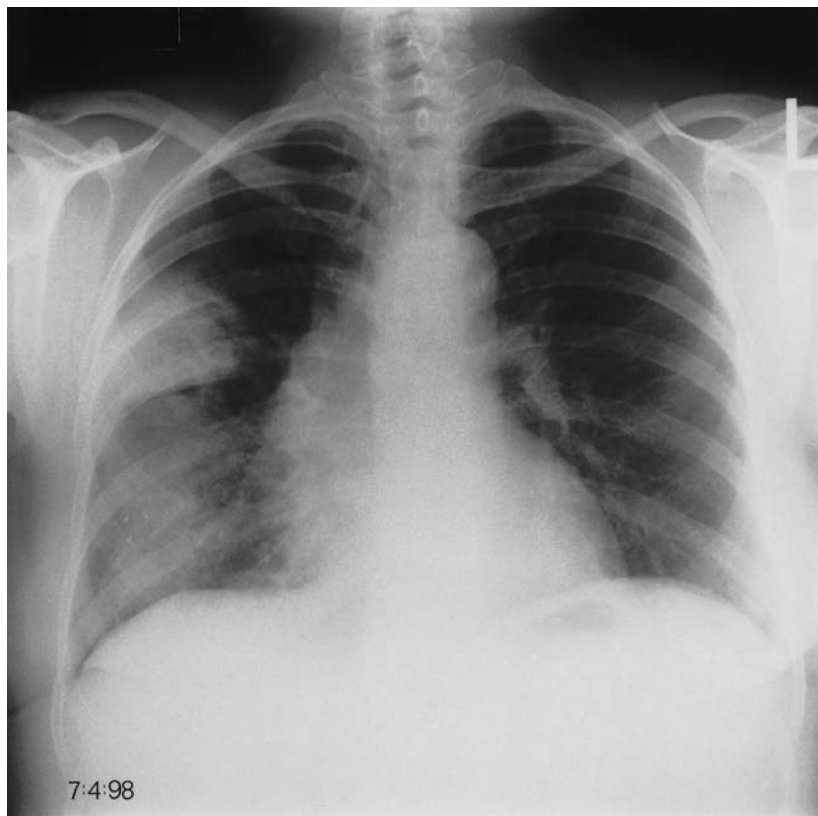
in a cell first causes the generation of an unstable ion pair,  $H_2O^+$  and an electron. These then form a hydrogen ion and a free hydroxyl radical. Further reactions result in the formation of other toxic species, including hydrogen peroxide. The presence of oxygen facilitates these reactions and high concentrations (or increased pressures) of oxygen sensitize tissues to the damaging effects of ionizing radiation [217,218]. Thus the mechanism whereby radiation may damage the lung is analogous to that of oxygen or paraquat toxicity.

As would be expected, the effects of radiation on the lung are principally on vascular endothelium and alveolar type II pneumocytes. The lung is relatively resistant to radiation up to a single dose threshold of about 6 Gy [217]. The risk of radiation damage thereafter increases sharply with increasing dose, from about 30% after a single dose of 8 Gy to 80% after 10 Gy. Higher doses may be withstood if spaced over longer intervals, with a 5% risk attending 25 Gy given over 4 weeks in 20 doses [217]. There is of course individual variability in response and other factors, such as oxygen therapy and cytotoxic drugs given simultaneously, may increase the risk [219,220].

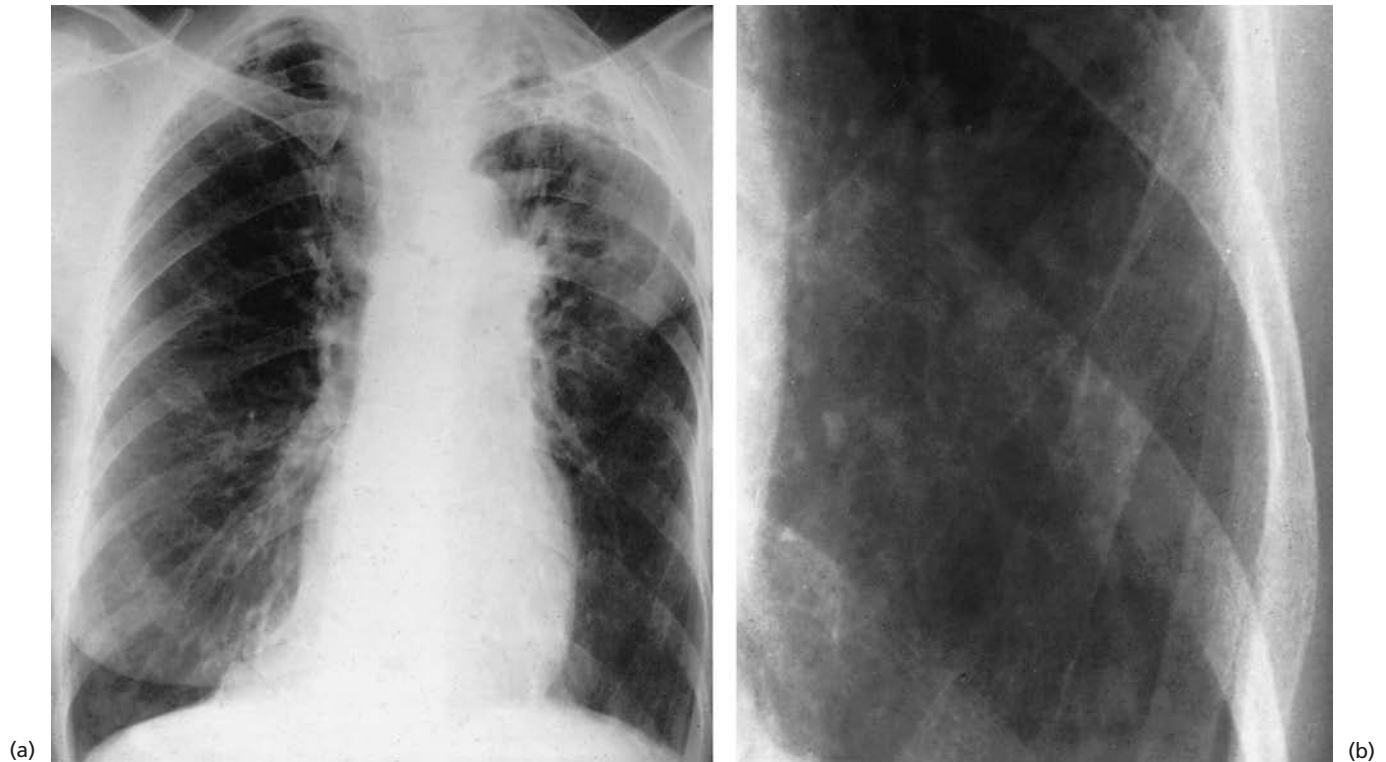
### Clinical features

Radiation pneumonitis is relatively uncommon with

modern techniques of radiotherapy. It is usually seen following mediastinal treatment of lymphoma or breast carcinoma but may occur after treatment of lung cancer, pulmonary metastases or even radioiodine therapy for lung metastases from thyroid carcinoma [221–223]. The condition usually presents 1–3 months after treatment is started, though it may occur earlier or later (Fig. 55.5). If the radiotherapy was localized the only signs may be radiological, although more generalized effects may cause progressive dyspnoea associated with repetitive inspiratory crackles on auscultation. There may be a dry cough, and pleuritic pain may indicate a radiation-induced rib fracture. Skin changes, erythema, dystrophy and telangiectasia often indicate the site of radiation. Unless very extensive and severe, the pulmonary changes are usually self-limiting. The breathlessness usually subsides slowly, over weeks or months, though the patient is often left with some residual dysfunction and studies on dogs have shown restriction and reduced *DLCO* to be likely sequels [224]. The radiological changes in the acute stage mimic pulmonary oedema, although they are normally confined to the site of treatment. Subsequent resolution in more severe cases is marked radiologically by the development of irregular fibrosis in the affected area (Fig. 55.6). Thickened pleura and dystrophic rib changes may be visible.



**Fig. 55.5** Radiation pneumonitis that developed 6 weeks after therapy for carcinoma of the right breast. Note the demarcation between normal and damaged lung medially.



**Fig. 55.6** End results of radiation therapy for breast carcinoma. Note the absent breast, left upper zone fibrosis (a) and dystrophic changes in the anterior part of the seventh rib (b).

### Pathology

Since the pathological changes have been largely described in people who have died after a course complicated by oxygen therapy and infection [225], description of the earlier changes relies largely on studies of small mammals [226,227]. The appearances of classical radiation pneumonitis mimic closely those of oxygen toxicity, with initial vacuolation and necrosis of endothelial and type I cells, oedema in the alveoli and interstitial tissue and hyaline membranes. Capillary lumens become occluded by thrombi and there is proliferation of type II pneumocytes. The end stage is diffuse interstitial fibrosis, though if recovery occurs the normal alveolar epithelium may become regenerated. However, more recently a form of pneumonitis has been recognized in which hypersensitivity appears to play a part [228,229]. In these cases even local radiation to a part of the lung may cause a bilateral lymphocytic alveolitis demonstrable by bronchoalveolar lavage and sometimes by clinical symptoms and signs, these features ultimately resolving without fibrosis. This may well form the pathological basis of the transient pneumonitis often seen clinically.

### Management

In most instances no special treatment is required as the condition is localized and resolves spontaneously. If it is sufficiently severe to cause breathlessness, most authorities would advise treatment with high doses (40 mg or more daily) of prednisolone, gradually reducing the dose as the condition responds [230]. Care should be taken to prevent infection and any evidence of this should result in early treatment with broad-spectrum antibiotics. If hypoxia occurs, only enough oxygen should be given to restore the  $P_{aO_2}$  to about 13 kPa (100 mmHg), since high alveolar tensions may aggravate the damage.

### Toxic oil syndrome

An epidemic disease characterized by diffuse neurological and vascular damage occurred in Spain in 1981 and was caused by the ingestion of contaminated rapeseed oil thought to have been denatured by aniline, though the toxic component has never been identified [231,232]. In those with respiratory symptoms, the initial illness was characterized by dry cough, dyspnoea, pulmonary oedema, fever and rashes. There was usually spontaneous recovery after 2–3 weeks and then, in a proportion, vascular lesions and fatal pulmonary hypertension occurred. At a later stage scleroderma, neuropathies and joint contractures were the main problems, and long-term lung

involvement was not prominent [233,234]. At necropsy, intimal proliferation and medial hypertrophy were prominent in muscular pulmonary arteries, with muscularization of pulmonary arterioles [235]. Evidence of vasculitis

was also found in systemic veins and arteries. It was felt that these lesions were analogous to those occurring after radiation, suggesting that they might have been caused by the release of free oxygen radicals.

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# SOME PAEDIATRIC INFLUENCES ON ADULT LUNG DISEASE

GEORGE RUSSELL

This chapter focuses on developments in our understanding and management of a few relatively common paediatric disorders that have implications for adult physicians. In the last two decades there have been major changes in the ability of paediatricians to ensure the survival of infants and children afflicted by illnesses that in the past would have proved fatal. These changes have led to the survival of many children with chronic respiratory ailments who are now entering adult life with impaired respiratory reserve. With the physiological decline in lung function that is an inevitable part of ageing, even such adults who are initially symptom-free are likely eventually to experience premature respiratory insufficiency and to have a considerable impact on adult respiratory services.

This impact has already been felt for cystic fibrosis, which enjoys the dubious distinction of being the most common recessively inherited fatal condition in populations of northern European stock, a gene frequency of 1 in 25 resulting in a disease prevalence of 1 in 2500. The prognosis for cystic fibrosis diagnosed during childhood is constantly improving, the current odds for a child born in 1983–85 entering his or her teens being just under 90% for girls and just over 90% for boys [1]. This means that the great majority of children with cystic fibrosis survive into adulthood, supporting previous estimates [2] that prolonged survival would soon be the norm. Not unexpectedly, prolonged survival has brought additional complications in its wake. In particular, diabetes mellitus and liver disease are seen with increasing frequency, with the result that the long-term care of affected individuals becomes ever more complex, posing major logistic and financial problems for adult respiratory services.

The identification of the gene responsible for cystic fibrosis has enabled accurate prenatal diagnosis following determination of the carrier status of the parents, either by initial examination of the mother's genotype followed by that of the father (sequential screening) or by examining DNA obtained from both parents simultaneously (couple screening). Whichever technique is adopted, the applica-

bility of this approach is limited by the impossibility of testing for more than a handful of the known pathological mutations in the cystic fibrosis gene and by the need to obtain genetic material from the father as well as the mother. Although prenatal diagnosis initially using amniotic fluid levels of microvillar enzymes and later specific gene testing has been available for more than a decade, there is no evidence that it has had any effect on the overall numbers of children born with cystic fibrosis in the UK [1], though the effect in individual centres has been dramatic [3]. It is therefore possible that if funding were made available for antenatal diagnosis, the numbers of affected infants might eventually fall.

Universal antenatal screening leading to termination of pregnancy raises important ethical issues. Although cystic fibrosis remains a fatal disorder, the constantly improving survival mentioned above, with further improvements such as gene therapy on the therapeutic horizon, make the case for termination much less clear-cut than was the case only a few years ago.

The other form of screening still under debate is neonatal screening, most efficiently performed by examining a blood spot for immunoreactive trypsin, followed by gene mutation analysis to eliminate the large numbers of false positives identified when immunoreactive trypsin is used alone [4]. This approach reduces the number of inappropriate treatments and investigations to which affected children are usually subjected before a diagnosis is made, and allows the family to make informed decisions regarding further procreation. Several studies have now shown that in the long term patients diagnosed by screening fare better in terms of nutrition and decline in lung function than those diagnosed clinically [5,6]. There is therefore considerable pressure to introduce universal neonatal screening, which may produce further improvements in the prognosis for affected children.

Another result of modern paediatric treatment has been the dramatic fall in neonatal mortality resulting from intensive care, which has led to the survival of increasing numbers of extremely premature infants who at one time



would have been considered previable. Unfortunately, the impressively good mortality statistics found in most neonatal units have been bought at a heavy price in neuro-developmental disability and, of interest to adult respiratory physicians, bronchopulmonary dysplasia [7], more commonly known simply as chronic lung disease.

The aetiology of chronic lung disease remains obscure, although its incidence is related to low birthweight and gestational age, the barotrauma of artificial ventilation, and oxygen administration in the neonatal period. Immature antioxidant defences may play a part; during fetal life the infant exists in a hypoxic environment and has no need of such defences, so that antioxidant enzyme systems do not appear until late in gestation [8]. The prematurely born infant is therefore ill prepared for the much higher oxygen tensions prevailing in the extrauterine world, particularly if surfactant deficiency necessitates the administration of high concentrations of oxygen.

Pathologically, bronchopulmonary dysplasia is characterized by diffuse alveolar damage with increased capillary permeability, with an infiltrate of inflammatory cells, principally neutrophils, and the release of inflammatory mediators including neutrophil elastase [9] and leukotrienes [10], which are presumably responsible for the bronchial hyperreactivity that characterizes the disorder in its later stages.

In the neonatal period, the diagnosis of bronchopulmonary dysplasia is based on respiratory distress lasting for longer than 4 weeks, oxygen dependency persisting beyond 36 weeks' postconceptual age [11] and a wide variety of radiographic abnormalities. In later infancy, laboratory assessment shows hypoxaemia and sometimes hypercarbia, associated with abnormalities of pulmonary function including increased airways resistance, air trapping with increased functional residual capacity (FRC), decreased lung compliance with increased work of breathing, bronchial hyperreactivity and, in some, pulmonary hypertension. These changes may be associated with growth failure, and it is commonly observed that the lung changes seldom improve until the child begins to thrive.

Management has tended to focus on anti-inflammatory agents such as dexamethasone [12], diuretics and the avoidance of barotrauma and hyperoxia by meticulous attention to ventilator technique. The condition tends to improve over time, and oxygen dependency seldom persists beyond the first year of life. However, functional abnormalities persist throughout childhood, with slightly impaired lung function at rest but substantial impairment of the ventilatory response to exercise and reduced aerobic capacity [13]. Few studies have been performed on adult survivors [14] but currently available information suggests that these children are entering adult life with considerably impaired lung function and exercise tolerance.

Recent improvements in the respiratory management of premature babies, such as high-frequency oscillatory ventilation and surfactant therapy, may have led to some reduction in the proportion of survivors of neonatal intensive care who have chronic lung disease [15], a benefit that may be offset by an overall increase in survival. The continuing increase in the prevalence of chronic lung disease now poses substantial financial and social burdens for society in general and affected families in particular. Zimmerman [16] cites a newspaper report estimating that in 1988 the annual cost of this condition was \$2.4 billion throughout the USA, a figure that has undoubtedly increased since then. As they appear in ever greater numbers over the next few years, the adult survivors of chronic neonatal lung disease will contribute significantly to the burden of adult lung disease.

The survival of sufferers from paediatric respiratory disease represents an obvious contribution to adult respiratory disease. More subtle are the long-term effects of environmental influences on the lungs of the unborn baby, of which the most obvious, and certainly the most extensively investigated, is maternal smoking. This is associated with a wide variety of adverse effects on the fetus, ranging from increased fetal loss by way of spontaneous abortion, stillbirth and neonatal death to growth retardation and an increased prevalence of respiratory symptoms during childhood. Data from the British Birth Survey showed that the adverse effects of smoking during pregnancy could be separated from those of passive smoking postnatally, and strongly suggested that intrauterine exposure was more important than postnatal exposure [17]. These epidemiological observations are supported by abnormalities of lung function; in two separate studies, Tager and colleagues [18] and Hanrahan and colleagues [19] have shown a decrease in maximum expiratory flow at FRC of about 50% in the offspring of mothers who smoked during pregnancy, pointing to the presence of significant airways disease. In an era when, contrary to the general trend in the UK, the prevalence of smoking is increasing in young females, the effects of maternal smoking are particularly worrying. Although the case for discouraging maternal smoking during pregnancy is overwhelming, in practice these mothers tend to stick tenaciously to their habit.

The role of intrauterine nutrition has attracted considerable interest since Barker's observations on the relationship between birthweight and the subsequent development of chronic obstructive pulmonary disease [20]. Although this study did not take account of prematurity or smoking, both of which are likely to have effects independently of birthweight, decreased lung function between the ages of 59 and 70 years and death from chronic obstructive pulmonary disease were related to low birthweight. Barker speculated that intrauterine influences which retard fetal weight gain may permanently

constrain the growth of the airways. The association of congenitally small airways with postnatal lung disease is supported by the observation of Martinez and colleagues [21] that children with evidence of impaired airway function in infancy are prone to develop wheeze in association with viral infection. Against a background of ever-increasing survival rates for premature and low birth-weight infants, these findings are a source of anxiety to neonatologists and chest physicians alike.

Interference with intrauterine lung growth also occurs in association with a variety of conditions that result in intrauterine compression or interfere with fetal breathing movements. These include the more obvious space-occupying lesions, such as diaphragmatic hernia and pleural effusion, as well as congenital lung abnormalities, such as cystic adenomatoid malformation, external compression from asphyxiating thoracic dystrophy, interference with respiratory muscle activity in spinal muscular atrophy, muscular dystrophy and anterior abdominal wall defects, and pulmonary constriction due to reduced amniotic fluid volume following prolonged rupture of membranes and renal agenesis. Studies on children who survived in previous generations suggest a relatively benign prognosis, with little interference with daily activities, although modest impairment of lung function is common [22,23] as is bronchial hyperreactivity [24]. Whether the prognosis for the current generation of children surviving more severe abnormalities with the help of high-frequency ventilation and extracorporeal membrane oxygenation will be equally benign remains to be seen, but it seems more than likely that survivors will enter adult life with more severely impaired lung function.

Even after delivery at a normal birthweight, the child's lungs are anatomically small, functionally immature and are still growing and developing. It is no great surprise therefore that they should be exquisitely sensitive to the effects of inhaled toxins and that passively inhaled tobacco smoke should have a marked effect on respiratory morbidity. The effects of passive smoking have been assessed in many studies over the years, with wide variations in the methods used to both assess exposure to smoke and define respiratory morbidity. Associations have long been established between passive smoking and pneumonia and bronchiolitis in infancy [25] and with wheeze, cough and other respiratory symptoms in older children [26,27]. Although the effects of passive smoking on lung function are less dramatic than those of intrauterine exposure to tobacco smoke, several studies [28,29] have shown significant adverse effects on lung function and growth. The overall effect amounts to a reduction in forced expiratory volume in 1s (FEV<sub>1</sub>) of the order of 5–10%. Passive smoking during childhood has also been associated with a variety of other effects during childhood, including bronchial hyperreactivity [30], glue ear and sudden infant death syndrome [31], and is said to

account for 17% of cases of lung cancer in adult non-smokers [32]. Smoking is strongly related to social deprivation, and in a recent study of Aberdeen schoolchildren we were unable to detect any effect of deprivation on respiratory morbidity that could not be explained by parental smoking.

Childhood infections also have important long-term effects on the lungs. In the past, measles and whooping cough were responsible for many cases of bronchiectasis, although this problem has now all but disappeared with the advent of successful vaccines for these conditions. These days, acute bronchiolitis is the most important lower respiratory tract infection presenting to paediatricians. It is an acute viral infection of the lower respiratory tract that affects large numbers of infants each winter, being by far the most common single cause of admission to hospital in this age group. It is usually, but by no means invariably, associated with infection by the respiratory syncytial virus (RSV), which can be identified in lower respiratory tract secretions by rapid immunofluorescent techniques. The infection usually begins in the upper respiratory tract, nasal obstruction frequently resulting in feeding problems. Over the next day or two, cough, wheeze and dyspnoea become progressively more severe. On examination, the findings include tachypnoea, inspiratory chest wall recession, evidence of hyperexpansion, and various combinations of fine and coarse crackles with wheezes. The illness runs a variable course, although most patients admitted to hospital require nasal suction, oxygen and nasogastric tube feeding. A few run a more severe course and require ventilatory support. The use of nebulized ribavirin in the management of these infants remains controversial [33]. However, there are hopes that an effective vaccine against RSV will be available soon, although paediatricians with long memories will recall that previous attempts to develop a vaccine were bedevilled by the development of vaccine-enhanced illness, reflecting the complex immunology of the disease.

It is unclear why some children develop bronchiolitis in response to RSV infection, while others develop nothing worse than a bad cold. A number of environmental factors have been implicated, particularly maternal smoking [34–36]. Although the evidence of a clinical association between bronchiolitis and atopy is conflicting, bronchiolitis is associated with increased numbers of airway mast cells [37] and the immunological response to RSV includes the production of IgE antibodies [38], which in turn is related to the frequency of subsequent wheeze.

Following the acute infection, there is considerable respiratory morbidity over the next few years, at least half the affected infants going on to develop recurrent wheeze. In many children these symptoms are transient and have disappeared by school age, but in others they persist into later childhood [36]. It is notable that most follow-up studies of infants who have had bronchiolitis have shown

that abnormalities of pulmonary function are much more common than symptomatic disability, so that yet a further group of children are entering adult life with reduced respiratory reserve, predisposed to chronic obstructive pulmonary disease in later life [39]. Bronchitis and pneumonia in early childhood have also been associated with chronic obstructive pulmonary disease in late adult life [40]; it is likely that many of these individuals actually suffered from bronchiolitis that had not been identified as a separate disorder during their infancy.

The most common chronic respiratory disease in childhood is asthma, the prevalence of which appears to be increasing for reasons that are unclear. In common with other atopic disorders, asthma has a strong genetic component [41]. A recent twin study from Norway suggested that about 75% of the variation in the liability to asthma was genetic, the remaining 25% being accounted for by environmental influences not shared by the twins [42]; given the extent to which twins normally share identical environments, these influences must indeed be subtle. Postulated environmental influences include maternal smoking (as discussed above), low birthweight, low maternal age [43], early exposure to allergens (including exposure *in utero*), exposure to viral infection [37], lack of exposure to infection, excessive vaccination, lack of bacille Calmette–Guérin (BCG) vaccination and reduced antioxidant reserves [44].

Although atmospheric pollution is popularly believed to be responsible for the recent increase in the prevalence of asthma, studies in children living in the Highlands of Scotland [45] have shown a high prevalence of wheeze and asthma in a notably unpolluted area, studies in the

north of England have shown no difference between the prevalence of respiratory symptoms between young men living in urban and rural areas [46], and studies in Surrey actually showed a significantly lower prevalence of asthma-like symptoms in children living near motorways [47].

Nevertheless, whatever the reason, it does appear that the prevalence of childhood asthma has increased [48] and is continuing to increase [49]; in a recent review, Sears [50] states that of more than 20 sequential studies, none has shown a decrease in asthma prevalence with time. Clearly the genetic constitution of the population has not changed in a single generation, and environmental influences must be responsible. The increase in asthma-like symptoms has been accompanied by a similar increase in eczema and hay fever [48,49], whereas the prevalence of wheeze triggered only by upper respiratory tract infection has remained relatively static at around 7%. Wheeze is roughly twice as common following atopy-related asthma in childhood as following infection-related wheeze [51,52] so unless a correctable cause is found for the increase in childhood asthma, adult respiratory physicians can anticipate a continuing increase in asthma-related activity over the coming decades. Based on data from the papers cited above, it can be estimated that we are on course for an adult asthma prevalence of 25%.

This brief review has tried to demonstrate that the prognosis and prevalence of many childhood respiratory diseases are changing, and that these changes are likely to be translated into important changes in the spectrum of disease seen in adult respiratory practice. As far as chest disease is concerned, the child is truly father of the man.

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# DIVING AND THE LUNG

STEPHEN J. WATT

The term 'diving' refers to activities carried out underwater that necessitate either a breath-hold or the use of breathing apparatus. It includes recreational snorkelling and scuba diving, deep breath-hold record attempts and a range of commercial activities using various types of breathing apparatus. It also includes specialized techniques such as closed-circuit breathing apparatus with oxygen for covert military operations and deep commercial diving using saturation techniques and the use of helium or other alternative inert gases. All these activities have important implications for respiratory physiology and pathology. What makes the underwater environment dramatically different from other toxic environments is the density of water and its impact on the ambient environmental pressure.

The lung is of critical importance in diving for several reasons. Apart from the necessity to maintain adequate gas exchange, the lung is the largest gas-containing space in the body and hence plays an important role in the maintenance of buoyancy. At the same time there is a risk of rupture due to overpressurization, which may lead to fatal consequences such as tension pneumothorax or air embolism. Furthermore, the lung has a crucial role in protecting the body from the pathological effects of gas bubbles formed during the ascent phase or decompression from a dive. Without this benefit, activities underwater would be much more restricted by decompression sickness.

This chapter describes the major effects of the underwater environment on lung physiology, potential pathological outcomes and the importance of assessment of lung function in determining an individual's fitness to dive.

## Physics and physiology

### Diving physics

On land at sea level, humans are exposed to an ambient pressure of 100 kPa (760 mmHg), this pressure resulting

from the mass of gas in the earth's atmosphere above sea level. Since gas is compressible, as altitude increases the pressure falls in a non-linear relationship with height. However, water is effectively non-compressible and is much denser than air. Therefore, underwater the pressure increases rapidly and linearly with depth; for every 10 m of seawater (msw) depth the pressure increases by 100 kPa. This substantial pressure change has important implications.

The gas laws are particularly important to the understanding of diving physiology. Boyle's law states that for a given mass of gas, the volume is proportional to the absolute pressure. Thus a balloon holding 10 L of air at sea level (100 kPa) reduces in volume to 5 L on descent to 10 msw (200 kPa) and to 1 L at 90 msw (1000 kPa). This is of direct relevance to the breath-hold diver who may take a large inspiration to total lung capacity (TLC) on the surface but at only 10 msw finds the lung volume close to functional residual capacity (FRC). The world record for breath-hold diving is in excess of 120 msw [1], which takes the diver's intrathoracic gas volume well below normal residual volume (RV). A diver using breathing apparatus underwater maintains relatively normal lung volumes, but a much greater mass of gas is required. The implications of the increase in gas density are described below.

Dalton's law states that in a mixture of gases, the total pressure exerted by the gas mixture is the sum of the partial pressures of each of the constituent gases in the mixture. Hence in air at 100 kPa, the pressure results from a  $P_{N_2}$  of 79 kPa, a  $P_{O_2}$  of 20.9 kPa plus small contributions from carbon dioxide and noble gases. If air is breathed at 10 msw, where the total pressure is 200 kPa, the resultant partial pressures are doubled, i.e. a  $P_{N_2}$  of 158 kPa and a  $P_{O_2}$  of 41.8 kPa. While gas concentrations are frequently used in medicine, the body's physiological response is to partial pressure; thus breathing air at 10 msw produces the same oxygen tension and physiological effect as breathing 40% oxygen at sea level.

Henry's law deals with the solution of gases and states

that the amount of gas dissolving in a fluid depends upon the partial pressure of the gas to which the fluid is exposed. This means that as the partial pressure increases, the amount of gas that can dissolve in body tissues increases. At sea level the average human has the equivalent of 1 L of nitrogen dissolved in body tissues. At 10 msw, after adequate time for complete equilibration, double that mass of gas has dissolved. This additional gas dissolved in tissues while the diver is exposed to increased pressure must come out of solution on or after return to the surface and is the source of the gas bubbles that cause decompression illness.

### Immersion

Immersion in water has a number of important consequences for the lung. The pressure differential from the feet to the chest when standing upright is almost 1.5 m of water. This is sufficient to have important circulatory effects. The additional hydrostatic pressure on the dependent limbs tends to force blood from the legs up into the chest. This has been measured and amounts to about 700 mL additional intrathoracic blood volume within the large vessels and the pulmonary circulation [2]. The increase in intrathoracic blood volume has secondary effects. Right heart pressures rise [2] and may result in a diuresis and hence a loss of total plasma volume [3]. The increase of blood volume in the pulmonary capillary vasculature may affect ventilation-perfusion balance mechanisms [3,4]. However, the most striking impact is a direct mechanical reduction in lung volumes, with a reduction in vital capacity (VC) of about 300 mL [5] that results mainly from the blood volume shift [2], though direct hydrostatic compression contributes. These measurements have been made in subjects standing erect in water with the head above the surface and are made after a period of stabilization [3,6]. In diving, posture is variable and so the available VC may change. The additional blood within the pulmonary circulation also appears to increase closing volume [7] and reduce flow rates at low lung volume [6]; hence it is associated with earlier closure of airways on expiration. This may be of considerable importance during rapid ascent as a possible cause of gas trapping [5,7].

The large pressure differential across the height of the body also imposes problems associated with the work of breathing. Normally, in the absence of airflow, there is no significant pressure differential between the mouth and the alveolar spaces of the lung. When submerged, there may be 30 cmH<sub>2</sub>O pressure differential between the mouth and the centre of the lung in the erect posture. This results in an additional workload to be overcome in order to inhale gas and imposes a further limitation on VC. The pressure differential is reduced when the diver is in a horizontal position and reversed when head down. In

practice divers usually find that a slight head-down posture is most comfortable during heavy exertion (finning). This reduces the workload of inspiration but imposes a small expiratory resistance.

### Breath-hold diving

Although breath-hold diving represents the simplest form of underwater activity, it generates some interesting physiological consequences. The breath-hold diver encounters all the problems of pressure change, immersion and buoyancy; in addition, gas exchange during a breath-hold dive is complex [8]. As the diver descends commencing with the lung at TLC, all the alveolar gas tensions rise in proportion to the increase in ambient pressure. Thus at 10 msw both alveolar  $PO_2$  and  $PCO_2$  have doubled. At depth,  $PO_2$  falls with consumption, while  $PCO_2$  is altered by production and solution. On ascent all gas tensions fall. If the alveolar  $PCO_2$  has been reduced by hyperventilation before the dive, there is a delay in stimulation of ventilation by carbon dioxide and no hypoxic stimulus as a result of the elevated  $PO_2$ . In this circumstance,  $PO_2$  may reduce sufficiently on ascent to result in an acute hypoxic episode known as shallow water blackout.

Although the importance of the diving reflex is uncertain in humans, it can readily be demonstrated and results in a significant bradycardia [9,10] and disturbance of left ventricular function [11]. At the same time, the efficiency of gas exchange is influenced by alterations in the distribution of pulmonary blood flow [12].

### Breathing apparatus

Diving means using underwater breathing apparatus. Although very good, most breathing apparatus systems produce an impact on ventilation. This is because there is an inevitable dead space, and a resistance to breathing during both inspiration (mainly until the demand valve opens) and expiration (breathing out through the exhaust valve). Though small, the combined effect of resistance and dead space causes a significant increase in the work of breathing associated with any given workload [13]. These effects are in addition to the reduction in VC and increase in the work of breathing associated with immersion.

The effect of immersion and breathing apparatus is well demonstrated in a study by Dressendorfer and colleagues [14] in which volunteers exercised in air and immersed in water to the neck with and without breathing apparatus. For similar levels of workload (oxygen consumption), minute ventilation was reduced from a control value of 146 L/min to 130 L/min when immersed and to 108 L/min when immersed and using breathing apparatus. A degree of carbon dioxide retention is inevitable.

## Gas density

With increasing pressure the diver's air or breathing gas becomes more dense. This imposes significant limitations on ventilation [15] that can be assessed by measurement of maximum voluntary ventilation (MVV). At 100 kPa, MVV is approximately 180–200 L/min. When breathing air, the effect of gas density is readily detected at quite shallow depths, for example at 30 msw (400 kPa) MVV is reduced to 100 L/min and at 50 msw (600 kPa) to 65 L/min [15,16]. On the surface, MVV is only sustainable for 20–30 s and the maximum sustainable ventilation over a period of several minutes is 70–80% MVV [17].

Underwater, for the same workload (oxygen consumption and carbon dioxide production) approximately the same minute ventilation is required to maintain a similar alveolar  $P_{CO_2}$ . Lung volume remains relatively unchanged. The mass of carbon dioxide produced remains the same, although it occupies a smaller volume within the alveoli. As a result the alveolar concentration of carbon dioxide is reduced but the partial pressure exerted is unchanged. The net effect of this is that if high levels of exertion are achieved underwater, it may be physiologically impossible to maintain adequate alveolar ventilation and carbon dioxide retention occurs. This is a well-recognized cause of loss of consciousness underwater. Various studies have demonstrated that divers tend to retain carbon dioxide [18–20] and that carbon dioxide retention underwater may reach dangerous levels without the diver recognizing the problem [21].

## Decompression illness

### Pulmonary barotrauma

Barotrauma is the term given to tissue damage that results from a change in pressure within a gas-containing space in or around the body. It can therefore affect the middle ear, sinuses, bowel, spaces between the body and the mask or suit and the lung. Pulmonary barotrauma is potentially the most serious pressure-related illness because of the severity of the outcome of arterial gas embolism.

Barotrauma may affect the lung in two ways. The lung may be compressed due to a rise in ambient pressure when the diver cannot breathe in (lung squeeze). This may occur either during a deep breath-hold dive or where breathing gas supply is lost during a rapid descent. The first scenario has been described above. The breath-hold diver takes a large breath, closes the glottis and descends. As pressure rises, the lung volume decreases. Around or below RV, there is increasing likelihood that the thorax and lung tissue are not adequately compliant to reduce in volume and hence the relative vacuum in the alveoli leads to rupture of alveolar walls and results in alveolar exudate and haemorrhage [22]. During the subsequent ascent, gas

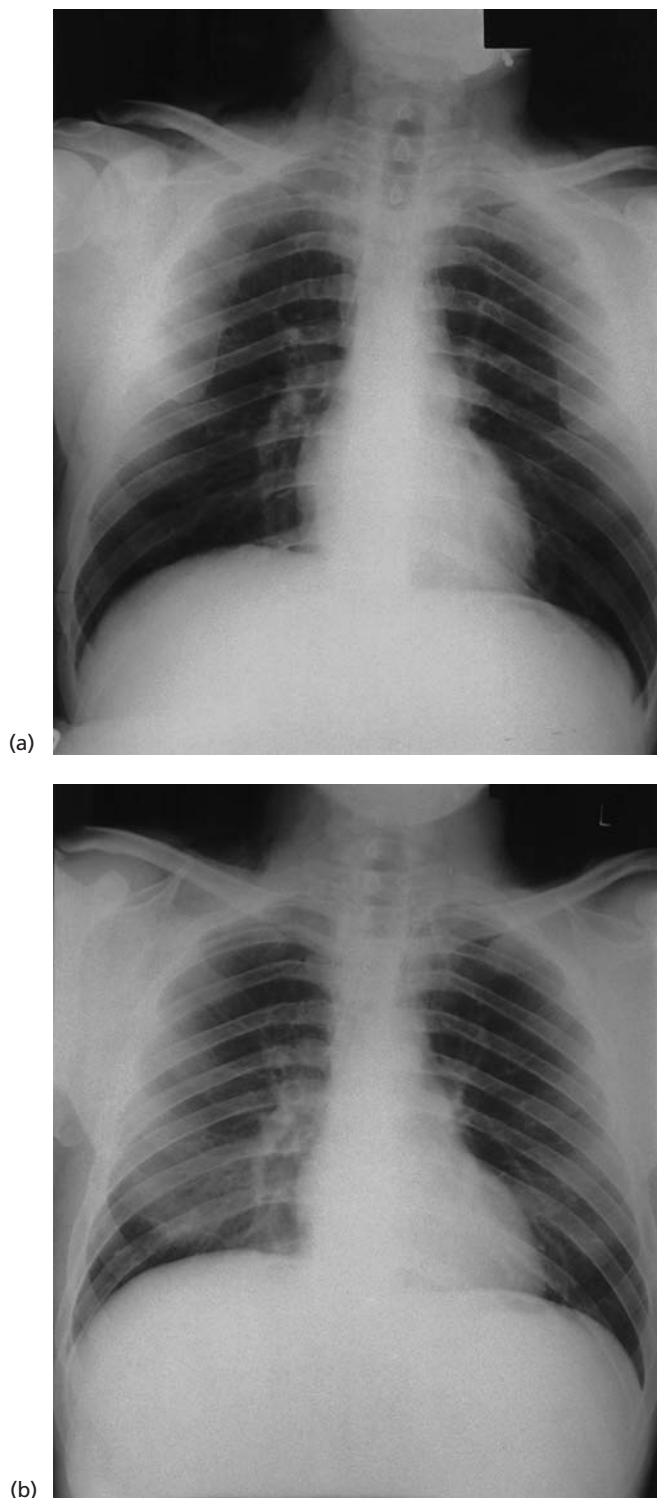
within the lung re-expands and the diver surfaces with symptoms of cough, haemoptysis and sometimes breathlessness [20]; disturbance of blood gas tensions may result from the alveolar haemorrhage.

This event is rare in circumstances where the diver has a breathing gas unless there is a failure of gas supply. In the absence of a non-return valve, a surface supplied diver's lungs are effectively compressed by the hydrostatic pressure. Alternatively it may affect a scuba diver attempting to descend quickly. To do this he or she maintains a low lung volume in order to reduce buoyancy. If at this point the diver is unable to breathe in due to loss of gas supply, there is increasing loss of buoyancy and acceleration downwards with progressive reduction of lung volume.

Barotrauma of the lung on ascent (burst lung) is of much greater importance both numerically and in terms of morbidity and mortality. It occurs when the diver is breathing compressed gas underwater. The diver breathes with normal lung volumes at depth. On ascent the volume of gas in the chest expands and the diver must therefore breathe out to enable the expanding gas to escape. During a controlled ascent this is achieved by breathing normally. During a rapid ascent the diver may need to breathe out continuously or at least keep the mouth and glottis open. If the expanding gas is unable to escape from the lung, the transpulmonary pressure increases and the lung may rupture. It seems that rupture most likely occurs at alveolar level and that gas then expands and spreads throughout the interstitial tissues of the lung. This may result in alveolar haemorrhage [23]. The gas makes its way following the line of least resistance to the hilum [24] and from there may spread up into the mediastinum (Fig. 57.1), down into the retroperitoneal space [25,26] or through the parietal pleura into the pleural space (Fig. 57.2). Alternatively, gas may rupture through the visceral pleura into the pleural space. Finally, the tissue damage within the lung may allow the gas access to the pulmonary venous system and expanding gas then passes to the left heart and into the systemic circulation resulting in severe neurological injury or death [27].

Theoretically, any pathological lesion that interferes with gas escaping from the lungs in an evenly distributed fashion may result in shear stress forces between parts of the lung and lead to rupture. In addition, a lung that has previously ruptured spontaneously is likely to be at increased risk. Lesions which might do this are localized bullae, areas of fibrosis or scarring or major obstructions to the bronchial tree. The importance of generalized airflow limitation is difficult to assess. On normal expiration the airways tend to close and trap gas in the alveolar space. However, on ascent, gas escape is only partly by normal expiration because expanding gas tends to splint the airways open and hence vents itself. Forceful attempts to expire might themselves be harmful by prevention of gas





**Fig. 57.1** (a,b) Two chest radiographs of a diver taken during decompression in a chamber after pulmonary barotrauma showing pneumomediastinum. Expansion of the mediastinal gas resulted in prolonged decompression.



**Fig. 57.2** Chest radiograph of a diver following pulmonary barotrauma of ascent showing extensive peripheral shadowing. Diver surfaced with tension pneumothorax.

escape because of airway closure. Such airway closure occurs at an earlier phase of expiration than normal because of the additional fluid in the pulmonary circulation.

A recent study of submarine escape trainees has demonstrated that the risk of pulmonary barotrauma appears to relate better to the lung volume, i.e. forced vital capacity (FVC), than to forced expiratory volume in 1 s ( $FEV_1$ ), though the association is weak [28]. This is a logical finding and is consistent with the other medical evidence available. In the water, VC is restricted by fluid shift to the lung but tidal volume remains unchanged. Inspiratory reserve volume (IRV) is, therefore, reduced. If during normal tidal breathing, a diver commences ascent but fails to breathe out, IRV represents the volume by which the lung can expand before reaching normal maximal volume. Hence if IRV is small as it may be in a diver with a low VC, the lung may be at greater risk of rupture.

In most cases pulmonary barotrauma occurs as a result of an uncontrolled ascent. Two common scenarios are recognized. Exhaustion of the scuba diver's compressed gas supply leaves the diver struggling to obtain a last breath of air from the empty cylinder. The diver has to make a potentially strenuous ascent and, despite knowing that there is no further breathing gas available, must remember to breathe out continuously. Although considerable effort is placed on diver training to cope with this event, it is difficult to breathe out adequately and it remains a high-risk

situation. An alternative but increasingly common scenario is loss of buoyancy control. As the diver commences ascent, air within the diver's dry suit or buoyancy compensator expands and provides increased buoyancy and an accelerating ascent. This gas must be dumped (exhausted from the suit) through valves in order to maintain neutral buoyancy and control. Valve failure or inversion into the feet-up position may make it impossible to dump gas and hence an explosive ascent to the surface with a grossly overinflated suit occurs.

As gas expands within the lungs and is unable to escape, the transpulmonary pressure increases and the lung may rupture when the pressure exceeds 60 cmH<sub>2</sub>O [29]. It appears that it is distension of the lung rather than simply the pressure that is important, since in animal experiments the transpulmonary pressure that can be tolerated can be substantially increased by supporting the chest with binders [29]. In the diver a certain amount of chest movement restriction may be imposed by suit and harness. Nevertheless, pulmonary barotrauma has been reported after dives from very shallow depths of less than 2 msw and has also been reported after breath-hold dives [30,31].

Pulmonary barotrauma should be suspected whenever respiratory symptoms occur after a dive, particularly if there is a history of rapid or uncontrolled ascent. In most cases the presentation is immediately after the dive but delay in onset of symptoms is reported [32] and may be common when pneumomediastinum is the only manifestation. Pneumothorax may present with typical symptoms following surfacing from a dive. However, if the lung ruptures during the ascent phase of the dive more than a few metres from the surface and produces pneumothorax, the continued expansion of the gas within the pleural cavity results in tension that may have fatal results. The symptoms and signs of pneumothorax are no different from pneumothorax in any other situation and treatment is also the same, with one exception. If pneumothorax occurs to a diver who is in, or retrieved to, a closed diving bell or decompression chamber, the opportunity exists to relieve symptoms by compression. This results in reduction of the volume of the gas in the pleural space and relief of tension. This offers an emergency therapy or means of controlling symptoms while arrangements for pleural drainage are made.

Pneumomediastinum usually results in central chest discomfort, hoarse voice and sometimes breathlessness. Symptoms are rarely sufficient to require active treatment, but again recompression does offer an emergency treatment if large volumes of mediastinal gas are causing circulatory disturbance. Pneumomediastinum has caused considerable difficulty when it has occurred during deep saturation diving, since the gas expands so much during decompression and must be absorbed during this period. The decompression may therefore have to be considerably

prolonged to allow time for gas absorption. Pneumomediastinum may present with some delay after surfacing from a dive with symptoms of neck discomfort and voice change associated with subcutaneous emphysema. Pneumoperitoneum is a relatively rare occurrence but causes diagnostic difficulty since the patient may present with abdominal pain and have radiological evidence of free gas in the peritoneum.

Pneumothorax, pneumomediastinum and pneumoperitoneum are all helped by breathing 100% oxygen since this speeds up the elimination of the inert gas from the gas space [33]. This technique depends on the concentration of oxygen rather than the partial pressure and hence is of very limited application in saturation diving since 100% oxygen can only be given on the surface or at relatively shallow depths (to 18 msw).

Arterial gas embolism usually presents with symptoms very soon after reaching the surface. The diver may give a shriek on arrival at the surface, probably due to the release of gas under pressure from the chest. It seems possible that it is at this time, when the intrathoracic pressure falls, that gas is best able to pass through the pulmonary venous system. Thus in at least some cases the arrival of gas in the cerebral circulation probably occurs within seconds of arrival on the surface. The presentation is with acute onset of major cerebral disturbance, loss of consciousness, blindness, hemiplegia, convulsion, etc. [27,34]. Sudden death may result from embolization of the coronary circulation. The natural history of this condition is variable, some patients making a rapid and complete recovery without treatment, others having permanent neurological injury despite rapid treatment [19,27]. Recompression rapidly reduces the volume of gas within the circulation and if achieved at an early stage may produce complete resolution of all symptoms [27]. Recompression is usually followed by hyperbaric oxygen treatment [35], which has three aims: (i) it reduces the inert gas load within the vascular space and other tissues, (ii) it may provide oxygenation to tissues that remain hypoxic as a result of the injury and (iii) it may help to prevent reperfusion injury in those tissues which had lost their blood supply.

Because of the severity of the outcome of pulmonary barotrauma, considerable efforts are made to prevent its occurrence. These efforts follow two avenues. The most important depends upon diver training, primarily to ensure that the circumstances leading to an emergency or uncontrolled ascent do not occur and, secondarily, to reduce the risks should an emergency ascent become essential. Considerable argument exists about whether practical emergency ascent training causes more harm than it prevents [36]. The second area is to identify individuals who may be at increased risk of pulmonary barotrauma. This is considered to be a crucial component of a diver's medical assessment for fitness. A variety of conditions have been considered potential risk factors, includ-

ing the presence of lung bullae or cysts [37], previous spontaneous pneumothorax, localized airways obstruction and generalized airways obstruction [38]. Theoretically any condition that impairs lung compliance may also represent a risk, particularly if this is patchy since this may result in shear stress within the lung as it expands. Impairment of lung compliance has been demonstrated in a number of survivors of pulmonary barotrauma [39] but it is not clear whether this represents a pre-existing risk factor or a result of the injury.

Barotrauma may also occur to the thorax rather than to the lung. A number of incidents have occurred where a diver has experienced an uncontrolled ascent that has resulted in overpressurization of the lung but without any evidence of its rupture. Nevertheless, these divers have suffered from considerable and prolonged chest discomfort which appears to arise from the chest wall. In some the symptoms settle over a few months but in others the discomfort has persisted for years.

Mild degrees of pulmonary overpressurization occurring on ascent but insufficient to cause barotrauma may result in restriction of venous return to the heart and syncope [40].

### **Decompression sickness (the lung as a bubble filter)**

The lung, or rather the pulmonary circulation, plays a critical role in the prevention of decompression illness. Decompression illness results from the formation of gas bubbles within body tissues from inert gas previously dissolved in tissues. As the ambient pressure falls, tissues become supersaturated with inert gas that may then come out of solution. Gas in tissues results in limb pain (the bends), constitutional symptoms of fatigue and malaise and diverse neurological manifestations. More severe episodes may cause respiratory symptoms, circulatory collapse and even death. Bubbles form in many tissues but a considerable proportion find their way into peripheral capillaries and travel through the venous circulation to the lung [41–43]. A gas bubble acts as a foreign surface, thus provoking a response from the coagulation system and being rapidly transformed into a small protein–platelet embolus with a gas nucleus [44]. These microbubbles pass into the pulmonary circulation and are trapped within the pulmonary capillary bed [45]. The quantity of gas bubbles formed during or after a decompression can be monitored using ultrasound imaging or Doppler techniques [46,47]. Neurological manifestations of decompression illness appear to be associated with the appearance of bubbles within the arterial circulation [47]. Bubbles may gain access to the arterial circulation in the presence of a right-to-left cardiac shunt, for example atrial septal defect [48] or patent foramen ovale [49,50], in the presence of intra-

pulmonary shunting or when the volume of bubbles is sufficient to cause a rise in pulmonary arterial pressure above a threshold, as has been demonstrated in an animal model [51,52]. There is growing evidence that pulmonary abnormalities that may be associated with a disturbance of pulmonary circulation are risk factors for neurological decompression illness [53].

Pulmonary decompression sickness presents with severe symptoms of chest tightness, breathlessness and cough and is due to massive bubble embolization of the pulmonary capillary bed, usually as result of severe decompression stress (omitted decompression). Fortunately, such presentations are rare but are often fatal and almost inevitably associated with severe neurological manifestations. However, mild respiratory symptoms of transient chest tightness and cough are commonly reported in divers shortly before the onset of neurological symptoms and may represent a lesser degree of pulmonary bubble embolization.

Obstructive airways disease has been identified as an independent risk factor [53] and there are anecdotal case reports of decompression sickness in association with unilateral absent pulmonary artery [50].

The process of bubble capture within the pulmonary capillary bed is also a cause of concern with regard to possible long-term effects. A fall in diffusing capacity (*DLCO*) occurs after deep saturation dives [54], where the potential for bubble formation is present over several days, but has also been reported after short air dives to 50 msw [55].

## **Other diving-related pulmonary illness**

### **Oxygen toxicity**

While oxygen is essential for life, it is unfortunately also toxic when breathed at increased pressure. Oxygen causes two major varieties of acute toxic effect. At partial pressures above about 130 kPa, neurological effects may occur that can include muscular twitching, jerks and convulsions. The risks increase with partial pressure and are also increased with exertion and carbon dioxide retention. Hence partial pressures of up to 300 kPa may be used therapeutically with a resting patient but pressures above 150 kPa are a significant risk to a diver in the water. A convulsion may have a fatal outcome for a diver using a simple scuba demand valve held in the mouth by the teeth, and hence a band mask or helmet that enables the diver to use an oronasal mask is a crucial safety precaution when oxygen-enriched breathing mixtures are used. Divers who use oxygen-enriched breathing gas mixtures to obtain a decompression advantage are at risk of cerebral oxygen toxicity [53].

Oxygen also exerts a direct toxic effect on the lung.

Minor abnormalities of lung function have been demonstrated after breathing oxygen at partial pressures of less than 50 kPa [56] and animal experiments have demonstrated histological abnormalities after exposure to oxygen at partial pressures of 60 kPa [57]. In practice, divers tolerate partial pressures of up to 50 kPa for prolonged periods without any obvious symptoms [58]. Above a partial pressure of 50 kPa the onset of symptoms is dose dependent in terms of both partial pressure and duration [59,60]. Acute symptoms of chest soreness on inspiration and cough may occur after 2–3 h at 300 kPa or after longer exposure at lower partial pressure [61]. If exposure is continued, the symptoms progress to include severe discomfort on inspiration, breathlessness and ultimately pulmonary oedema and respiratory failure with the development of diffuse alveolar damage. There have been a number of attempts to characterize the physiological abnormality. The earliest abnormality on investigation is a reduction of VC [61], although it is not clear whether this is a direct result of early development of oedema or simply a result of discomfort on inspiration. At a later stage a more obvious restrictive defect develops and is associated with impairment of diffusing capacity ( $DL_{CO}$ ) [61]. This is a reversible effect and symptoms usually subside over a period of 24–48 h after the end of exposure. The mechanism of oxygen toxicity appears to be the result of local tissue  $PO_2$  increasing the concentration of oxygen free radicals and overcoming the body's normal defence mechanisms. This results in a primary endothelial lesion [62,63]. Evidence for the vascular nature of the lesion is supported by animal studies demonstrating abnormal endothelial cell biochemistry [64–66] as well as by human studies [67,68].

In practice, the development of pulmonary oxygen toxicity presents a problem in the management of decompression illness where divers are treated with quite prolonged periods of hyperbaric oxygenation. This is particularly true when the provocative dive involved the use of oxygen during the decompression or when treatment needs to be repeated. However, tolerance to oxygen can be increased by brief interruptions to the exposure [69,70] and hence most treatment regimens [58] use intermittent oxygen rather than continuous treatment. The use of relatively hyperoxic breathing gas mixtures during saturation diving has also raised concerns about possible long-term effects [71]. It has been standard practice during saturation diving for the breathing gas in chambers to be maintained with a partial pressure of oxygen of about 40 kPa [58]. While divers are working in the water this is increased to about 80 kPa and in the decompression phase to about 50 kPa. Hence divers may be exposed to partial pressures above 40 kPa for periods of up to a month at a time. Small decrements in diffusing capacity ( $DL_{CO}$ ) have been observed after deep saturation dives [54,72] and there is

some evidence to suggest that oxygen exposure may be at least partially responsible [73].

### Near drowning

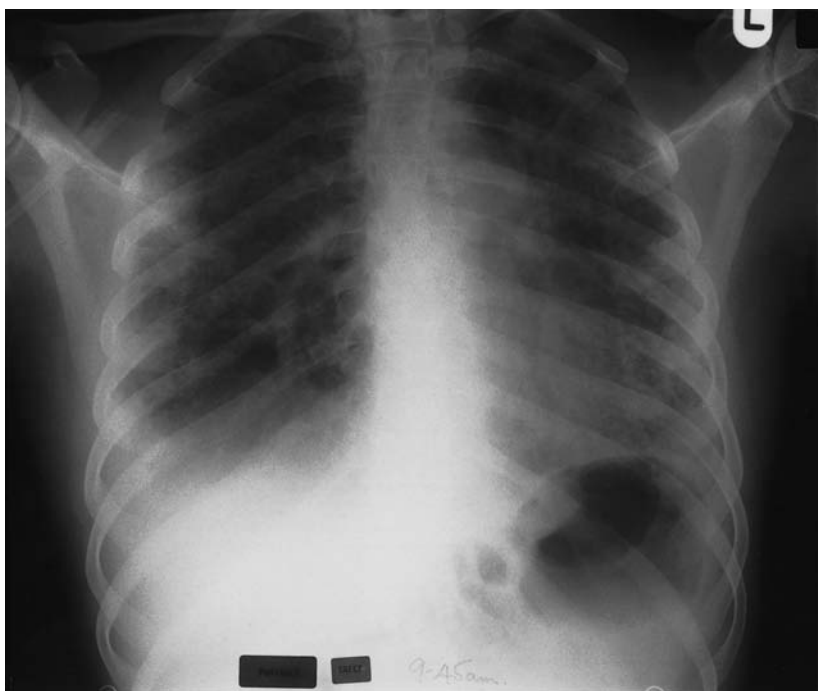
Many emergency situations in diving may lead to inhalation of water and partial or near drowning. Lesser degrees of water inhalation are probably very common due to leaky demand valves and may be the cause for the so-called saltwater aspiration syndrome [74]. It appears that humans who drown may inhale only very small quantities of water [75]; animal models have shown that very small amounts of inhaled water produce substantial disturbance of lung function, with reduction in lung volume and fall in both compliance and  $SaO_2$  [76]. Hence patients who have suffered a near-drowning incident are inevitably hypoxaemic with a substantial shunt [77]. Clinical examination may reveal little or no abnormality. A chest radiograph may also be normal but may show the development of diffuse alveolar damage (adult respiratory distress syndrome) during the first 12–24 h (Figs 57.3 & 57.4). Hence such patients should always be assessed in hospital and remain under observation during the first 24 h. Management is supportive and may require administration of oxygen, ventilation, antibiotic therapy for secondary infection and other intensive care support. Most patients recover fully, although complete recovery of lung function may take months. A few patients show evidence of permanent lung injury [78] but of more significance is the substantial proportion who survive with permanent neurological injury following the period of hypoxaemia [79].

Most near-drowning accidents in divers occur when the diver is on or close to the surface. However, inhalation of water can occur as a result of various situations at depth, including buddy breathing exercises, failure of demand valve or exhaustion of gas supply. In these situations the immediate effect of water inhalation is partially masked by the increased partial pressure of oxygen in the breathing gas. For example, at 20 msw the diver breathing air has a partial pressure of oxygen equivalent to breathing 60% oxygen on the surface. This may be sufficient to maintain a normal  $SaO_2$ . However, the exertion required to ascend, while at the same time the partial pressure of oxygen in the alveoli is falling, may result in loss of consciousness on arrival at the surface due to acute hypoxia [80,81].

Many diving fatalities are recorded as drowning and while this may be the final pathological insult, other events may have led to incapacitation in the water. The postmortem examination of divers is complex since the presence of gas in tissues may be of considerable importance. Radiological examination [82] and other specialized techniques may be valuable [83,84].



**Fig. 57.3** Chest radiograph of a diver after a near-drowning incident showing bilateral lower zone interstitial shadowing. Diver recovered with administration of supplementary oxygen only.



**Fig. 57.4** Chest radiograph of a diver following a severe near-drowning incident showing widespread interstitial shadowing. Diver developed adult respiratory distress syndrome and was left with permanent impairment of lung function.

## Trauma

Commercial divers are exposed to a number of underwater hazards that arise from the use of special tools. The use of oxygen cutting equipment has become widespread. This technique involves production of an electric arc using a welding rod. However, the rod is hollow and oxygen is

fed under pressure through the rod into the arc in order to accelerate the rate at which the metal is burned. A number of major injuries have occurred as a result of this technique in which either oxygen or steam has collected in the pocket in close vicinity to the cut in progress and then exploded. The effects of the underwater blast have included direct chest trauma, pneumothorax and damage to the diver's

helmet resulting in near drowning. Underwater blast may result in extensive tissue injury, particularly where there is a tissue–gas interface such as at the lung surface [85,86] (Fig. 57.5). Characteristically divers sustaining this injury suffer considerable widespread chest pain suggestive of multiple rib fractures. The management is largely dictated by the depth of the incident and whether the diver is recovered to the surface or to a diving bell and pressure chamber.

Although diving illness and environmental problems have been the major contributors to diving fatalities in the past [87], these problems have become progressively better controlled and trauma is becoming increasingly important as a cause of both morbidity [88] and mortality.

### Hypoxia

In most circumstances the diver breathes a gas that has a partial pressure of oxygen higher than that in air on the surface. However, hypoxia may occur in a number of specific circumstances. The diver may be supplied with a breathing gas mixture containing too little or no oxygen. For example a mixture containing only 2% oxygen provides an adequate partial pressure at 100msw but results in severe hypoxaemia at 10 or 20msw. The breathing gas



**Fig. 57.5** Chest radiograph of a diver taken in a saturation chamber following an underwater explosion showing a pneumothorax on the right and extensive peripheral shadowing more marked on the left.

may be contaminated, for example the intake for an air compressor may include exhaust gas from the compressor's petrol engine resulting in carbon monoxide toxicity. The diver may lose breathing gas supply, and during the exertion of returning to the surface oxygen consumption may exceed the total available in the lung [80,81].

Rebreathing apparatus, which is extensively used for covert operations, also carries a risk of hypoxaemia. This is essentially a closed-circuit breathing system dependent on absorption of carbon dioxide and an adequate supply of oxygen. The supply of oxygen to the circuit needs to be adequate to meet the oxygen consumption of a diver, which may be high when the diver is shallow and not impeded by gas density, yet controlled such that at deeper depths when the diver is resting the oxygen partial pressure does not reach potentially toxic levels. These requirements demand complex equipment and training of the divers.

### Cold gas

Diver's breathing gas is always cold since, with the exception of closed-circuit apparatus, it is almost inevitably supplied from a compressed gas source. The implications of breathing cold dry gas may be important for individuals with cold-induced wheeze. There are also considerable difficulties when helium is used as the inert gas because of its thermal characteristics. Helium has very high thermal conductivity and as a result respiratory heat loss is greatly increased, since the breathing gas acts as a heat conductor from the body core [89]. As the depth and gas density increases, the heat capacity of the breathing gas increases to the extent that respiratory heat loss exceeds the body's total heat production and hypothermia becomes inevitable unless the breathing gas is heated. In practice, this becomes essential below depths of 180msw. Attempting to breathe cold helium–oxygen mixtures at great depth is difficult to tolerate and induces bronchorrhoea.

Cold exposure also has a significant impact on the circulation, with peripheral vasoconstriction, shift of fluid volume to the core and a resulting increase in pulmonary blood volume and rise in right heart pressures [90]. These effects are additive to those of immersion and may contribute to the phenomenon of immersion-induced pulmonary oedema [91], a condition that appears to be more likely in individuals with established or labile hypertension.

### Long-term effects of diving on the lung

Considerable concern exists about the possibility that diving may have some adverse effect on the lung. There is no doubt that divers have larger lung volumes than standard reference populations [92–95]. This may be partly the

result of selection but there is evidence from submarine escape tank instructors that a significant increase in lung volume can occur during a term of duty [96], presumably as a result of repetitive breath-hold diving acting as respiratory muscle training. However, in populations of commercial and military divers a consistent finding is a greater increase in FVC than FEV<sub>1</sub> [94,97]. Further investigation of the resulting reduction in the FEV<sub>1</sub>/FVC ratio has indicated reduced flow at low lung volumes, which may represent a pathological injury to small airways [98–100]. Few longitudinal studies are available but do suggest a reduction in lung volume at a faster rate than anticipated from standard prediction equations [71,101]. These data are difficult to interpret since the change in lung volume during early adult life may not follow a progressive decline even though lung growth may continue until the late twenties [102]. If correct, a more rapid decline than predicted equations suggest may not be abnormal. After deep saturation dives, small but significant reductions in diffusing capacity (*DLCO*) have been observed [54,93]. In some cases there has not been complete recovery. The two factors that may contribute to this are an effect due to long-term exposure to an elevated partial pressure of oxygen, insufficient to induce acute symptoms [73,103], and an inflammatory response to repetitive delivery of gas bubbles to the pulmonary vasculature during prolonged decompressions. Bubbles certainly result in an acute effect on the pulmonary vascular bed [104–106] and the extent of recovery is unclear. However, this effect would also be anticipated in air divers, who do not appear to be subject to the same effect on lung function [107].

## Assessment of fitness to dive

### Rationale

For the reasons obvious from the foregoing discussion, assessment of pulmonary fitness is of considerable importance to the diver. In the UK, commercial divers must undergo a statutory medical examination on an annual basis according to guidelines issued by the Health and Safety Executive [108]. Similar but less extensive medical examination systems are operated by the sport diving organizations and there is a considerable literature concerning this subject [109,110]. Although it is often argued that recreational diving does not require the same medical standards as commercial diving, the safety issues are the same and in practice the risks associated with recreational diving are often greater. It is more important to consider fitness in relation to the type of diving the individual will undertake.

In the UK, the medical examination of commercial divers must be carried out by a doctor approved by the Health and Safety Executive. Although the medical examination of sport divers may be performed by any doctor,

there is a strong argument for seeking advice from a doctor with appropriate knowledge of diving and the medical issues involved.

The objectives of assessment of fitness are to ensure that the potential diver is not suffering from a pre-existing condition that represents an increased risk to the health of the diver and his/her buddies and to ensure an adequate exercise capacity in order to cope with the physical exertion of diving. These two objectives are closely related since involvement in a rescue of an injured or incapacitated diver may be the most strenuous activity a diver has to undertake. It is important to recognize that all diving activities rely upon the divers providing mutual support in the event of emergency. In recreational diving this is known as the buddy system; in most commercial operations, a standby diver is a legal requirement. The diver's ability to respond to assist another diver forms the most important baseline for standards of fitness in terms of exercise capacity. It is reasonable for any diver to expect that other divers who may be required to assist in an emergency are not inefficient in this respect as a result of poor fitness.

### Medical history

The medical history should be free from symptoms of undue exertional breathlessness, cough, chest pain or other limitations to exercise. A history of significant lung disease that may have resulted in a permanent impairment of lung function or structure should be investigated further. Significant kyphosis or other restriction of thoracic movement, diaphragmatic paralysis, etc. represent contraindications. Previous spontaneous pneumothorax is a contraindication as this indicates the presence of an anatomical defect that has ruptured under normal environmental conditions. Although the risk of recurrence falls with time, such defects are more likely to rupture under conditions of increased transpulmonary pressure and the occurrence of a pneumothorax underwater is likely to be fatal due to the tension associated with increasing pleural gas volume on ascent. Conversely, following an uncomplicated traumatic pneumothorax the individual may be able to return to diving, provided that complete recovery occurs. In this situation it is presumed that the lung was normal initially and that complete recovery can occur. Hence provided that lung function and chest radiography returns to normal, the individual can return to diving; high-resolution CT provides greater confidence of the absence of any structural lesion after such trauma. Thoracic surgery is generally considered to represent a contraindication since there is a high risk of pleural adhesion following thoracotomy. For this reason surgical prevention of recurrent pneumothorax by pleurectomy does not change the situation regarding unfitness to dive.



### Exercise underwater

Unfortunately, there is very little information available that provides an accurate measure of the workload in terms of oxygen consumption associated with a diver rescue. Similarly, the relationship between aerobic performance on the surface and work capacity in the water is uncertain. Exercise tests underwater using fin swimming as the exercise have demonstrated that oxygen consumptions of up to 2.5 mL/kg/min can be achieved [18]. This is substantially less than levels achieved on the surface during treadmill walking, which may reflect the different types of muscles involved and the fact that the diver is weightless.

Despite these limitations some assessment of exercise capacity is valuable. In the absence of contrary evidence, it can be assumed that there is a relationship between performance on the surface and underwater ability. A reasonable fitness standard is to require divers to achieve an aerobic performance level that is not below the 50th percentile for individuals in that age group. However, since exercise tolerance falls with age, it would be prudent to use age 40 as the reference age group for all divers over 40. In practice this standard presents little difficulty for the vast majority of divers both recreational and commercial.

### Lung function

The diver's lung function should be normal or, if there is any impairment, this should not be sufficient to affect the diver's ability to exercise underwater. The diver's lungs should not have any anatomical or physiological abnormality that increases the risk of pulmonary barotrauma and the diver should not have any condition that might impair the function of the lung as a bubble filter.

From considerations of pulmonary physiology during exercise and diving, the symptomatic effect of a significant deviation from normal lung function is likely to be magnified in the underwater environment. Hence anyone with abnormal breathlessness on the surface should be considered unfit to dive. The possible exception to this is asthma where the symptoms and functional abnormality is transient (see below).

### Investigations

A chest radiograph is considered essential before commencing diving and is an absolute requirement for commercial divers, although some sport diving associations permit diving without a previous chest film. The purpose of the chest radiograph is to exclude major anatomical defects such as bullae, areas of fibrosis or scarring that may contribute to air trapping or be associated with impaired compliance and hence represent a risk

factor for lung rupture [37,38]. Small old scars due to previous pulmonary tuberculosis do not appear to represent a risk.

Lung function is usually assessed by simple spirometric indices of FEV<sub>1</sub>, FVC and peak expiratory flow rate or flow-volume loop analysis. The purpose is to exclude individuals with diminished lung volume or evidence of airways obstruction. Airways obstruction and the associated air trapping may represent a risk factor for pulmonary barotrauma, although the evidence to support this theoretical risk is limited. However, given that medical examiners have tended to exclude those with obvious abnormalities from diving, the absence of epidemiological evidence to support a risk is not all that surprising. Fortunately, pulmonary barotrauma is a very rare problem and in most cases there is an obvious dive-related provocative factor. This makes assessment of the risk associated with a pre-existing medical problem very difficult. A recent study of submarine escape trainees has demonstrated that the risk of pulmonary barotrauma appears to relate better to the lung volume, i.e. FVC, than to FEV<sub>1</sub>, although the association is weak [28].

The results of lung function tests should be considered in association with the exercise test result. An individual with poor exercise performance and impaired or marginally reduced lung function resulting in poor exercise tolerance is very likely to have substantial difficulty underwater and is unfit. Conversely, if lung function is good, the individual with poor exercise tolerance should be able to demonstrate an improvement with training. A repeat FEV<sub>1</sub> after an exercise test also provides a simple screen for the presence of exercise-induced wheeze.

### The lung as a bubble filter

This is a more controversial area but one likely to become of much greater importance in the future. It is established that the lung acts as a filter to remove bubbles from the circulation and that appearance of bubbles in the arterial circulation is associated with decompression sickness. The Divers Alert Network (DAN) study [111], which set out to look for an association between asthma and pulmonary barotrauma, found an association with diving incidents but not with barotrauma, suggestive of a possible increased risk of decompression illness. This may be related to intrapulmonary shunting since cardiac shunt is a well-recognized risk factor [48–50]. A study by Wilmshurst and colleagues [53] also provides evidence for a relationship between decompression illness and lung disease.

### Returning to dive after a diving accident

There is little published information about the risk of returning to dive following a diving injury. A critical issue

is whether lung function returns to normality after an episode of pulmonary barotrauma. There is some published evidence of individuals having repeated episodes [20], although not all these cases had objective evidence of lung rupture. Colebatch and colleagues [39] found evidence of impairment of lung compliance in survivors of pulmonary barotrauma but it is unclear whether this abnormality existed before, or resulted from, the incidents. It is generally agreed that a diver who experiences an episode of pulmonary barotrauma during normal diving practice should be regarded as having a pre-existing risk factor and be advised not to dive. The diver in whom pulmonary barotrauma occurs as a result of an explosive ascent may be assumed to have had normal lungs before the incident. Hence if a complete recovery is made with a return to normal lung function and no anatomical abnormality can be demonstrated by high-resolution or spiral CT, a return to diving may be possible.

### Asthma

Asthma represents a special situation because it is increasingly common, a growing number of asthmatic subjects wish to dive and because symptoms are transient. The issue has been extensively considered [112,113]. There is no doubt that some asthmatics can and do dive regularly [114] but they may be at increased risk. The DAN study in the USA found that although there was no over-representation of people with asthma among individuals with episodes of pulmonary barotrauma, there was an over-representation of asthmatics when all categories of diving accident were considered together. This is probably a significant finding since many asthmatic patients have received and taken medical advice not to dive. Similarly in an Australian study of diving fatalities, 9% of cases had a diagnosis of asthma [115]. There are various anecdotal reports of both barotrauma in patients with asthma [116] and acute breathlessness occurring in the water [117]. It seems reasonable that there is an increased risk but it may not apply to all patients with asthma.

Potential problems for the diver with asthma would include impairment of exercise capacity, inability to tolerate breathing apparatus, effect of medication on cardiac function, incapacitation due to an episode of wheezing while underwater (which may be provoked by breathing cold gas), breathing dense gas and the possible increased risk of decompression sickness.

Bronchodilator agents, particularly  $\beta_2$  stimulants, all have a cardiac effect that may result in unexpected interaction with the cardiac stimuli associated with diving such as immersion, cold and the diving reflex. On the other hand, their potential protective effect against episodes in the water is used as an argument to support their regular use before diving by some. The diver should be able to go into the water without significant risk of an episode occurring, and the need or desire to take a dose before a dive suggests that symptom control is inadequate. Other agents used prophylactically, such as salmeterol or formoterol, also indicate more severe symptoms or greater difficulty in control. Theophyllines are a contraindication because of cardiac and gastric side-effects and because (at least in the UK) their use indicates poor control [118]. Intensive bronchodilator therapy and theophylline therapy may represent a risk for decompression illness as a result of intrapulmonary shunt.

At present, some patients with asthma may be certified fit to dive provided that they can meet the following criteria.

- 1 When well they are free of symptoms, with normal lung function and no impairment of exercise capacity.
- 2 They should not dive if they have current symptoms.
- 3 They should not have exercise- or cold-induced symptoms.
- 4 Their asthma should be stable, predictable and well controlled and they should not have a regular need for use of relief bronchodilator.

- 5 Patients whose asthma is well controlled on inhaled steroids may meet these criteria even if they use inhaled bronchodilator regularly before each inhaled steroid.

To establish compliance with these criteria an accurate record of previous health from a general practitioner is essential. Asthmatics should be able to demonstrate normal exercise tolerance and the absence of exercise-induced symptoms. Patients whose asthma is brittle, who have had a recent history of severe episodes or who have a regular requirement for relief inhaler therapy or other additional support therapy should be advised not to dive. Above all, patients with asthma need to be informed of the possible increase in risk for asthmatics who dive and that diving when their asthma is troublesome may substantially increase the risk. They should be aware of how to control these risks by modifying their diving practice. Unfortunately, it is very difficult to predict how a patient with asthma will respond to their first diving experience [117].

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# ASSISTED VENTILATION

JOHN M. SHNEERSON

## Principles of ventilation

Mechanical ventilators transfer gas into and out of the lungs with the aim of optimizing oxygen transport and carbon dioxide elimination from the body. To achieve this they have to not only ventilate the lungs but also ensure that the mixing of gases within the lungs is efficient, that ventilation and perfusion are well matched and that the ventilator itself does not impair cardiac output. The ventilator therefore acts as an external pump that supplies energy to supplement or replace the activity of the normal respiratory pump. In addition, the ventilator has to fulfil at least some of the roles of the respiratory control system by determining the pattern of respiration. None of the currently available ventilators approaches the complexity and adaptability of the normal respiratory control system, although the microprocessors of modern ventilators are becoming increasingly sophisticated. There is an increasing number of methods of respiratory support that vary in the degree of assistance they provide and which almost merge with spontaneous respiration.

All the positive-pressure ventilators that are applied to the airway work on the principle that if the pressure in the ventilator exceeds that in the patient's alveoli, gas will enter the lungs. This contrasts with spontaneous and negative-pressure ventilation, in which the alveolar pressure is less than atmospheric pressure during inspiration. Positive-pressure ventilators require a source of pressurized gas to be delivered at a controllable flow or pressure to the patient without dilution with ambient air. The flow of inspired gas is intermittent in true mechanical ventilation but may be continuous in for instance continuous positive airway pressure (CPAP) support. The expired gas is conducted away from the patient without contaminating the inspired gas except in the dead space of the circuit close to the patient. Expiration is usually passive and due to the elastic recoil of the lungs and chest wall, but can be modified in various ways by the ventilator as well as by the patient's effort.

Negative-pressure ventilators differ from positive-

pressure systems in that a subatmospheric pressure is applied intermittently around the chest and abdomen within a rigid and impervious enclosure so that air is drawn in through the mouth and nose. No appliance is required around or inside the airway and a source of pressurized gas is not needed since the energy of the ventilator is applied to the chest wall rather than to the airway. Negative-pressure systems are therefore a method of external ventilation in contrast to internal ventilation as typified by positive-pressure systems using a tracheostomy or endotracheal tube.

## Control of inspiration

There are a number of ways in which inspiration can be influenced by the ventilator controls, the most important of which are discussed below.

### Initiation of inspiration and termination of expiration

This is often called ventilatory triggering or cycling, although the latter term is confusing because it is also used to designate the changeover from inspiration to the start of expiration. Inspiration can be initiated by one or more of the following methods.

#### *Time*

The expiratory time can be preset so that inspiration follows after a predetermined interval or, on some ventilators, the total time for the inspiratory cycle can be set and the inspiratory–expiratory (I/E) ratio fixed.

#### *Pressure*

The development of a negative pressure by the patient's inspiratory effort can be sensed by the ventilator controls and used to trigger the inspiratory phase of the machine. The usual trigger threshold is 0.5–2 cmH<sub>2</sub>O. Lower thresholds may lead to triggering of the ventilator by, for

instance, cardiac impulses, small leaks or non-respiratory movements. Conversely, if the threshold is too high the patient's inspiratory work may be excessive and failure to trigger the ventilator may lead to incoordination between the patient and the ventilator.

### *Flow*

Inspiration can be triggered when the flow generated by the patient increases above a threshold value set by the ventilator. This is used with some pressure-preset ventilators.

### *Volume*

Inspiration can be initiated when a preset volume has been expired.

### **Termination of inspiration and initiation of expiration**

Inspiration can be terminated by time, pressure, flow or volume criteria. In general the termination of inspiration by pressure is unsatisfactory and leads to incoordination between the patient and the ventilator. Flow cycling promotes coordination but is only suitable for pressure-preset ventilators. Time or volume cycling are appropriate for constant-flow generators.

### **Inspiratory pressure and flow waveforms**

#### *Flow generators*

Ventilators that generate a predetermined flow rate and which have a fixed inspiratory time deliver a predictable tidal volume. The inspiratory flow may be constant, a half sine, ramp or a reverse ramp waveform, although there is remarkably little difference between these in most clinical situations. The adequacy of the mixing of inspired gas with air already in the lungs probably depends more on the inspiratory time than on the pattern of flow. The tidal volume is hardly altered by changes in the elastance or resistance of the ventilator circuit or patient, but in the presence of a leak the flow remains unchanged and the volume delivered to the patient falls. The airway pressure is determined by the elastance and resistance of the upper airways, lungs and chest wall and of the ventilator and circuit.

#### *Pressure generators*

This type of ventilator generates a predetermined pressure waveform that is often but not always a square wave. The inspiratory flow rate and tidal volume is determined by the transpulmonary pressure, which in turn is determined by the elastance and resistance of the lungs and the

patient's effort. The transpulmonary pressure is greatest initially when the pleural pressure is least and the inspiratory flow rate then decreases towards zero as the pressures in the airways equilibrate. Pressure generators do not provide a fixed tidal volume since this varies with the elastance and resistance of the patient, ventilator and circuit, although they can compensate for leaks by increasing their flow rate in order to maintain the preset pressure waveform.

### **Inspiratory limitation**

Inspiratory limitation is a technique used to protect the patient against an excessive pressure or volume delivered by the ventilator. The unwanted gases are vented through a relief valve. Protection against high pressure is needed particularly with flow generators when the elastance and resistance are increased, and against increased volume delivery with pressure generators when they are reduced or if the patient's inspiratory effort increases.

### **End-inspiratory pause**

An end-inspiratory pause is the period after the delivery of the inspired gas but before expiration starts. The airway pressure falls to a plateau level which, since there is no airflow, reflects the elastance of the respiratory system and is independent of the airflow resistance. During the pause, air enters alveoli which have prolonged time constants and their recruitment is thought to improve ventilation-perfusion matching, particularly in patients with diffuse lung diseases.

### **Sigh**

A sigh can be mimicked by positive-pressure ventilators by the introduction of a periodic large inspiration. The depth of the mechanical sigh is usually 1.5–2 times the usual tidal volume and the frequency is often between 1 in 60 and 1 in 100 breaths. Sighs can reverse small airway closure and improve ventilation-perfusion matching but are not as effective as positive end-expiratory pressure (PEEP) or other manipulations of the ventilator controls, such as increasing the tidal volume.

### **Inspiratory–expiratory ratio, frequency and inspiratory–expiratory times**

These various indices of ventilation are interrelated and alteration of one influences the others. Shortening the inspiratory time increases the flow rate in volume-preset generators and, particularly if it falls to less than about 1s, the distribution of the inspired gas to the alveoli is impaired. Conversely, a prolonged inspiratory time may be uncomfortable and although it promotes gas mixing it



also increases the mean airway pressure. A reduction in the expiratory time may lead to air trapping and increased end-expiratory pressure (auto-PEEP).

An increase in the respiratory frequency at any fixed I/E ratio reduces both the inspiratory and expiratory time. An I/E ratio of 1:2–2.5 is satisfactory for subjects with normal respiratory mechanics. A lower ratio reduces the mean airway pressure and increases the cardiac output but at the cost of a deterioration in ventilation–perfusion matching. Increasing the I/E ratio has the opposite effect. The extreme is inverse ratio ventilation, where the inspiratory time exceeds the expiratory time. This assists oxygenation through prolonging the inspiratory time and increasing the end-expiratory volume but may significantly reduce cardiac output.

### Control of expiration

The most important methods of influencing expiration include the following.

#### Expiratory retard

This is a method of prolonging expiration by increasing the resistance of the expiration valve, usually by narrowing its diameter. It is equivalent to pursed-lip breathing in emphysema. Like this, it moves the equal pressure point proximally and so reduces air trapping. It differs from PEEP or CPAP in that the resistance does not have a threshold value above which it is brought into action. Expiratory retard has the disadvantage of raising the mean intrathoracic pressure and reducing cardiac output.

#### Negative end-expiratory pressure

Negative end-expiratory pressure can be achieved by entraining air in the expiratory limb of the ventilator circuit by the Venturi effect. This reduces the expiratory pressure and thereby increases the venous return to the right ventricle. However, it may cause narrowing or closure of small airways and distal lung collapse.

#### Positive end-expiratory pressure

PEEP is the maintenance of pressure above atmospheric at the end of expiration but is in practice applied throughout the expiratory phase. The term is restricted to a positive pressure applied during ventilation, in contrast to expiratory positive airway pressure (EPAP) or CPAP, which refer to manipulations during spontaneous breathing. PEEP is maintained by introducing a threshold resistor in the expiratory circuit. It tends to prevent airway closure during expiration with the result that the end-expiratory volume increases. This improves ventilation–perfusion matching

and raises  $P_{ao_2}$ , particularly in restrictive disorders such as diffuse lung fibrosis and neuromuscular diseases [1]. The elastance of the lungs falls unless they become hyperinflated, in which case it increases. The increased lung volume and intrathoracic pressures may also lead to pneumothorax and other pulmonary barotrauma. Cardiac output and venous return are reduced as a result of the increased mean intrathoracic pressure. This may be clinically important especially if the cardiac output is already low, if the blood volume is reduced or if autonomic reflexes are impaired.

### Modes of ventilation

There is a spectrum of respiratory assistance between the extremes of spontaneous independent respiration and completely controlled mechanical ventilation (Figs 58.1 & 58.2). In the centre of this spectrum are the partial ventilatory support techniques which, if they can maintain ventilation adequately, are usually preferable to controlled ventilation since ventilation–perfusion matching is better and respiratory muscle strength and coordination are preserved. Partial support techniques can be adjusted according to the patient's requirements. For instance, the frequency, tidal volume, level of pressure support and method of triggering can all be individually adjusted so that the patient has some degree of control over the respiratory pattern. The nomenclature of the modes of ventilation is complex and inconsistent [2], but in general they are distinguished by the methods by which inspiration is assisted or triggered. The most important techniques are discussed below.

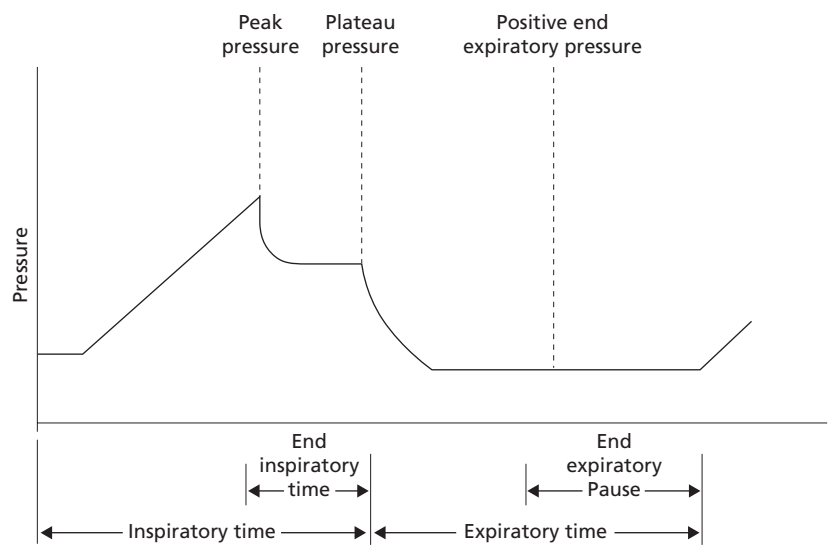
#### Controlled mechanical ventilation

Controlled mechanical ventilation delivers inspired gas at a preselected pressure (pressure controlled) or volume (volume controlled) with a fixed inspiratory and expiratory time. These techniques are suitable if the patient is unable to trigger additional breaths but not when respiratory drive and muscle strength remain. Controlled mechanical ventilation is indicated if the patient is sedated and given muscle paralysing agents, is unconscious, or has no respiratory muscle effort due to complete paralysis of the respiratory muscles as in high cervical tetraplegia.

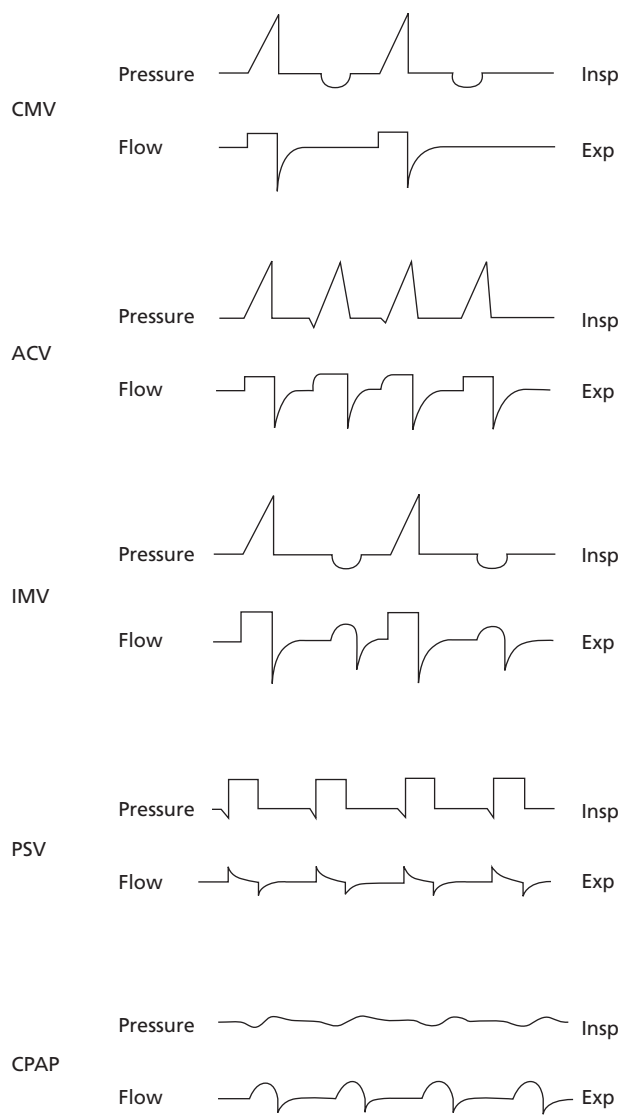
#### Assist and assist control ventilation

In these techniques a preset tidal volume is delivered by the ventilator with a preselected inspiratory time. The ventilator can be cycled into inspiration by time or this can be triggered by a reduction in pressure caused by the patient's inspiratory effort. However, in assist ventilation a back-up rate provided by time-cycling into inspiration is





**Fig. 58.1** Pressure–time relationships during controlled mechanical ventilation with positive end-expiratory pressure.



**Fig. 58.2** Flow and pressure changes with different modes of ventilation. During controlled mechanical ventilation (CMV), patient effort does not result in airflow in contrast to assist control ventilation (ACV). The flow rate is determined by the patient when using pressure support ventilation (PSV), continuous positive airway pressure (CPAP) and spontaneous breath with intermittent mandatory ventilation (IMV).

absent. The degree of patient effort can be modified by altering the pressure threshold for triggering into inspiration and the back-up rate. Assist control is a safer technique than assist if there is any doubt about the respiratory drive or respiratory muscle strength or endurance.

### **Intermittent mandatory ventilation and synchronized intermittent mandatory ventilation**

In intermittent mandatory ventilation (IMV) and synchronized intermittent mandatory ventilation (SIMV), the ventilator delivers breaths of a preset volume with a preset inspiratory time. Additional spontaneous breaths can be taken through the ventilator, which therefore should have a low resistance and an adequate supply of fresh gas available, usually from a reservoir, between the controlled breaths. In IMV the machine breaths are delivered at regular intervals independent of the timing of the patient's spontaneous breaths, but in SIMV they are synchronized within limits with the patient's spontaneous breaths. This avoids breath stacking, which is common with IMV. The patient's work of breathing can be regulated by changing the IMV or SIMV rate and by the addition of inspiratory pressure support to the spontaneous breaths. IMV and SIMV therefore provide a combination of assisted and spontaneous inspirations that differ in their pressure and flow characteristics.

### **Inspiratory pressure support ventilation**

With this technique the ventilator delivers an inspiration with a preset pressure waveform that usually results in a decelerating or reversed ramp pattern of airflow (Fig. 58.3). Inspiration is terminated either by a fall in the

flow rate or by time; the expiratory time is determined either by the patient pressure- or flow-triggering the next inspiration or by time. The patient therefore has more control over the respiratory pattern than with the previous modes but a preselected tidal volume is not guaranteed. This depends on the elastance and resistance of the patient's respiratory system and the ventilator circuit, as well as on the patient's inspiratory effort. Pressure support ventilation does not provide a reliable tidal volume if the patient's mechanics change. However, it is able to compensate for air leaks. The ventilator is usually flow-cycled, which gives a shorter response time than with pressure cycling. Pressure support enables the work of breathing to be graduated by altering the applied inspiratory pressure.

### **High-frequency ventilation**

High-frequency ventilation is the term used to describe ventilatory techniques in which the respiratory frequency is greater than 60/min. Air can be delivered using conventional positive-pressure ventilators at a high frequency, with jet ventilators and high-frequency oscillators. Oscillation can be applied directly to the column of gas in the airway or externally to the chest wall. This method can be used without intubation, although mechanical coupling to the patient is often difficult. With each of these techniques both inspiration and expiration are usually active and although the tidal volume is smaller than with conventional frequency ventilation, alveolar ventilation can be maintained. The pressure swings are much less than with conventional techniques and this minimizes the risk of pulmonary barotrauma and the reduction of cardiac output. However, high-frequency ventilation may increase the end-expiratory volume, particularly if the



Fig. 58.3 Bilevel pressure-support ventilator.

expiratory time is excessively reduced. It has not found wide application but can be of value with laryngeal surgery and in the management of bronchopleural fistulae, since the inspired gas is not preferentially directed through the low-impedance fistula as it is in conventional ventilation.

### Other modes

A wide range of other modes of ventilation has been introduced over the last few years, including proportional assist ventilation, mandatory minute ventilation and airway pressure release ventilation. The current indications for these are limited [3].

### Aims of ventilation

Mechanical ventilation is only one component of the overall management of patients with ventilatory failure, and it is important to have clearly defined aims whenever a patient is ventilated. These vary between individuals but the most important are described below.

### Control of arterial blood gases

In general, the  $P_{O_2}$  should be kept between 8 and 12 kPa (60–90 mmHg), at which levels the oxygen saturation is usually over 90%. This may require supplemental oxygen as well as ventilation if the gas-exchange function of the lungs is severely impaired. Wherever possible, the  $P_{CO_2}$  should be brought within the normal range in order to improve the hypercapnic drive and to make withdrawal of ventilatory support easier. Occasionally, patients with very abnormal respiratory mechanics cannot be ventilated without the peak inspiratory pressure rising to levels where barotrauma is a significant risk (40–50 cmH<sub>2</sub>O) and in these situations controlled hypoventilation (permissive hypercapnia) may be the best policy [4,5]. Conversely, hyperventilation to reduce the  $P_{CO_2}$  to around 4 kPa (30 mmHg) is indicated if ventilation is used to reduce intracranial pressure.

### Substitution for a failed or inactivated respiratory pump

In certain circumstances, for example anaesthesia, the patient carries out no respiratory work and the ventilator substitutes for this. The controlled mode in which the patient's tidal volume, respiratory frequency and inspiratory and expiratory times are preset is usually used.

### Supplementation of the patient's respiratory activity

In these circumstances the patient contributes to respira-

tion but the ventilator acts as an additional external energy source. It is important to try to synchronize the patient's and the ventilator's respiratory cycles. For instance, if the patient exhales during an inspiration with a volume-preset ventilator, the pressure limit would be reached early and air vented from the system. Conversely, with a pressure-preset ventilator, synchronization of the patient's inspiration with the ventilator's inspiration increases the tidal volume.

### Modification of the patient's respiratory activity

The ventilator not only provides respiratory support for the patient but also interacts with the patient's respiratory control system and modifies the respiratory pattern. This may occur as a result of an improvement in the blood gases, which alters the biochemical respiratory drive, and also by relieving anxiety and discomfort by providing adequate respiratory support. More complex interaction is also possible involving breath-to-breath and intra-breath reflex changes to the respiratory drive, which are determined by the type of ventilatory support [6].

### Treatment of the underlying condition

Mechanical ventilation can to a limited degree treat as well as support ventilatory failure. Most of its effects are transient, but with long-term nocturnal ventilation some must persist long enough to explain the clinical and physiological improvement seen during the day. The possible mechanisms of these improvements are changes in the following parameters.

#### Respiratory drive

Mechanical ventilation can improve respiratory drive by lowering  $P_{aCO_2}$  and relieving hypoxic depression of the respiratory centres and sleep deprivation. It also has more subtle and dynamic interactions with the patient's respiratory drive through reflexes, as mentioned earlier.

#### Respiratory muscle function

Respiratory muscle fatigue has been postulated as a cause of ventilatory failure and of difficulty in weaning, although this has only been demonstrated in a few circumstances. It is more likely that the respiratory control mechanisms adapt to prevent fatigue developing. Nevertheless, the practice of resting the respiratory muscles, particularly during acute illnesses or when the patient is systemically unwell, is probably advisable in order to avoid near-fatiguing work. In other circumstances, increasing the patient's work of breathing using partial respiratory support techniques may increase respi-

ratory muscle strength and endurance and improve their coordination.

### **Respiratory mechanics**

Ventilation can improve both lung and chest wall compliance though these effects persist for only a short period after ventilation has been discontinued [7].

### **Ventilation–perfusion matching**

Gas exchange in the lungs depends on the degree of matching of ventilation and perfusion, and this is hard to optimize during ventilation. Regional perfusion is affected by factors such as gravitational forces, lung disease, vascular tone and lung volume as well as cardiac output. The increase in intrathoracic pressure with positive-pressure ventilation reduces intrathoracic blood volume, right ventricular inflow and left ventricular outflow. These problems are most marked if the inspiratory pressure is high and the inspiratory time prolonged or if the mean expiratory pressure is raised as with PEEP and CPAP.

The distribution of inspired gas is very heterogeneous in lung disease. Overdistention of alveoli is thought to be the cause of pulmonary barotrauma. This may be manifested as pneumothorax, pneumomediastinum, subcutaneous emphysema, interstitial emphysema or pneumopericardium. These complications appear to be most closely related to the peak inspiratory pressure and the tidal volume.

In general, ventilation–perfusion matching usually improves if the inspiratory time can be prolonged, with or without an end-inspiratory pause to assist equilibration of gases within the alveoli, and if the tidal volume is increased, with or without PEEP or sighs to prevent airway closure.

### **Control of upper airway function**

An impaired cough, swallowing or speech is common in neuromuscular disorders. Airway protection and access to tracheobronchial secretions with a cuffed tracheostomy or endotracheal tube may be as important as ventilatory support. The same considerations apply to patients who are unconscious, for instance after a drug overdose.

### **Complete or partial weaning**

Ventilation is usually only a temporary phase, although occasionally long-term nocturnal non-invasive ventilatory support is required. It is particularly effective in neuromuscular and skeletal disorders but also in selected patients with chronic airflow obstruction [8]. In effect,

these patients are only partially weaned although they may return to an active life during the day.

## **Gas exchange during ventilation**

The main aim of ventilation is to sustain adequate alveolar gas exchange for the patient's metabolic requirements. However, not all the gas leaving the ventilator reaches the alveoli and it has three distinct destinations, as discussed below.

### **Leaks**

The gas leaving the ventilator follows the path of lowest impedance, which may be into the lungs or through leaks in the system. These may occur within the ventilator or its circuit, at the interface with the patient or within the patient. For instance, gas may leak around a cuffed endotracheal or tracheostomy tube or around a face or nasal mask; with the latter, leaks through the mouth are commonly a problem as well. Leaks within the patient may occur through a bronchopleural fistula or by air passing through the cricopharyngeal sphincter into the oesophagus rather than the trachea.

### **Dead space ventilation**

There are two main parts of the dead space: the volume of the ventilator circuit and the anatomical and physiological dead space. The volume within the ventilator and its circuit depends on the length and diameter of the connecting tubing plus the pressure under which the gas enters the circuit. The tubing is distensible and accommodates 2–3 mL of gas for every 1 cmH<sub>2</sub>O inspiratory pressure (the compressible volume). The volume of the interface of the system with the patient, such as a face or nasal mask, also contributes to the dead space. The dead space of a nasotracheal or orotracheal tube is greater than that of a tracheostomy tube, and with a face mask the dead space exceeds that of a nasal mask or mouthpiece.

Within the patient, the anatomical dead space may be partially bypassed by a tracheostomy but not by non-invasive techniques. The physiological dead space usually increases during ventilation, especially if this causes hyperinflation.

### **Alveolar ventilation**

The rest of the inspired gas is distributed to the alveoli according to factors such as the inspiratory time, the inspiratory pressure and flow waveform and the elastance and resistance of the patient's respiratory system. In most lung diseases the mechanical properties of the lungs are heterogeneous and inspired gas is distributed irregularly. An increase in tidal volume or inspired pressure may simply

distend those alveoli with the shortest time constants without improving gas exchange. Recruitment of alveoli with longer time constants may be achieved by adding an end-inspiratory pause or by prolonging the inspiratory time.

## Tracheostomy and endotracheal tube ventilation

### Composition of tubes

Rubber tubes were used for many years but they tend to perish and are irritant, probably because of the sulphides they contain. As a result most modern tubes are made of silver or synthetic materials. Silver tubes are light and inert and their thinness increases the ratio of internal to external diameter. They also have efficient low-resistance speaking valves. They are expensive but durable. Most modern endotracheal and tracheostomy tubes are synthetic, usually plastic, acrylic, silicone or PVC. They are virtually non-antigenic and most are thermoplastic so that they adapt to the shape of the patient's airway once they are in place. This pliability reduces the risk of tracheal injury. Polyurethane armoured tubes contain a coiled steel spring that prevents them kinking at sites of pressure such as close to the teeth.

### Length and diameter of tubes

An endotracheal or tracheostomy tube should be no longer than anatomically required so that its dead space is reduced to a minimum. A tube that is too long may enter one or other main bronchus, usually the right, so that only this lung is inflated and the other collapses. Conversely, if

the tube is too short the cuff may damage the vocal cords and the tube may become displaced. Translaryngeal and tracheostomy tubes have a significant resistance which, if airflow is laminar, increases in inverse proportion to the fourth power of the radius. A slightly narrower tube therefore has a disproportionately large effect on airflow resistance. With narrow tubes it may be difficult to obtain an adequate seal with the tracheal wall when the cuff is inflated. However, larger tubes are more likely to traumatize the trachea and larynx and make it more difficult to speak. In general, the diameter of an endotracheal or tracheostomy tube should not exceed two-thirds the diameter of the trachea.

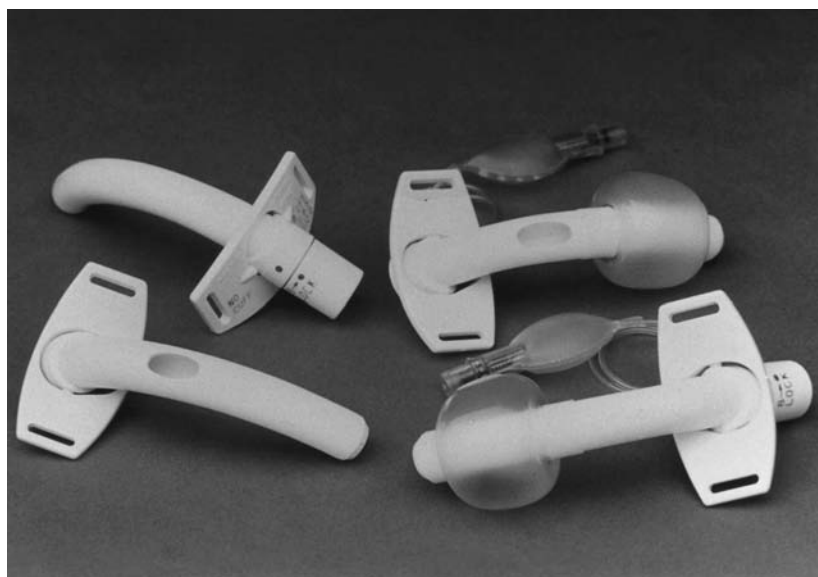
### Special tube features

Some tracheostomy tubes have a fenestration or hole in the outer tube that is designed to lie in the tracheal lumen to assist expiration of air through the vocal cords and upper airway during speech and weaning (Fig. 58.4).

Inner tubes are not a feature of translaryngeal tubes but are useful for tracheostomy tubes when these are likely to be required for prolonged periods. The inner tube is slightly longer than the outer tube and as a result secretions accumulate on it rather than on the outer tube. The inner tube can be removed and cleaned, usually twice daily, so that the outer tubing needs to be changed less frequently than would otherwise be the case. The inner tube occludes any fenestration and attaches to the ventilator connections and speaking valves.

### Cuffed and uncuffed tubes

Cuffless tubes were used almost exclusively before the



**Fig. 58.4** Synthetic tracheostomy tubes. Clockwise from bottom left: uncuffed fenestrated, non-fenestrated, cuffed fenestrated, non-fenestrated.

Copenhagen poliomyelitis epidemic of 1952 [9], but since that time they have been largely superseded by cuffed tubes. Nevertheless, cuffless tubes have the advantages that pressure necrosis of the tracheal wall due to the cuff does not occur. It is easier to speak with a cuffless tube since it occupies less of the tracheal lumen than a cuffed tube.

Cuffless tubes are used in particular in neonates and young children, in whom tracheal damage can easily occur with a cuffed tube, and in adults when there is upper airway obstruction and no risk of aspiration. The most common situation is after laryngectomy, but they are also used during weaning from positive-pressure ventilation and in some patients for long-term tracheostomy ventilation when speech is required and aspiration is not a problem [10].

Cuffless tubes do not protect the airway and the leak of air during inspiration through the upper respiratory tract can be uncomfortable and poorly tolerated. For these reasons, cuffed tubes are more commonly used. The new low-pressure high-volume cuffs have superseded the older high-pressure low-volume cuffs and have greatly reduced the risk of tracheal damage. The pressure required within the cuff depends on the airway pressure during ventilation and on the pressure required to prevent aspiration of material into the tracheobronchial tree. This is determined by the relative diameters of the trachea and tube, the elastance of the cuff, and on the height of the column of secretions lying above the cuff and their density. The factor limiting cuff pressure is the circulation of blood through the tracheal capillaries, and therefore it should be kept below 25 cmH<sub>2</sub>O wherever possible. The pressure on the anterior wall of the trachea is usually greater than on the posterior wall because the latter is more distensible, and cuff damage is therefore usually greatest anteriorly.

### **Early complications** (see ref. 11)

#### *Pneumothorax, pneumomediastinum and mediastinal emphysema*

These complications occur in up to 5% tracheostomies.

#### *Incisional haemorrhage*

Troublesome postoperative bleeding occurs in about 5% of tracheostomies. The wound should be packed and if the bleeding persists surgical exploration may be required.

#### *Tube displacement*

This can be a serious complication if it occurs during the first 4–5 days postoperatively. It is usually the result of inadequate securing of the tube and may be precipitated

by a bout of coughing. A false channel anterior to the trachea can easily be created during attempts to reinsert the tube. This is best attempted using a fiberoptic laryngoscope or bronchoscope as a guide.

#### *Tube blockage*

This may be due to accumulation of mucus or blood within the tracheostomy tube and can usually be prevented by frequent suctioning.

#### *Tracheostome wound infection and tracheobronchial aspiration*

Aspiration is usually due to an inadequately inflated cuff.

### **Late complications**

#### *Tracheal stenosis and related complications*

These are most common in infants and elderly patients and if the cuff pressure is excessive, particularly if the tube is of wide diameter or moves excessively. Damage may occur at the site of the tracheostome itself, at the level of the cuff or at the tip of the tracheostomy tube, especially if the tube is too large or if it is positioned at an incorrect angle. The initial changes are loss of the ciliated epithelium and mucous glands and development of squamous metaplasia. Following this, the mucosa may ulcerate and the cartilage can be damaged. This leads to dilatation, the formation of a flaccid segment of trachea, or to fibrous stenosis. These complications may require resection of the affected segment, repeated dilatations or stenting.

#### *Tracheo-oesophageal fistula*

This occurs in less than 1% of tracheostomies and is due to necrosis of the posterior wall of the trachea. It is often associated with the presence of a nasogastric tube in the oesophagus. It should be suspected if food or other gastric contents can be aspirated from the trachea, if there is an air leak around the cuff associated with abdominal distension, or if an increasing amount of air is required to fill the cuff. Surgery is required to repair the defect.

#### *Tracheo-innominate artery fistula*

This is due to erosion through the tracheostomy anteriorly at the level of the clavicle. It may present with obvious pulsation of the tracheostomy tube or small (sentinel) haemoptyses. Repositioning of the tube or use of a tube of a different length may be required. Urgent surgical treatment is needed, although only about 25% of patients survive.

**Tube obstruction**

This is usually due to secretions and should be prevented by adequate humidification and frequent suctioning.

**Tracheobronchial aspiration**

This is usually due to use of an inadequate cuff pressure or inappropriate deflation of the cuff.

**Swallowing difficulty**

The presence of a tracheostomy tube may impair elevation of the larynx, which is required to open the cricopharyngeal sphincter and to enable swallowing to proceed normally [12].

**Tracheostome infection**

This is a common problem in intensive care units but is infrequent when long-term tracheostomies are cared for in the home.

**Mask and mouthpiece ventilation**

Nasal intermittent positive-pressure ventilation was introduced in the early 1980s and since then has become widely used [13]. The ventilators that are suitable are similar to those used with tracheostomies and endotracheal tubes, although humidification of the inspired air is usually not required since the air passes through the upper respiratory tract.

**Nasal and face masks**

Nasal ventilation is possible with cannulae that fit within the nose and which distend during inspiration to seal on to the mucosa. They may cause pressure areas and soreness and an alternative is a design that seals on to the external nares. However, this type of interface can become displaced and in general a mask is preferred [14]. The standard nasal masks are made of silicone and fit snugly around the nose (Fig. 58.5). It is important to select a mask of the correct width and length in order to minimize air leaks and the risk of pressure areas, particularly over the bridge of the nose. Some models have a foam nasal support that reduces the pressure in this area. The masks are secured by straps which are tightened gently. The tension should be equal all around the mask so that it fits closely. Some designs of headgear have soft cotton caps to increase the stability of the mask (Fig. 58.6).

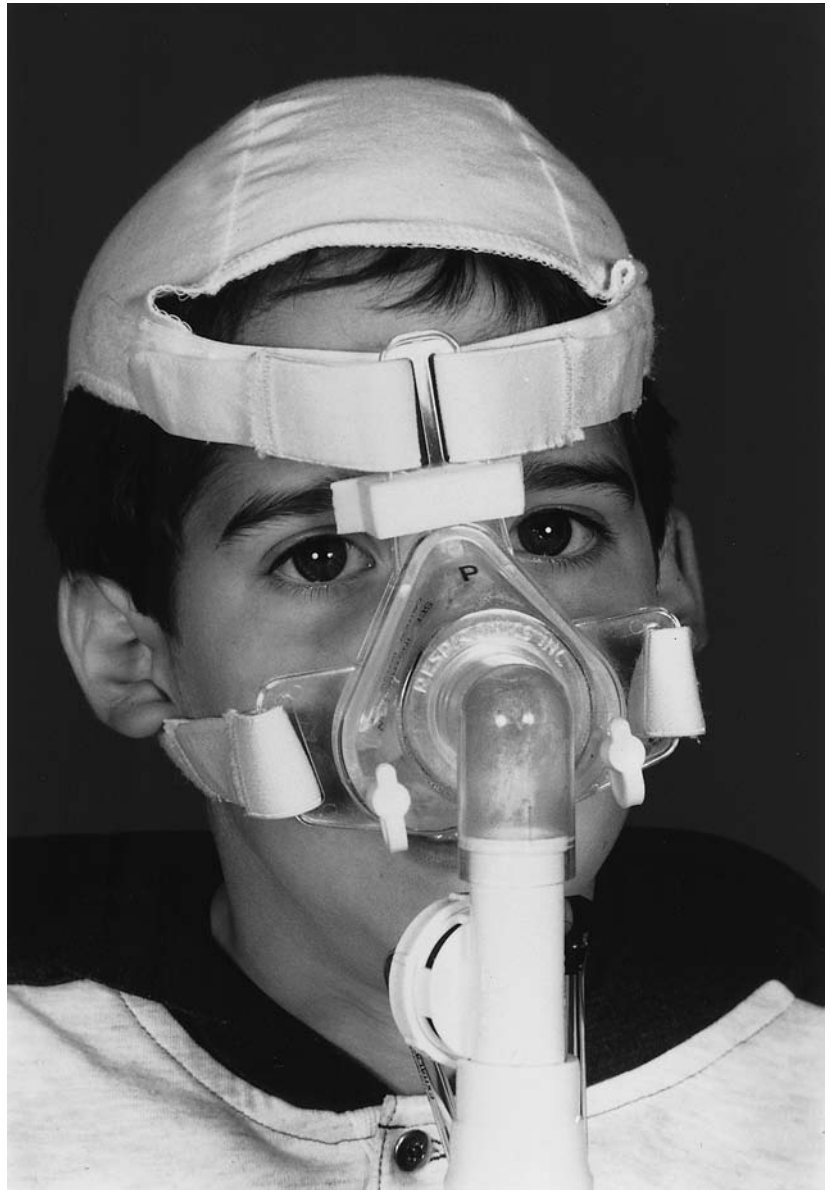
Face masks surround the mouth as well as the nose, but otherwise they work on similar principles to nasal masks. However, the standard designs are less comfortable and less well fitting than the standard nasal masks. Face masks also have a greater dead space, with a risk of rebreathing, and tend to be more claustrophobic than nasal masks.

Individually made masks are an alternative to the standard models. They may be more comfortable and reduce the air leaks and the dead space. There are a variety of methods of constructing individually made masks, but most involve making a mould of the nose.



**Fig. 58.5** Silicone nasal ventilation mask.





**Fig. 58.6** Nasal mask and headgear in position on patient.

## Complications

### *Nasal ulcers*

Ulceration of the skin over the bridge of the nose is a common problem [15]. It is usually due to the mask being fitted too tightly or to prolonged initial use of mask ventilation before the skin has hardened (Fig. 58.7). The use of high airway pressures that require the mask to be tighter than usual in order to minimize air leaks may contribute to skin ulceration. Occasionally the ulcer becomes infected, usually with *Staphylococcus aureus*, and it may be difficult to continue with mask ventilation until the ulcer heals. It is important to try to prevent ulceration of the skin, although

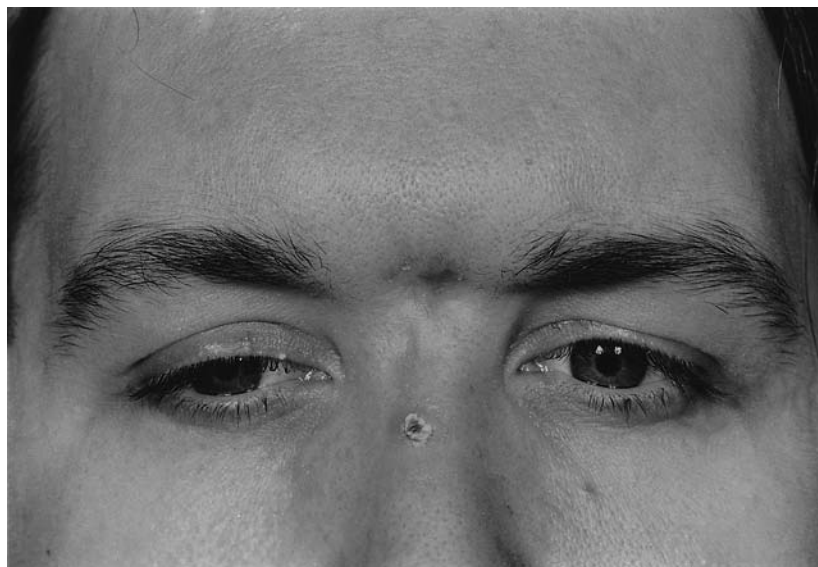
once this is established it may be necessary to either protect the skin with Granuflex or change to an alternative method of ventilation such as nasal seals, at least temporarily.

### *Displacement of the mask*

This is usually the result of a poorly fitting or inadequately secured mask; some patients regularly remove the mask, particularly during sleep.

### *Air leaks around the mask*

These are usually due to poorly fitting or inadequately



**Fig. 58.7** Scar on bridge of nose and crusting inferiorly from use of two different nasal masks.

secured masks but may be difficult to avoid, especially with face masks. Air leaks may lead to conjunctivitis if they are directed into the eyes.

#### *Air leaks through the mouth*

These are a problem particularly if the pressure within the mouth is high or if the oral muscles are weak or inactivated, for instance during rapid eye movement (REM) sleep. A chin strap or collar may be required to help close the mouth, and attention to the head and neck position and ventilator settings is required. If these methods fail, a face mask rather than a nasal mask should be used.

#### *Upper airway and head symptoms*

These are related to the high flow or pressure of dry air entering the upper airway. A dry or blocked nose may develop but are less common than with CPAP. A dry mouth occurs particularly if there is a large mouth leak. Nasal symptoms often respond to a steroid inhaler and adjustment of the ventilator settings may be of help.

#### *Abdominal distension*

This is caused by air entering the oesophagus rather than the trachea. It is most common in patients with neuromuscular disorders in whom the pharyngeal pressure during inspiration exceeds that which the cricopharyngeal sphincter can withstand. The airway pressure is raised if the elastance or resistance of the lungs and chest wall is increased or if there is poor coordination between the patient and the ventilator. Frequent belching, nausea,

vomiting, abdominal distension and the passing of flatus may develop. Reduction of the peak airway pressure is usually indicated, although this may reduce the alveolar ventilation unless other adjustments are made to the ventilator settings. Better coordination between the patient and ventilator lowers the pharyngeal pressure and may relieve the patient's symptoms.

#### *Upper airway obstruction*

This may occur at any level in the upper airway between the base of the tongue and the larynx. The mechanisms are uncertain but probably include passive airway closure possibly related to the flow or pressure waveform in the upper airway and active contraction of the upper airway muscles [16]. It can be detected by ballooning of the cheeks or neck and by failure of the chest and abdomen to expand during the ventilator's inspiratory phase. It often causes an increased mouth leak and occasionally abdominal distension, particularly if the obstruction is at laryngeal level. Attention to the head and neck position, provision of a collar and improved coordination of the patient and ventilator's respiratory cycles may all be of help.

#### *Initiation of mask ventilation*

Patients who have never tried nasal or face mask ventilation often find it difficult to adjust to the mask and to the high flow of air required. After an initial explanation it is best to place the mask over the patient's nose or face in a comfortable position with a low inspiratory flow rate or pressure. The mask position is checked to make sure that there is little air leak around it. The tidal volume or pressure support level is gradually increased while the trigger

threshold is kept at a low level. Attention is paid to the patient's comfort and with reassurance the ventilator settings are adjusted in order to ensure adequate alveolar ventilation, that the patient feels enough air is being delivered and that the timing of inspiration and expiration is appropriate. The expiratory time is adjusted so that it is slightly longer than the patient's usual expiratory time in order to encourage triggering of the next inspiration. The headgear is then secured and further fine adjustments to the ventilator settings carried out, ideally in the light of continuous monitoring of oxygen saturation and transcutaneous  $P_{CO_2}$ .

### **Mouthpieces**

Positive-pressure ventilation through the mouth has never been widely used, possibly because of difficulties in developing a satisfactory mouthpiece [17]. The types of ventilator used are similar to those for nasal, face mask, tracheostomy and endotracheal tube ventilation. The inspired gas requires humidification since it bypasses the nose, which is the physiological air conditioner. The ventilator circuit usually needs careful mounting so that the mouthpiece is stable and does not become displaced.

A variety of mouthpieces have been developed but none are very satisfactory. Most include a flange that lies between the lips and the teeth. Plaster moulds of the upper and lower teeth can be taken so that mouthpieces can be fashioned to fit precisely, but in general those that contact the tongue or palate are poorly tolerated and lead to the production of excessive saliva. Mouthpieces are held in place by straps which operate on a similar principle to those of nasal and face masks; in some designs these form an external seal over the lips as well as stabilizing the mouthpiece.

### **Complications**

The main complications of mouth positive-pressure ventilation include the following.

#### ***Nasal leaks***

These are significant in around 50% of subjects but are determined by palatal function at least as much as by nasal patency. Leaks are also determined by mouth pressure, which varies with the elastance and airflow resistance of the lungs and chest wall. Nasal leaks can be reduced by nasal plugs or nasal clips.

#### ***Dental complications***

Mouthpieces may loosen teeth and change their position. This often results in an open bite or a gap where the

mouthpiece is positioned. This can be avoided by individually moulded dental acrylic bite plates, although a lip seal is needed with these as well to prevent any air leaks from the mouth. Dental development is particularly impaired in children below the age of 4 years.

#### ***Mouth leaks***

These are a problem particularly if there is weakness of the lips or cheek muscles, as in many neuromuscular disorders.

#### ***Abdominal distension***

The factors causing this are similar to those described for nasal and face mask ventilation.

### **Advantages and disadvantages of mask and mouthpiece ventilation**

A tracheostomy is indicated in order to bypass upper airway obstruction, to gain access to tracheobronchial secretions and, if the tube is cuffed, to attempt to reduce aspiration as well as to provide ventilatory support. The non-invasive techniques only achieve the latter but all have the advantage of not requiring an artificial airway, which impairs coughing, swallowing and speech, and they can be used intermittently. This makes them suitable for patients who are being weaned from ventilation or who require intermittent long-term use. However, they are unsuitable if the patient is unconscious, uncooperative or requires continuous ventilation for more than 2 or 3 days, or has a weak cough with profuse tracheobronchial secretions. Masks and mouthpieces do not protect the airway and a significant risk of aspiration is generally considered to be a contraindication to their use. Nasal ventilation is usually the method of choice, although a face mask may be required if air leaks through the mouth are a problem. Mouthpiece ventilation is an alternative and is also indicated for intermittent use during the day if the patient is almost completely dependent on the ventilator. The subject can take occasional ventilator breaths between spontaneous respirations. At night there is an increased risk of displacement of the mouthpiece relative to nasal and face masks unless the mouthpiece is carefully constructed.

### **Negative-pressure ventilation**

With all the negative-pressure techniques, the chest and abdomen are enclosed in an airtight rigid chamber; in most of the earlier designs the rest of the body up to the neck was also enclosed in the chamber [18]. The advantages of this are that chest wall expansion is not limited by contact with the sides of the negative-pressure device and

only one airtight seal around the neck is required. The first of these ventilators to be effective clinically was the 'iron lung' or tank ventilator developed by Drinker in 1928 [19]. This and subsequent modifications were widely used during poliomyelitis epidemics until the 1950s [9] but since then have been largely superseded by positive-pressure techniques. Negative-pressure systems comprise both the chamber, which interfaces with the patient, and a ventilator or pump that provides the source of energy to support respiration.

### Types of ventilator

Negative-pressure ventilators or pumps are pressure generators that work in the controlled mode. Most are servo-controlled and their speed of response determines how completely they adapt to changing air leaks. The extent to which the preset pressure is maintained in the presence of a constant leak also varies between ventilators [20]. The negative pressure required to ventilate each patient is determined by the elastance and resistance of the patient's respiratory system and the ventilator circuit. The peak negative pressure is in practice usually 30–40 cmH<sub>2</sub>O [21] but depends in part on the pressure waveform generated by the ventilator. The peak pressure required is least when a square pressure wave rather than a half sine wave is produced. Upper airway obstruction is a complication [22,23], probably related most closely to the peak negative pressure and therefore should be less of a problem with ventilators producing a square pressure wave. The frequency and I/E ratio should be adjusted to be comfortable for each patient and to facilitate coordination with the ventilator.

### Types of chamber

#### Tank ventilation

Most of the modern tank ventilators are constructed of aluminium although some are plastic. The patient's body rests on a mattress within the chamber and a headrest supports the head and neck and prevents kinking of the upper airway. In some tank ventilators the head or feet can be elevated and in others the whole tank can rotate 180° in order to facilitate postural drainage [24]. Some observation of the patient is possible through portholes, which also enable catheters and monitor leads to be passed and physiotherapy to be carried out (Fig. 58.8). This type of ventilator has the disadvantage that access to the patient is limited and it is large, heavy and expensive. There are few centres in the UK with experience in their use. An airtight, comfortable neck seal is difficult to achieve and patients often find it awkward to lie in one position for long periods.

#### Jacket ventilation

With jacket (wrap or poncho) ventilators the functions of rigidity and imperviousness to air are separated into two structures. An inner framework of metal or plastic provides the rigidity and this is covered by an airtight garment. This seals around the arms, neck and usually the waist. Some designs have a back plate and some include the legs as well as the trunk. The air within the jacket is intermittently evacuated by a pump similar to that used for tank and cuirass ventilation.

Jackets, like tank ventilators, do not restrain the



**Fig. 58.8** Tank ventilator: patient receiving physiotherapy while being treated.

expansion of the rib cage or the abdomen but can be awkward to put on and cold because of air leaks. They are slightly more efficient than cuirasses, although their greater size and cumbersome nature has restricted their use.

### Cuirass ventilation

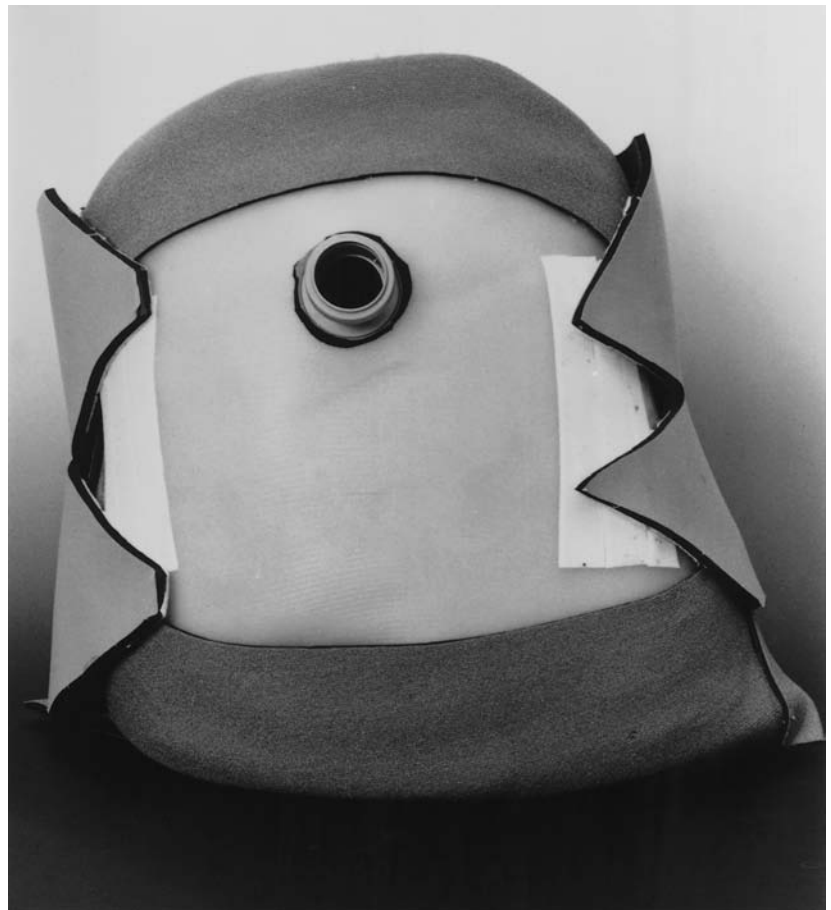
The earlier cuirass models were often ineffective because they fitted poorly and were inadequately designed. Individually constructed cuirasses are much more comfortable and effective in reducing leaks and are less likely to cause pressure sores (Fig. 58.9). They should enclose the anterior abdominal wall, which is then able to expand during inspiration. Movement of the lateral aspect of the chest should also be unrestricted. Individually constructed cuirasses can be made to fit patients even if there is a severe thoracic deformity such as scoliosis [25] (Fig. 58.10), although the cuirass may need to be modified if the patient grows or changes in weight. They are light and durable and unlike nasal and face masks do not cause claustrophobia. They rarely cause abdominal distension via aerophagy but can induce upper airway obstruction,

particularly during REM sleep. This may be due to loss of tone of the upper airway dilator muscles or to loss of the normal sequence of activation of the upper airway muscles during inspiration. Obstruction can be minimized by lowering the peak airway pressure and by selecting a negative-pressure pump producing a square pressure wave.

## Acute respiratory failure

### Indications for ventilation

The most common indications for ventilatory support in acute respiratory failure are severe pneumonia, asthma, adult respiratory distress syndrome (ARDS) and acute infective exacerbations of chronic bronchitis and emphysema. There are no fixed criteria for initiating ventilatory support but in general this is required if the arterial blood gases are deteriorating, particularly if  $PCO_2$  is rising, and if the patient is becoming confused, distressed or hypotensive. In acute as opposed to acute-on-chronic respiratory failure, intubation is almost invariably required together with sedation with or without muscle paralysis.



**Fig. 58.9** Cuirass ventilator showing velcro attachment for back strap and connector for ventilator circuit.



Fig. 58.10 Cuirass in position on patient.

Patients with asthma have expiratory flow limitation that leads to an increase in the end-expiratory volume and pressure (auto-PEEP) unless the expiratory time is sufficiently prolonged for the tidal volume to be completely expired. In order to preserve an adequate expiratory time, the inspiratory time is shortened and the respiratory frequency reduced. A small tidal volume is required to minimize the risk of barotrauma, which correlates with the peak inspiratory pressure. PEEP may be required to overcome auto-PEEP.

Patients with pneumonia have an increased pulmonary elastance that may lead to high peak inspiratory pressures with a volume-preset ventilator unless this is pressure-limited. Pressure-controlled ventilation with a rapid respiratory rate may be preferable. Similar considerations apply to patients with ARDS, although if this is severe the

inspiratory time may need to be prolonged so that it is longer than the expiratory time (inverse ratio ventilation) in order to improve oxygenation and to recruit alveoli with long time constants. The disadvantage of this is that the mean intrathoracic pressure increases and this reduces cardiac output and may cause auto-PEEP to develop. At a low level this may be beneficial in holding open small airways but at higher levels can be associated with excessive hyperinflation.

The optimal management of acute infective exacerbations of chronic bronchitis and emphysema has not been established. In some studies approximately 25% of patients admitted to hospital required intubation and the survival to discharge from hospital was 60–75% [26,27]. Recently, non-invasive ventilation has been recommended as an alternative to intubation, but none

of the studies has shown any survival benefit [28–30]. However, non-invasive ventilation may allow intubation to be avoided in some patients, particularly those whose respiratory failure is not very severe and who do not have profuse secretions [28–30]. Ventilation with a face mask is usually preferably to a nasal mask because most of these patients have large air leaks through the mouth. It is important that the cause of the acute infective exacerbation is promptly and effectively treated while ventilation is being supported.

## Weaning

Weaning implies two separate but closely related processes: the termination of mechanical ventilation and the removal of any artificial airway. In general the indications for weaning are the opposite of those for initiation of mechanical ventilatory support, and the factors that prevent weaning are similar to those that cause respiratory failure and require ventilatory support. The most important of these factors are listed below.

**1 Respiratory drive.** This may be reduced if the level of consciousness is impaired by sedatives for instance, or if the patient is deprived of sleep. It is also reduced if there is a metabolic alkalosis or chronic hypercapnia.

**2 Respiratory pump.** Respiratory muscle function can be impaired by malnutrition, hypoxia, hypercapnia, acidosis, hypercalcaemia, hypophosphataemia and hypomagnesaemia.

**3 Airflow obstruction.** Hyperinflation increases lung elastance and places the inspiratory muscles at a mechanical disadvantage, as well as rendering them too short to generate their maximum force. Airflow obstruction also increases the resistive work of the respiratory pump.

**4 Alveolar disorders.** Pulmonary oedema, pneumonia and other alveolar disorders increase lung elastance and the work of breathing as well as impairing gas exchange.

**5 Metabolic demand.** This is increased if the patient is febrile or anxious.

**6 Cardiovascular effects.** Oxygen transport is reduced by factors such as anaemia, low cardiac output or hypoxia, which may lead to pulmonary vasoconstriction.

Most of these factors are amenable to treatment, which should be carried out before trying to wean the patient from the ventilator. In general, weaning should be attempted when the capacity of the respiratory pump exceeds the load on it. A variety of predictors of successful weaning have been suggested [31,32] but are of limited value; these include tidal volume greater than 5 mL/kg, forced expiratory volume in 1 s (FEV<sub>1</sub>) greater than 10 mL/kg, vital capacity greater than 10–15 mL/kg, maximum inspiratory pressure greater than 20–30 cmH<sub>2</sub>O, minute ventilation less than 10 L/min and maximum voluntary ventilation twice the resting minute ventilation. In practice an overall clinical assessment is

usually more accurate and it is particularly important to bear in mind the patient's level of consciousness and ability to cough and swallow before weaning is attempted.

Many patients can be weaned rapidly with a short trial of T-piece spontaneous breathing followed by extubation. This principle can be extended so that patients breathe spontaneously for gradually lengthening intervals over a period of days or sometimes weeks but receive ventilatory support in between. Alternatively, gradual weaning can be achieved not by intermittent spontaneous ventilation but by steadily reducing the degree of support that the ventilator supplies. Partial respiratory support techniques are suitable for this method of weaning [33,34]. With assist control, for instance, the trigger threshold can be gradually increased and with IMV and SIMV the frequency of the machine breaths is reduced. With pressure support ventilation the pressure level is gradually lowered. In these ways the patient's work of breathing can be graduated and steadily increased. If weaning is delayed, non-invasive techniques, including nasal and face mask ventilation and tank ventilation, may be required, although in practice many patients undergo a tracheostomy before these techniques are used [35,36]. Non-invasive ventilation should not be used for weaning unless the patient's swallowing and coughing have been assessed or if there is upper airways obstruction.

## Long-term ventilatory support

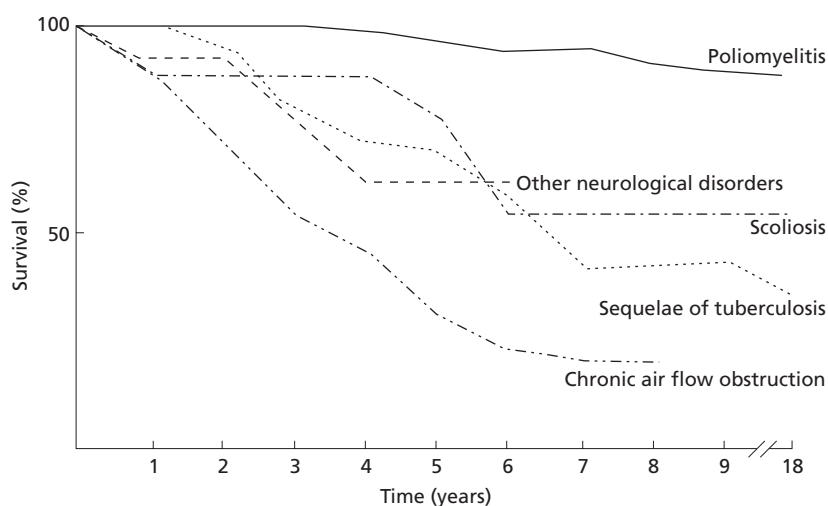
### Indications

Long-term ventilatory support is usually indicated if respiratory failure causes troublesome symptoms, potentially serious complications such as polycythaemia or pulmonary hypertension or is likely to lead to these problems or to premature death. Symptoms may include frequent waking from sleep at night, feeling unrefreshed on waking in the morning, early morning headaches, daytime sleepiness and personality change, physical fatigue, breathlessness or ankle swelling. These symptoms can be effectively relieved by both positive-pressure and negative-pressure ventilation [37]. Long-term ventilation has also been attempted prophylactically in patients with Duchenne's muscular dystrophy before ventilatory failure has developed but this has not proved to be of any benefit [38].

### Effects on prognosis

The effect of ventilation on prognosis has not been definitely established as there have been no long-term controlled studies. However, survival in neuromuscular and skeletal disorders with home ventilation is good, especially in scoliosis and non-progressive neuromuscular dis-





**Fig. 58.11** Actuarial survival during treatment with ventilatory assistance. (From Shneerson [49] with permission.)

orders [39–42] (Fig. 58.11). In rapidly deteriorating conditions the prognosis is determined not only by the ventilatory failure but also by other complications, such as bulbar dysfunction which may lead to aspiration pneumonia [43]. In chronic bronchitis, emphysema and bronchiectasis, the prognosis is worse than in neuromuscular and skeletal disorders [42,44–46]. The survival with tracheostomy or nasal mask ventilation is similar to that observed with long-term oxygen therapy using oxygen for 12 h or more daily [47,48]. However, comparisons between these studies are difficult, since it is uncertain whether patients started on oxygen and mechanical ventilation at similar stages in their natural history and none has controlled for smoking, which may have been more important than either of the treatments in influencing survival.

The prognosis for patients with the sequelae of tuberculosis, including those who underwent a thoracoplasty, lies between these two groups, presumably because these subjects have both a chest wall defect due to surgery and extensive lung disease as a result of the tuberculous infection [50]. Non-invasive ventilation has also been used successfully in selected patients with cystic fibrosis [51], particularly as a bridge to transplantation.

### Effects on quality of life

There are few studies of the effects of long-term ventilation on quality of life but the published reports suggest that this can be good [52–54], even in progressive neuromuscular disorders [55–57]. The quality of life is related less to the physical limitations than to the mental state of the patient. All the techniques for supporting ventilation do nevertheless interfere to some extent with the activities of normal life, and in some cases with the patient's self-esteem. Nocturnal support is less intru-

sive than continuous treatment and in general patients prefer non-invasive systems to tracheostomy ventilation [58].

### Physiological effects of treatment

The arterial blood gases can be improved both during the day and at night. This improvement is apparent within a few days, complete within around 1 month and, in the absence of progression of the underlying disorder, these values are usually maintained for several years [39,41,59,60]. The mechanisms by which the blood gases are improved are not clear, but the most important effects probably include the following.

#### Improvement of the respiratory drive

Ventilation can influence respiratory drive by lowering  $P_{aCO_2}$ , which reduces the cerebrospinal fluid bicarbonate level and thereby increases the response to hypercapnia. Hypoxic depression of the respiratory centres can also be reversed and restoration of a more normal sleep architecture relieves sleep deprivation and increases the respiratory drive through mechanisms that are largely unknown at present.

#### Relief of respiratory muscle fatigue

Muscle fatigue has been postulated as a cause of respiratory failure but it is more likely that the central respiratory control mechanisms adapt their output to prevent fatigue from developing. None the less, it is possible that ventilatory support provided in the long term, even if only at night, improves respiratory muscle strength, endurance or coordination so that spontaneous ventilation is more effective during the day.

### Other mechanisms

An improvement in chest wall compliance, caused by a reduction in the stiffness of the soft tissues of the chest wall (due to the restricted range of tidal movements) and also by a decrease in lung elastance via reopening of small airways, may contribute to the blood gas changes. Other effects of ventilation, such as improvement in ventilation-perfusion matching and relief of upper airway obstruction, are transient.

### Selection of method of ventilatory support

Patients with poor bulbar function impairing swallowing and coughing are at risk of aspiration and usually require a cuffed tracheostomy tube. A tracheostomy is also needed if there is upper airway obstruction that prevents the non-invasive techniques from being effective. However, these are preferable for patients without these complications and in whom support is required only intermittently. This is usually confined to the night-time but some subjects require some additional support during the day. If ventilation is required for more than about 16 h per day, tracheostomy ventilation may be more convenient than non-invasive techniques, particularly in young children. Patients who are totally dependent on the ventilator are usually best treated with tracheostomy ventilation.

The choice between a nasal or face mask positive-pressure system and negative-pressure ventilation can be difficult. Many patients with neuromuscular and skeletal disorders can be adequately ventilated by either method, and whichever is preferred by the patient should be provided. For patients with severe hypoxia and hypercapnia and with markedly abnormal respiratory mechanics, mask ventilation appears to be more effective than negative-pressure ventilation. If mask ventilation is selected, the question arises as to whether to choose a volume- or pressure-preset system. The former compensates better for abnormal respiratory mechanics since it delivers a fixed tidal volume but is less able to cope with leaks either around the mask or through the mouth. A pressure-preset ventilator should be preferred if leaks are a problem and usually if the patient has a strong respiratory drive or an erratic respiratory pattern. These instruments not only have better flow-triggering systems than volume-preset ventilators but also generate a higher tidal volume in response to continuing inspiratory effort during the machine's inspiratory cycle. However, pressure-preset ventilators are unreliable if the patient's respiratory mechanics change, for instance due to retained secretions, bronchoconstriction or changes in sleep stage or, in the longer term, with changes in weight or during infections. The addition of PEEP may be of use in patients with upper

airway obstruction causing sleep apnoeas in addition to ventilatory failure and if auto-PEEP is present and is significantly increasing the initial inspiratory work of breathing.

### Home or hospital care

Ventilatory support is almost invariably initiated in hospital, often in intensive care units, although long-term hospital care is rarely preferable once the medical condition is stable. Whether treatment in the home is successful depends on the ability of the patient, the family and other attendants or carers being physically able to manage the equipment and also on their understanding of how to use it and cope with any problems that may develop. It is important to assess the psychological state of the patient and the type and extent of support from his or her family before discharge.

Patients who require home ventilation often have other disabilities such as limb weakness that may prevent them from becoming independent in managing their equipment. The patient's previous ability to cope with stress and acceptance of the respiratory support equipment are two factors that predict whether the patient will be able to continue with ventilatory support. These issues are particularly important with the more invasive forms of treatment, especially those requiring a tracheostomy. It is important to try to motivate the patient and family by realizing not only what the outcome might be if treatment is discontinued but also the benefits likely to be obtained if treatment is successful.

Ventilatory support should be as safe in the home as in hospital if care is taken in stabilizing the patient's condition before discharge. Occasionally, deaths occur in the first few days after discharge but these are remarkably few in large centres [61].

An important aspect of home care is the degree of independence that it enables the patient to maintain. This should be encouraged while the patient is still in hospital by gradually transferring responsibility for the patient's care from the health professionals to the patient and family and other carers [62]. Before discharge it is important to assess all the practical aspects of care in the home and to make any necessary modifications and to anticipate any difficulties which might arise.

Care is usually cheaper if the patient is cared for in the home rather than in hospital. This is particularly so if non-invasive forms of ventilatory support are provided, but for patients with multiple disabilities, usually due to chronic neuromuscular disorders, home care can be more expensive [63]. The cost is mainly determined by the number and grade of carers required. There may be as many as 10 for a patient with a high cervical spinal cord lesion.

Once the patient has returned home, it is important that he or she knows how to cope with any problems that may arise. Ideally a hospital telephone helpline number should be available continuously. It is usually not necessary to monitor any physiological indices such as oxygen satura-

tion in the home, although regular clinical reassessment is essential since the patient's condition may alter and the ventilatory requirements change. All ventilators need regular servicing, and accessories such as nasal masks need replacing.

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# LUNG TRANSPLANTATION

TIMOTHY W. HIGGENBOTTAM

Clinical lung transplantation, which developed during the 1980s [1], has awakened interest in many hitherto neglected chronic lung diseases. Its emergence not as an experimental but as a clinical treatment has not only spurred our understanding of the new diseases associated with the transplant lung, but has also seen the introduction of new alternative medical and surgical treatments of chronic lung disease.

## Philosophy of lung transplantation and its consequent limitations

The replacement of diseased organs with healthy engrafted ones offers a number of therapeutic opportunities for the patient with chronic lung disease.

1 It enables replacement with lungs able to provide adequate ventilation and gas exchange in patients with respiratory failure [2].

2 Where there is advanced pulmonary hypertension, a normal pulmonary vascular resistance can be restored [3].

3 Extensive lung sepsis, as in cystic fibrosis, can be treated by removal and replacement with relatively clean and uninfected bilateral lung grafts [4].

It is important to understand that a transplant patient has traded the old diseased lungs for engrafted organs that to varying degrees are involved in an alternative chronic disease, namely lung rejection. Depending on the adequacy of control of rejection with immunosuppressive treatment, the normal function of the graft will decline over time and most transplant patients are ultimately likely to die of a transplant-related disease [5].

Donation of organs, except in the case of living related donors (see below), requires that a person has to die. An obligation of the transplant doctor is to make the most effective use of this precious gift. Presently, the need in lung disease is to extend the life of a fatally ill patient. Selection of patients involves the most careful assessment of their untreated chances of survival, and this is then compared with the chances of survival after the lung

transplant. Study of the natural history of many chronic lung diseases has been stimulated by this need [6].

Human donation of organs for transplantation can clearly never offer sufficient transplants to treat a significant number of patients with chronic lung disease, and thus only a selected few can benefit. This realization has spurred the quest for xenograft or animal organ transplantation and, more recently, has encouraged thought of cloning organs from single stem cells.

## History

Few of the early lung transplant recipients treated during the 1960s survived more than a few days. Technical problems with the surgery, acute lung injury of the engrafted lung and poorly effective immunosuppressive treatments all contributed to these failures [7].

In 1979 the first reports appeared of the use of cyclosporin as an immunosuppressive drug in patients with liver and renal transplants. This fungal-derived antibiotic was significantly better than the earlier immunosuppressives, azathioprine and steroids. Cyclosporin was tried first in cardiac transplants and in 1981 its use was reported in lung transplantation [1].

The initial operation of choice was heart-lung transplantation, where the graft is made up of the heart and lungs harvested *en bloc* in a single exercise. This operation provides an immediately functioning heart even when the underlying disease is advanced. Pulmonary hypertension secondary to uncorrectable congenital heart disease is the main indication for this form of surgery. Few centres worldwide are still using this method, as the alternative, double lung transplantation, allows the donor heart to be used separately in another cardiac recipient.

In the 1980s, Cooper developed the single lung transplant [8]. Initially used in patients with cryptogenic fibrosing alveolitis, this was soon extended for use in emphysema. *En bloc* double lung and, more recently, sequential bilateral lung transplantation are used in

patients with lung sepsis and in patients with primary pulmonary hypertension. The initial immunosuppressive treatment was with cyclosporin and steroids, azathioprine being added later. New therapies are coming into clinical practice each year offering fewer side-effects and better immunosuppression. A major contribution to the advance of this form of surgery was the development of techniques in medical management that allowed early diagnosis of complications, rejection and infection and simplified the patient's home care. These are described later.

## Indications

All forms of life-threatening chronic lung disease can be treated with this form of treatment.

### Emphysema and chronic obstructive lung diseases

These cause respiratory failure, and patients often die of intercurrent pneumonia or hypercapnic respiratory failure. Over the last decade there have been several studies of the natural history of these diseases. An adult with a forced expiratory volume in 1 s (FEV<sub>1</sub>) of less than 1 L or under 25% of the predicted value has only a 30% chance of surviving untreated for 3 years. However, medical treatments, specifically long-term oxygen therapy, can double the survival chance in those patients with an FEV<sub>1</sub> of less than 1.5 L, Pao<sub>2</sub> less than 6.5 kPa (50 mmHg) and Paco<sub>2</sub> greater than 6.5 kPa (50 mmHg).

Patients are now selected according to their FEV<sub>1</sub> values and when long-term oxygen therapy is no longer effective or cannot be considered because of the risk of hypoventilation causing significant hypercapnia. An alternative surgical treatment that should now be considered is lung volume reduction surgery for patients without respiratory failure where diffuse disease is observed on high-resolution CT (HRCT) [9] (see Chapter 23). HRCT is used prior to consideration of lung transplantation, not only to confirm the diagnosis of emphysema but also to detect evidence of bronchiectasis. This renders single lung transplantation unsatisfactory, as infection can spread from the native to the engrafted lung. Therefore the finding of bronchiectasis requires bilateral lung transplantation.

### Pulmonary fibroses

To the specific condition of cryptogenic fibrosing alveolitis one can add other forms of diffuse lung fibrosis, including sarcoidosis and diffuse fibrosis associated with the connective tissue diseases including scleroderma, as suitable for consideration for transplant surgery.

The characteristic feature of advanced lung fibrosis found in these conditions is the poor prognosis. In cryptogenic fibrosing alveolitis only a few patients make any sig-

nificant response to medical treatment. When decline in lung volumes or diffusing capacity for carbon monoxide (DLCO) occurs in an otherwise suitable patient despite appropriate corticosteroid and immunosuppressive therapy, it is wise to refer early in the progression of disease for consideration for surgery [10]. As noted in Chapter 31, a number of patients with cryptogenic fibrosing alveolitis show rapid progression and if such patients are not controlled with limited doses of corticosteroids they also should be referred early for consideration for transplantation.

Ideally there should be histological proof of diagnosis in patients with diffuse lung fibrosis, as a number of diseases can be difficult to differentiate from cryptogenic fibrosing alveolitis (see Chapter 31). In explant lungs the author has observed *Mycobacterium tuberculosis*, plexogenic pulmonary hypertension and carcinoma in clinically diagnosed patients.

### Primary pulmonary hypertension

The natural history of this disease is now well described and the effectiveness of medical treatments known (see Chapter 26). This has allowed a straightforward approach to selection of patients for surgery [10]. The prognosis can be determined by the haemodynamic measurements obtained at a diagnostic right heart catheter study and from this analysis treatment can be determined [11].

1 Medical treatment in the form of anticoagulation is offered to all patients. This improves survival, presumably by reducing intravascular pulmonary thrombosis.

2 In those patients with a right atrial pressure below 2 kPa (15 mmHg), a cardiac index above 2.1 L/min/m<sup>2</sup> and an S $\bar{v}$ O<sub>2</sub> of more than 63% and in whom there is a capacity to vasodilate when given prostacyclin, a potential treatment is an oral calcium channel blocker such as diltiazem. Given in a dose to maintain a systemic arterial pressure of 100/70 mmHg, this often improves symptoms and survival.

3 When the patient has developed right heart failure, i.e. right atrial pressure greater than 2 kPa (15 mmHg), cardiac index less than 2.1 L/min/m<sup>2</sup> and S $\bar{v}$ O<sub>2</sub> less than 63%, a continuous intravenous infusion of either prostacyclin or iloprost (a stable analogue) improves survival and quality of life.

Lung transplantation is considered when this sequence of medical treatment fails to control symptoms and where there is evidence that the disease is progressing. It has been suggested that prostacyclin and iloprost can achieve 5-year survival rates of 80%, which exceed the rates seen with transplantation [11,12].

### Cystic fibrosis

Lung transplantation has contributed to the unravelling of

the genetics of this common inherited disease (see Chapter 30). It was demonstrated early in the 1980s that when patients with cystic fibrosis underwent heart–lung transplantation the typical mucosal abnormality of ion transport did not recur in the engrafted lung [13]. This excluded notions of a contributing humoral factor and placed the pathogenic emphasis on the mucosa.

The main prognostic measures in advanced cystic fibrosis are FEV<sub>1</sub> values below 25% of those predicted, arterial hypoxia with  $P_{aO_2}$  values below 6.5 kPa (50 mmHg) and, most importantly, an elevated  $P_{aCO_2}$ , which provides evidence of hypoventilation. Hypoventilation carries a poor prognosis [14].

Patients can be considered for transplantation before the development of respiratory failure when there is a history of life-threatening haemoptysis or uncontrolled pulmonary sepsis. In these circumstances a careful appraisal of the patient is required, weighing up the relative risks of the underlying pulmonary problem and the risks from lung transplantation.

### Tumours

There is only limited information on the outcome of lung transplantation on patients with cancers. However in other forms of solid organ transplantation it is recommended that 5 years' freedom from the original cancer should elapse before transplant surgery is considered [10]. This advice precludes the use of lung transplantation as a treatment for all forms of lung cancer. Certainly case reports indicate a high recurrence rate for even tumours of low malignancy such as alveolar cell carcinoma [10].

One special indication for lung transplantation is the development of diffuse lung fibrosis as a result of chemotherapy for lymphomas. Again the empirical advice is to wait for a 5-year period of freedom from relapse before surgery is considered.

### Lung transplantation in children

The results of lung transplantation have been poorer in children, considered as a group, than in adults. This has been the result of higher incidence rates of pulmonary infections and greater difficulty in the diagnosis and treatment of acute lung rejection [15]. However, in the child with advanced lung disease transplantation offers an effective treatment. The main indication is pulmonary hypertension, either primary or secondary to congenital heart disease or pulmonary dysplasia. A number of children with cystic fibrosis require transplant surgery, although the usual age range for transplantation in this condition is 18–25 years.

Assessment of the patient's untreated survival chances is undertaken in the same way as in the adult. The recom-

mendation is that this is performed in a unit specializing in childhood lung transplantation.

## Surgical techniques

### Heart–lung transplantation

The era of lung transplantation began in 1981 with the successful use of heart–lung transplantation (HLT) for pulmonary hypertension [1]. After excision of the heart and lungs of the donor *en bloc*, the trachea is anastomosed in the recipient just above the carina. The integrity of the anastomosis is maintained as a result of extensive collateral arterial blood supply to the lower trachea from the coronary arteries. Airway complications had been a major limiting factor in earlier attempts at lung transplantation. The advantages of HLT include the benefits from simultaneous engraftment of the heart, allowing immediate restoration of normal cardiac output, an important factor in patients with severe pulmonary hypertension.

The operation requires cardiopulmonary bypass. As a result, there is an age limit for patients of 55 years. There is also a significantly higher risk of perioperative bleeding despite the introduction of aprotinin to limit this complication. Further disadvantages are that the heart can also be involved in chronic rejection, although this is not isolated from the same process in the lungs. The use of both lungs and heart limits the number of potential recipients who can benefit from the donation. The 'domino' operation, where the recipient's heart is used and donated to a second recipient, is one way of maximizing effective use of the organs [16].

As a result of the limited number of donors, most centres have confined HLT to the treatment of pulmonary hypertension secondary to uncorrectable congenital heart disease. However, certain centres have retained HLT for cystic fibrosis and primary pulmonary hypertension. Internationally the results are poorer from HLT than from other forms of lung transplantation [15].

### Single lung transplantation

Single lung transplantation was first used to treat cryptogenic fibrosing alveolitis but quickly gained a place also for emphysema [9]. Its advantages are that potentially two lung recipients and one cardiac recipient can be treated with organs from one donor. No cardiopulmonary bypass is needed and so patients up to the age of 65 years are being considered for this form of transplantation. Perioperative bleeding is limited.

A number of technical innovations to achieve good healing of the bronchial anastomosis have been tried. These include wrapping the omentum around the suture line or telescoping the donor bronchus into that of the recipient. Each approach has its advocates but careful har-



vesting of the graft appears equally important in determining successful outcome. It is essential to exclude bronchiectasis in patients with either cryptogenic fibrosing alveolitis or emphysema, as the remaining native lung infects the transplant and compromises the chances of success. HRCT is the test of choice.

Operations for single lung transplantation in patients with emphysema involve selection of donor lungs that have a total lung capacity (TLC) to match that predicted by the height and age of the recipient. After surgery the lungs adopt the size determined by the thoracic vertebral height; as a result a patient with emphysema has a reduction in TLC, while in cryptogenic fibrosing alveolitis the TLC increases [17]. This nicely demonstrates an important physiological point, namely that the volume of the lung is determined by the size of the thoracic cavity.

### Double lung transplantation

This operation is now performed as two sequential lung transplants, one side followed by the other. There usually is no need for cardiopulmonary bypass. Again the risk of bleeding is less than in HLT. This is the operation of choice for cystic fibrosis and bronchiectasis, and is also now advocated for patients with primary pulmonary hypertension [18]. Single lung transplants are used in some centres for this disease, although acute pulmonary oedema in the postoperative period and disabling breathlessness if obliterative bronchiolitis develops in the graft limit the efficacy of this operation. Again the opportunity to use the donor heart for another cardiac recipient is retained.

### Living-related donation of lungs

The delays in obtaining donor organs and the rapid decline in the clinical state of children with cystic fibrosis awaiting a lung transplant led to the development in California of the procedure of living-related donation [19]. Both parents of a cystic fibrosis child donate a lobe of lung, which are then tailored to fit into the thorax on each side. The risks to the donor have been determined to be small and the engraftment is no worse than with cadaveric transplant. The need for close matching between the donor and recipient is not necessarily a limiting factor, as more distant relatives than parents have been used as donors. This procedure has been mainly restricted to children with cystic fibrosis.

### Selection criteria

Patients evaluated for lung transplantation should have received maximal or optimal medical treatment for the disease but nevertheless have declining lung function. Lung transplantation is rarely an option for the acutely ill

patient requiring intensive care. Concurrent illness should be adequately treated and preventative care instituted for common illnesses [10].

Older patients survive less well than the younger transplant patient. Currently the maximum ages advised for surgery on the basis of survival chances are 55 years for HLT, 65 years for single lung transplantation and 60 years for double lung transplantation. Certain medical conditions that affect the results of lung transplantation can be considered to be contraindications if untreated, and some of these remain absolute contraindications. Current corticosteroid therapy is not a contraindication, but the dose should be reduced to 20 mg or less per day.

For every patient an individual assessment is needed and careful counselling is required. Most centres admit the potential recipient for a period of time to engage all the specialists involved and to undertake appropriate tests.

### Relative contraindications

- 1 Symptomatic and asymptomatic osteoporosis require treatment before transplantation of the lungs. This requires full investigation and appropriate objective measurements of improvement by bone densitometry.
- 2 Severe musculoskeletal disease of the thorax.
- 3 Obesity or cachexia; weight needs to be between 70 and 130% of the ideal.
- 4 Substance abuse, including nicotine, alcohol and narcotics. Freedom from abuse for 6 months is needed.
- 5 Psychosocial problems must be resolved before surgery.
- 6 Requirement for invasive ventilation is a relative contraindication but this is not applied to patients on non-invasive ventilatory support.
- 7 Colonization with fungi and mycobacteria are not absolute contraindications but special care needs to be observed where single lung transplantation is considered.

### Absolute contraindications

- 1 Major dysfunction of another organ, such as liver or kidneys, precludes lung transplantation, unless combined multiorgan transplantation is considered.
- 2 Progressive neuromuscular disease.
- 3 Infection with human immunodeficiency virus (HIV).
- 4 Infection with hepatitis B (antigen positivity) and hepatitis C with liver disease.

### Donor selection and lung preservation

Selection of donors has become a critical part of the lung transplant programme. Less than 30% of potential donors can contribute lungs, a situation quite unlike that with other solid organ transplants. This reflects the frequency with which the lungs are infected or oedematous in

patients who have died from brain injury or stroke. Patients cannot become donors if positive for HIV or hepatitis B or C nor if they have evidence of malignant disease.

Lung donors are confined to people who have been non-smokers under the age of 45 years. The ideal lung donor should have a clear chest radiograph, normal gas exchange and no evidence of pneumonia. Most centres send out teams to manage potential donors in order to reduce the risks of fluid overload and to check for pneumonia prior to death. Assisted ventilation is optimized before the harvesting operation.

The donor operation involves cannulation of the pulmonary artery and infusion of either prostacyclin or prostaglandin E<sub>2</sub> [20]. This causes vasodilatation of the pulmonary circulation in order to allow the cold preservation fluid to be subsequently distributed through the lungs. It may also have some cytoprotective effects. The lungs and heart or heart–lung block are preserved inflated at 4°C. A number of different types of preservation fluid are used but all are limited to total ischaemic times below 4 h. If this time is exceeded, the engrafted lungs develop significant reperfusion injury.

Donors and recipient are matched according to ABO blood group. Usually cytomegalovirus-positive donors are matched with positive recipients.

## Perioperative care

Intravenous immunosuppressive treatment is given before surgery in the form of cyclosporin, azathioprine and steroids, which are continued postoperatively until food is taken by the patient. Early extubation, allowing the patient to breathe spontaneously soon after surgery, is the ideal. Mobilization and oral feeds are started as soon as possible. The main limitation to this is acute lung injury after surgery and this usually occurs as a result of surgical complications. Patients are given broad-spectrum antibiotics and fluid is restricted to avoid pulmonary oedema. Nursing takes place in a separate intensive care area, although isolation is no longer practised. Once mobilized, the patients can return to general wards.

## Management of complications

There are two main acute complications: infection and rejection of the lung. These occur most frequently in the first postoperative months but can occur at any stage of the transplant. Many of the early developments in lung transplantation focused on the diagnostic techniques and methods of monitoring graft function.

### Daily spirometry

For adults, both acute rejection and infection of the trans-

planted lungs cause a fall in FEV<sub>1</sub>. Using daily measurement with a pocket spirometer it is possible to detect the complication before chest radiographic abnormalities develop [21]. The fall in FEV<sub>1</sub> is an indication, along with the respiratory symptoms of breathlessness and cough, for undertaking a transbronchial lung biopsy and bronchial lavage.

### Transbronchial lung biopsy

It was early realized that histology of small lung biopsies of the lung transplant is able to differentiate lung infections from acute lung rejection [22]. Characteristically the histology in rejection shows a perivascular infiltrate of activated lymphocytes. Occasionally the bronchioles are also involved in a similar infiltration. Treatment is with daily intravenous methylprednisolone (0.5–1 g) for 3 days followed by oral prednisolone in reducing dosage over 3 weeks. The lymphocytic infiltration clears with this treatment.

Common opportunistic infections can also be recognized from the histology of the biopsies. In cytomegalovirus pneumonia there are characteristic inclusion bodies in the epithelial cells. A foamy intra-alveolar exudate is seen in *Pneumocystis carinii* pneumonia. Herpes simplex infections also have characteristic inclusions. Bronchial lavage allows further cytological examination and culture for bacterial infections.

### Immunosuppressive treatment

The principal immunosuppressive treatments are cyclosporin [8] (or the equivalent tacrolimus [23]), azathioprine (or mycophenolate [24]) and oral prednisolone. The doses of cyclosporin or tacrolimus are monitored by means of blood levels of the drug. Renal function is carefully monitored as both cyclosporin and tacrolimus injure the kidneys. The white cell count is maintained at  $6 \times 10^9/L$  if azathioprine is used. There are a large number of new immunosuppressive treatment regimens under investigation [25] and the pattern of treatment will certainly change over the next few years.

### Prophylactic antibiotic and antiviral treatment

All patients receive immediate prophylactic postoperative antibiotics. After 2 days, guided by the cultures of the bronchial aspirate from the donor lungs, further antibiotics are given. Patients receiving organs from a donor with positive serology to *Toxocara* spp. receive pyrimethamine postoperatively [1].

During periods when augmented immunosuppression is used to treat acute rejection, it is useful to cover patients who received organs from a cytomegalovirus-positive donor with intravenous ganciclovir. Oral co-trimoxazole

is used in the same way to avoid *P. carinii* pneumonia during augmentation of immunosuppression.

## Results

### Heart–lung transplantation

The outcome of HLT is that most patients attain their predicted normal values for FEV<sub>1</sub>, vital capacity and TLC within 3 months of the surgery [26]. Their exercise tolerance is not as good as predicted for their height and age, probably as a result of the denervated heart being unable to increase cardiac output equivalently to normal [27]. In contrast, denervation of the lung affects neither control of breathing nor the perception of breathlessness. Indeed bronchoconstriction can be demonstrated in the transplanted lung, particularly at times of acute rejection when bronchial hyperresponsiveness as seen in asthma is well described. In all these functions, vagal innervation of the lungs appears unimportant [28].

### Single lung transplantation

As one native lung remains, the improvement in lung function is less impressive than with double transplantation or HLT. However the FEV<sub>1</sub> and TLC return towards normal and the exercise tolerance often exceeds that seen after HLT [9].

### Double lung transplantation

These patients benefit from two lungs and retain a normally innervated heart. Lung function is normal and exercise capacity exceeds that seen after HLT.

## Later complications

A number of chronic complications limit the success of lung transplantation and contribute to early deaths.

### Airway anastomosis

Tracheal and bronchial dehiscence are recognized complications of poor vascularization of the anastomoses. While uncommon in HLT, errors in surgical technique in single and bilateral lung transplantation are punished by this problem. Diagnosis is by a combination of bronchoscopy and HRCT. Conservative management is the only successful approach, but fatalities are common.

More common in single and bilateral lung transplantation are the complications of either bronchial stenosis or bronchomalacia. The diagnosis is made by bronchoscopy and treatment is with expandable Gianturco stents. These complications are both the result of ischaemia of the anastomosis.

## Obliterative bronchiolitis

This is the most common cause of late death from lung transplantation and contributes significantly to morbidity after surgery. It is estimated that in 5 years one-third of patients die from this complication, one-third are disabled by it, while the remainder remain free of the problem [5]. The principal risk factor appears to be the frequency of acute rejection in the first 3 months after surgery [29]. Some have also implicated infection, as with cytomegalovirus. The abnormality is a proliferative obliteration of the bronchioles by a fibromuscular process [30]. It is often associated with bronchiectasis and suppurative airway disease [31].

The functional consequence of obliterative bronchiolitis is irreversible airways obstruction, characterized by a progressive fall in FEV<sub>1</sub>. Augmentation of immunosuppression can limit the rate of loss of function but seldom restores lost FEV<sub>1</sub>. A simple descriptive scheme of the disorder depends on the degree of fall in FEV<sub>1</sub> and is called the bronchiolitis obliterans syndrome grading [26]. It has predictive value for survival. Presently the only preventive treatment that has been shown to work is the use of nebulized budesonide, an inhaled corticosteroid, usually effective in asthma. When this is given for a year in daily doses of 500 µg to patients experiencing more than three rejection episodes in the first 3 months, it not only prevents obliterative bronchiolitis but also reduces the patient's requirements for oral prednisolone [32].

## Effectiveness and costs

There has been sufficient time to observe the long-term effectiveness of lung transplantation in extending life and improving the quality of life. However there have been no randomized controlled trials of transplantation nor any direct comparisons with medical treatments. The few studies of the quality of life after transplantation have in the main been descriptive rather than analytic. Studies of cost are now being undertaken and some preliminary work has been reported.

## Survival

There are differences in the ability of HLT and single and bilateral lung transplantation to extend life. These reflect frequency of use and the number of centres undertaking sufficient transplants to maintain skills. International registries report annually on outcome data [15]. There are ranges of values that should help the clinician decide on the merits of the operations.

- 1 HLT: 5-year actuarial survival 30–60%.
- 2 Single lung transplantation: 5-year survival 60–80%.
- 3 Bilateral lung transplantation: 5-year survival 50–70%.

The original disease also influences outcome. Emphysema provides the best survival figures for single lung transplantation. Primary pulmonary hypertension has the poorest survival figures from any type of lung transplant surgery in adults. Children also have poorer survival figures.

### Quality of life

Observational studies comparing patients before and after lung transplantation indicate substantial improvements for all three transplant operations [33]. Many of the measurements relate to activity and these correlate well with the enhanced exercise tolerance. Clearly all these studies focus on those patients who are well and do not systematically study those who have complications such as obliterative bronchiolitis.

### Costs

A few studies have addressed the costs of lung transplantation. Ramsey and colleagues [34] considered cost in relation to the improvement in quality of life. In particular, the cost per quality-adjusted life-year (QALY) was estimated. A figure for single lung transplantation in the USA was \$176 000 per QALY. Most of the costs concern the initial hospital costs, although a significant cost is incurred by complications such as bronchiolitis and infections. No such figure has been calculated in Europe. For comparison, in the UK the usual limit for cost-effectiveness of a new treatment is regarded as £25 000 per QALY [35].

One alternative approach to costs has been to consider the comparative costs of medical care, and this has been used to study cystic fibrosis [36]. Of interest, overall there was no cost reduction after lung transplantation surgery. Furthermore, there was no overall reduction in the number of admissions to hospital. These observations are of importance when a clinician advises the patient in making choices of types of care.

### The future

The prospects for lung transplantation are not limited by the costs but more by the availability of potential donors. It has been estimated that in the UK some 900 patients would benefit from lung transplantation each year. The total number of deaths from head injuries and strokes

where transplant organs could be donated is about 2000 per year [37]. Even with a perfect donation scheme there remains a large difference between the resource and the need. This has led to a number of strategies to increase the availability of transplantable organs.

### Xenograft transplants

The use of organs from another animal species has been prevented by an acute haemorrhagic injury, understanding of which has recently rapidly expanded [38]. It appears that there is an acute activation of complement, the process being facilitated by two receptors expressed on human endothelial cells, decay accelerating factor (DAF) and membrane cofactor protein (MCP). Research workers have overcome this by using transgenic animals, where the human receptors DAF and MCP are expressed on the endothelium of the pig [39]. Such animals can be used to donate hearts and kidneys, and it is possible that the lungs might also be used. Routine immunosuppressive therapy is still required to prevent the cellular and humoral rejection.

Sadly, however, this form of transplantation probably will not become a reality. There is evidence that the porcine genome contains retroviruses that are expressed in human cells when exposed to pig cells, and currently there is a moratorium on this form of transplant surgery.

### Cloning of organs

This has all the elements of science fiction. However the notion is that from a single cell it should be possible to develop a complete organ. Limited success has been reported experimentally with limbs and if achieved this would clearly offer the opportunity of using the patient's own tissue to develop a new organ such as a lung.

### Conclusion

We are entering the third decade of lung transplantation. New issues of cost and effectiveness need to be studied. Immunosuppressive therapies are improving, both in effectiveness and avoidance of toxic effects. Potentially new sources of organs may become available. After a prolonged stage of evaluation and experiment, lung transplantation is now established as an effective treatment for specific types of disease.

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# TERMINAL CARE IN RESPIRATORY DISEASE

DOUGLAS SEATON

I have often thought upon death, and I find it the least of all evils.

*Francis Bacon (1561–1626)*

Death must be distinguished from dying, with which it is often confused.

*Sydney Smith (1771–1845)*

The inevitability of death, its unpredictability, the surprising perception that it can be regarded as a benign event and the important distinction between death itself and the process of dying are all germane to any consideration of medical care in its broadest sense; for no matter how hard we strive to educate ourselves about the prevention of disease and the provision of 'healthcare', all clinicians are, in the natural course of events, also responsible for the provision of 'dying care', and can do much good to patients and their relatives by a kindly and sensible approach to these matters. The opportunities for such care begin with the realization that the coming of death as a consequence of a firmly diagnosed disease is certain and not far removed in time and that increasing attention should be paid to the relief of suffering, both physical and psychological. It is at this point of realization that efforts may be turned away from the trials of investigative procedures or attempts at cure that rather than prolonging life may in reality be simply making the process of dying more protracted.

## Truthful explanation

The possession of the knowledge that a patient is dying gives the physician an opportunity to offer appropriate support to all concerned. Imparting this knowledge can be distressing for the patient and the family as well as the doctor, and how this is done is a delicate matter for which no simple formula exists. Events unfold according to circumstances so that sometimes the patient learns before close relatives, sometimes the reverse occurs and sometimes the truth is told to both together. It is common for the spouse or relatives to seek to protect the patient from the

knowledge that their disease is incurable and fatal. Such reactions are natural enough, particularly when voiced in response to the sudden realization of the true state of affairs. They may sometimes be right, at least for a time, but more often than not their judgement in this situation is inevitably clouded by emotion, for the deliberate concealment of the truth from the patient is an act of denial that increases the stresses between individual members of the family, the patient and the doctor, creating a world of make-believe in which interpersonal relationships become strained and in which suspicion, fear and mistrust are fostered. Family members who take this view may be reassured that in the doctor's experience patients who are denied the truth are likely to suffer more than those who have a greater awareness of their situation so that they can come to terms with it.

How patients are told that their illness is fatal is a matter of individual judgement. It is most difficult when the patient is outwardly in reasonable health, in which case the concept may be introduced gradually in terms of what can and cannot be done in the way of management. This often allows the patient to ask the relevant questions and to be supplied with answers that lead as far towards the truth as he or she wishes to go at that particular time. These disclosures should be made gently and by degree. A 'screening question' may be asked at the outset to try to establish the patient's perception of the position. The whole truth need not come out at first but a line of communication is set up so that the patient can establish trust in the doctor and in the authenticity of the information supplied, but can also be given time to adjust to the new situation that has arisen. This stepwise approach seems entirely reasonable and care should be taken not to 'assault the patient with truth' that he or she is not yet ready to handle [1]. Not infrequently the patient has realized the seriousness of the position and that recovery is not taking place. In this situation fairly frank explanations of the true state of affairs may bring a sense of relief, being received with openly expressed gratitude.

When the truth is told it should be accompanied by a

positive statement of the physician's intention to continue to offer supportive treatment and to deal with symptoms effectively whenever they should happen to arise. A failure to provide such assurances may produce a sense of abandonment and isolation stemming from the belief that 'nothing more can be done'. The provision of a firm statement of support may help to provide the patient with a much-needed sense of security and comfort despite the fact that life is drawing to its conclusion.

## Relief of symptoms

Although much can be done to relieve the physical and psychological symptoms of patients who are dying, there is evidence that our hospitals have fallen short of meeting basic needs [2,3]. The first step is to question the patient carefully about those symptoms that are most troubling. Where there is doubt in the presence of multiple symptoms, the principal symptom is usually easily sought out by asking the question: 'If there was one symptom that you could get rid of, which one would you choose first?' The answer frequently helps the physician to direct therapeutic efforts more usefully, while still taking account of secondary symptoms. A more formal symptomatic enquiry, system by system, may unearth other information of value in general management.

Whereas the event of death itself may be regarded as a merciful release, the process of dying can hardly be regarded as pleasurable, and the prospect of physical discomfort may produce a good deal of trepidation. Firm reassurance that uncomfortable symptoms will be effectively combatted may ease the mind of the worried patient. It is up to the individual physician to be sufficiently informed about the various therapeutic options available in order to fulfil such a promise. Clearly therapeutic intervention cannot abolish discomfort totally but it can nevertheless provide a considerable measure of relief.

## Pain

The perception of pain is entirely subjective and may well be influenced by mood, so that if individuals are depressed, anxious or lonely, painful sensations are likely to be more problematical than if their mood has been elevated by any of a number of circumstances, among which is included the provision of kind and courteous general care.

Having established that pain is present, some effort must be made to assess its significance. Patients may sometimes behave in a more reticent and stoical manner towards their medical practitioner than to other members of their family, and a clearer picture of the degree of incapacity caused by pain may be obtained from the spouse, partner or the nursing staff.

Once it has been established that pain is a problem, attention should be turned towards the likely cause. This can usually be inferred from the site and nature of the discomfort, which may be due to involvement of the chest wall, bones, nerves, nerve roots or brain. Patients with cancer more often than not have more than one pain and how far to investigate the source depends upon their general condition. In appropriate circumstances, plain radiographs, isotope bone scans or CT may be required. This is only the case if the result of the investigation is likely to influence management; for example, if it is suspected that there is localized involvement of bone or other structures that may respond to palliative radiotherapy. The instigation of adequate analgesia need not await the results of such tests. Patients are likely to benefit from a frank explanation of the cause of the pain, and if this is not forthcoming will only be worried all the more by doubt and uncertainty, whereas if they are clear about the mechanism then they will be better able to adjust and come to terms with it.

Although it is possible to grade pain according to a visual analogue scale and to record the degree of incapacity by devices such as the Karnovsky scale [4], from a practical standpoint, in patients with cancer, pain may be regarded as mild if it responds adequately to a simple non-narcotic analgesic such as paracetamol or aspirin, and moderate if it requires a weak narcotic analgesic such as codeine or dextropropoxyphene (commonly prescribed with paracetamol as co-proxamol). Any pain that is uncontrolled by the foregoing or is partly controlled but still significantly limits activity should be regarded as being severe and should be treated with a potent opioid (narcotic) analgesic such as morphine [5]. There is a plethora of analgesic preparations available and rather than wander randomly through a jungle of unfamiliar or less well-known preparations, it behoves the physician to develop a simple therapeutic 'three-rung ladder' (Table 60.1) and stick to it [6].

**Table 60.1** Vertical progression of oral analgesia in cancer-associated pain (see text).

	Same daily dose	Once or twice daily
Morphine sulphate (controlled-release preparations)		
Morphine sulphate (immediate-release preparations)	5–10 mg titrated upwards	Every 4 h
Co-codamol 30/500	Two tablets	Every 4–6 h
Codeine phosphate	30–60 mg	Every 4–6 h
Paracetamol	1 g	Every 4–6 h



### Lower rung

Paracetamol is a suitable lower-rung preparation often used for mild pain relief. Aspirin, which has both analgesic and anti-inflammatory properties, may be taken as an alternative at a dose of 600 mg every 4–6 h, although one of the many other non-steroidal anti-inflammatory drugs may be used instead. Aspirin intolerance may be reduced if it is taken after meals.

### Middle rung

Drugs belonging to the family of weak opioid analgesics, such as codeine or dextropropoxyphene, occupy the middle rung. Dihydrocodeine is a semisynthetic analogue that has no particular advantage over the standard weak opioid codeine. In the UK, dextropropoxyphene 32.5 mg is commonly prescribed in combined form with paracetamol 325 mg as co-proxamol. Combinations of codeine with paracetamol also exist and when these are used it makes sense to prescribe a formulation that contains a therapeutic 30-mg dose of codeine (co-codamol 30/500) rather than one of those containing only 8 mg (co-codamol 8/500), unless the patient is very elderly in which case increased sensitivity to codeine and other narcotics may occur. These middle-rung analgesics are likely to be more acceptable than morphine to patients earlier in their disease, and when taken in combined form with paracetamol are probably as effective as low-dose morphine.

### Upper rung

Strong opioid analgesics like morphine and diamorphine are on the upper rung of the analgesic ladder. Some physicians may feel a reluctance to prescribe regular opioids unless they regard the patient as 'terminal'. Any such fears are misplaced and morphine may be continued safely for many months if need be. Stepping sideways on a ladder has never been a very wise course of action and if a non-opioid or a weak opioid analgesic proves ineffective at standard dosage, there is no point in using another similar drug; one should rather go directly to a strong opioid such as morphine (referred to by Sir William Osler as GOM or 'God's own medicine').

The principles are that this drug is prescribed orally by preference, that it should be taken regularly to prevent pain from recurring, that the dose should be tailored upwards according to the patient's needs and that there is no upper dose limit; thus the patient's pain may require anything between 2.5 mg and 2500 mg every 4 h to control it, good control being commonly achieved with 250 mg daily or less.

Morphine may be dispensed as an oral solution (mor-

phine elixir), the prescription having to be written in full in order to comply with the law [7] and to avoid embarrassing delays and telephone calls from the outpatient pharmacist, for example 'morphine hydrochloride 5 mg, chloroform water to 5 mL'.

Alternatively there are now prepared proprietary formulations of morphine sulphate solution such as Oramorph oral solution in strengths of 10 mg per 5 mL and 100 mg per 5 mL. The amount to be dispensed must be written *in figures and words*, for example 'supply 200 mL (two hundred millilitres)', followed by the amount to be taken, for example '10 mL every 4 hours'.

The same applies to morphine sulphate 10 and 20 mg immediate-release tablets (Sevredol). There is no particular advantage in prescribing oral diamorphine rather than morphine itself, as the former is itself biotransformed to morphine and other metabolites. The advantages of parenteral diamorphine are outlined below.

Morphine 5 or 10 mg every 4 h is a reasonable starting dose for pain that is continuous, as is frequently the case with malignancy, although 2.5 mg may be preferred in an elderly or frail patient or one with renal insufficiency. This continuous type of pain should not be treated with as-required or prn prescriptions, unless these are used to augment a regular strong opioid analgesic should breakthrough pain occur between doses. Such top-up or rescue supplementation can be given as often as necessary (e.g. hourly) but is an indication that pain control is incomplete and that the regular 4-hourly doses need to be increased. Doses of morphine sulphate oral solution or tablets are therefore increased gradually according to response, the usual dose for control being 5–30 mg every 4 h, although as mentioned above sometimes very much larger amounts are required. A steady pharmacokinetic state is reached in about 24 h and the dose can therefore be adjusted daily. It is usual to increase the dose by 30–50% at each step and a double dose at bedtime helps to ensure sleep. An example of morphine dose titration is given in Table 60.2.

As frequent dosage can be tiresome for the patient and awkward for the ward, modified-release morphine sulphate tablets (5, 10, 15, 30, 60, 100 and 200 mg) provide a convenient alternative for maintenance treatment, once the patient's total daily dose requirements (including rescue doses for breakthrough pain) have been determined using the 4-hourly regimen, being prescribed *at the same total daily dose* but using a 12-hourly regimen (e.g. MST Continus) [9]. The top-up or rescue dose of immediate-release morphine should be one-third of the 12-hourly dose of MST Continus, this being equivalent to an extra 4-hourly dose (Table 60.2). Modified-release morphine sulphate capsules (30, 60, 90, 120, 150 and 200 mg) for once-daily dosing have become available more recently (MXL). The modified-release preparations tend to

**Table 60.2** Morphine dose titration: an example of initial treatment with a standard formulation leading to maintenance treatment with a twice-daily controlled-release formulation. (After O'Neill [8] with permission.)

Day	Doses given	Total on that day	Starting dose on next day
Day 1	10 mg 4-hourly, plus three 10-mg prn doses	90 mg	15 mg 4-hourly (90/6)
Day 2	15 mg 4-hourly, plus two 15-mg prn doses	120 mg	20 mg 4-hourly (120/6)
Day 3	20 mg 4-hourly <i>Pain is controlled, no breakthrough dosage required</i>	120 mg	
Day 4 and on	60 mg twice daily ( <i>controlled release</i> ) plus 20-mg prn doses (standard formulation) should breakthrough pain occur		

achieve an attenuated peak plasma level in about 2–4 h compared with about 1 h for the immediate-release preparations.

It is clear from the foregoing that 'normal' doses of narcotic analgesics, such as might be used for the short-term relief of postoperative pain, do not apply in the management of chronic pain associated with incurable cancer. Respiratory tolerance to these high doses develops [10].

#### Route of administration

When analgesics are required, the oral route should be used wherever possible as injections are inconvenient for patients and increase their sense of dependence on those who are taking care of them.

If the patient cannot swallow, then strong opioid analgesics should be given either as morphine suppositories (morphine sulphate or hydrochloride suppositories 10, 15, 20 or 30 mg) or by injection. In the lower dose range of morphine, buprenorphine 200–400 µg sublingually every 6–8 h is an alternative. Buprenorphine binds partially to opioid receptors and may block the access of full agonists, such as morphine, to the same receptors, thereby partially antagonizing its effect if taken concurrently. A transdermal formulation of the potent opioid analgesic fentanyl has been developed, being applied in the form of a cutaneous patch. These are changed every 72 h and are available in different strengths designed to deliver 25, 50, 75 and 100 µg of fentanyl per hour. The system appears to be effective but as with other controlled-release formulations, immediate-release preparations may still be required for breakthrough pain [11,12].

Diamorphine (heroin) tends to be preferred for injection in the UK as it is more soluble than morphine; 20 mL of water is required to dissolve 1 g of morphine, whereas

only 1.6 mL is needed to dissolve 1 g of diamorphine. It is an advantage to be able to give the same dose in a smaller volume in patients who need large doses of subcutaneous opioid [13]. There is no point in giving diamorphine orally as it is a prodrug of morphine. Diamorphine is only legally prescribable in the UK and Canada. Hydromorphone, which has now become available in the UK (so far only in oral form, 1 mg dose equivalent to 7.5 mg morphine), has similar properties and is used in place of diamorphine in the USA and elsewhere (where a parenteral form is available). When used subcutaneously, diamorphine should be given at one-third of the oral dose of morphine that had previously controlled pain satisfactorily, in order to achieve the same effect, whereas if subcutaneous morphine is used it should be given at half the oral dose. If intravenous morphine is used (e.g. in patients with peripheral venous shutdown or in those who already have intravenous access established for some other reason), the equivalent dose is one-third of that given orally [14]. It is not usual practice to give morphine intramuscularly in a palliative setting as subcutaneous injections are less painful. A fine 'butterfly' needle may be used for regular subcutaneous injections.

A syringe driver (such as a portable, pocket-sized Graseby type MS16A pump) is a very useful method for delivering diamorphine in the terminal phase when the patient is disinclined or unable to swallow, being less disturbing than repeated injections. It may also allay fears on the part of the relations that the last dose of a 4-hourly subcutaneous morphine regimen 'carried off' the patient should death happen to come shortly after such an injection. However, it is a mistake to use this form of treatment while the patient is still able to swallow comfortably. Diamorphine is available in 5, 10, 30, 100 and 500 mg ampoules. Water for injection rather than 0.9% saline should be used for strengths greater than 40 mg/mL in order to avoid precipitation. The pumps run at a preset rate measured in millimetres of syringe plunger movement per hour. Thus the diamorphine (and any other compatible medication that needs to be infused as well) may be made up with water or saline to 8.5 mL total volume, which when drawn up in a 10-mL disposable plastic syringe occupies 50 mm of barrel length. The driver can then be set to run at 2 mm/h, emptying its contents over 25 h. The syringe is connected to the patient by a disposable butterfly cannula with integral 60 or 100 cm tubing, the butterfly needle being bent to about 45° and secured on the upper arm, thigh, abdomen or chest with a light proprietary dressing such as OpSite or Tegaderm. The conversion from oral morphine to 24-h or, in this case, 25-h subcutaneous diamorphine is achieved by dividing the previous day's dose of oral morphine by three (Table 60.3). A list of drugs compatible with diamorphine is contained in the British National Formulary [14].

**Table 60.3** Approximate dose equivalence of some opioid analgesics to oral morphine.

	Ratio
Diamorphine orally	2:3
Diamorphine subcutaneous	1:3
Morphine intravenous	1:3
Morphine subcutaneous	1:2
Morphine per rectum	1:1
Hydromorphone orally	1:7.5

For the oral route morphine is preferable to diamorphine; for the parenteral routes diamorphine is preferable to morphine (see text).

### Bony pain and sequelae

Bone pain, like visceral and neuropathic pain, tends to be somewhat less responsive to narcotic analgesics. When pain is localized and caused by direct involvement of the chest wall by tumour or by bony metastases, palliative radiotherapy may be very helpful and can often be delivered as a single treatment to a painful area. Indometacin (indomethacin) or other non-steroidal anti-inflammatory drugs may be useful in controlling bony pain, presumably as a result of their inhibition of prostaglandins, which are released during osteolysis [15]. They may also be used to supplement a regular strong opioid in the same situation [16]. In the same manner these drugs are very effective in relieving the pain of hypertrophic pulmonary osteoarthropathy (see Chapter 41). Preliminary data exist to suggest that bisphosphonates, such as oral clodronate or parenteral pamidronate, might be helpful in reducing bone pain from metastatic disease [15,17].

Pathological fractures of long bones are fortunately an infrequent occurrence in lung cancer. When they do occur they are almost always situated in the femur or the humerus. An orthopaedic opinion should be sought unless the patient is very close to death, as otherwise internal fixation and postoperative radiotherapy need to be considered. Sometimes prophylactic internal fixation is carried out when a large lytic metastasis is found in a weight-bearing long bone, this again being followed by radiotherapy. Patients with spinal instability secondary to destructive metastatic bony involvement may require orthopaedic stabilization followed by radiotherapy.

Those with spinal cord compression may be treated by surgical decompression and stabilization or by radiotherapy or both. Surgery is more likely to be undertaken in those with paraplegia or urinary retention of less than 24 h duration, when the block on magnetic resonance imaging or CT involves less than three contiguous vertebral segments and when the patient's life expectancy is likely to be more than a few weeks [18].

### Intractable pain

Pain in lung cancer that persists despite treatment with large doses of narcotic analgesics is unusual, 80% of patients responding to the measures outlined above. Occasionally, pain is difficult to control and alternative methods may be required to achieve adequate relief. Morphine is usually effective in controlling 'tissue-damage' (or nociceptive) pain, in which the pain is produced by the stimulation of nerve endings in non-neural tissue, whereas it tends to be ineffective in neurogenic pain (e.g. trigeminal neuralgia, postherpetic neuralgia, thalamic pain and pain from brachial plexus involvement by tumour), in which impulses are produced as a result of neural dysfunction and do not follow classic pain pathways. The reasons for the occasional resistance of tissue-damage pain to the action of morphine may be related to the ratio of one of its opiate receptor-binding metabolites (morphine 3-glucuronide) to another (morphine 6-glucuronide) in different patients, the former tending to antagonize analgesic activity whereas the latter is itself a potent analgesic. Thus those with a high ratio of 3-glucuronide/6-glucuronide may be relatively resistant to the analgesic effect of morphine on nociceptive pain and may experience so-called paradoxical pain [19]. It has been suggested that these patients may be more responsive to methadone, which follows different metabolic pathways to morphine [20]. Patients with neurogenic pain may sometimes respond to a tricyclic antidepressant such as amitriptyline (for 'burning' discomfort) or to an anti-convulsant such as sodium valproate or carbamazepine (for 'shooting' pains). The analgesic effect of the tricyclic group appears to be unrelated to any antidepressant effect and these drugs (mixed reuptake inhibitors) seem to be more effective in this regard than the newer selective serotonin reuptake inhibitors such as paroxetine. The dose of amitriptyline should be started as low as 10 mg at night in order to improve patient acceptability, and should be titrated up at weekly intervals with proper explanation of its minor but tiresome adverse effects. Low doses in the range 25–75 mg nocte are usually settled for and an added benefit is a degree of nocturnal sedation. Failure of amitriptyline to control opioid-resistant neurogenic pain may then lead to the substitution of sodium valproate, titrating up from 200 mg twice daily to a maximum of 1600 mg daily or, alternatively, carbamazepine starting with 200 mg at night increasing to 400 mg twice daily according to tolerance and response [21]. Dexamethasone 8 mg daily may reduce oedema around tumours that are compressing nerves.

One non-invasive technique that can be beneficial in chest wall pain is transcutaneous electrical nerve stimulation (TENS), in which patients must be taught properly how to deliver an electrical stimulus from a small battery-operated device by cutaneous surface electrodes either to

the painful area itself or to the nerve roots subtending that area. The stimulus, which the patient must feel, is transmitted by myelinated fibres to the spinal cord, thereby blocking the transmission of pain signals according to the gate control theory of pain [22]. It is not easy to know which patients are likely to respond and any beneficial effect may gradually decline over some weeks.

Nerve blocks are a matter for the specialist in pain relief and are carried out in appropriate circumstances as a last resort; these procedures should be planned after due discussion with the patient and the close relatives. They involve the injection of a neurolytic substance such as phenol or alcohol into the immediate proximity of the appropriate nerve trunk or root, with permanent alteration of nerve function [23]. The likely effects, which may be motor as well as sensory, may be simulated if a local anaesthetic block is used first. Intractable thoracic pain may respond to paravertebral or intercostal nerve block. Another technique for nerve block involves the use of a cryotherapy probe. Clearly, the source of the pain needs to be accurately determined and the destruction of nervous tissue selective in order to relieve pain successfully and to avoid motor damage. Dorsal sensory nerve roots may be interrupted by radiofrequency thermocoagulation, a technique that can also be used to carry out a percutaneous spinothalamic tractotomy. The application of these specialized procedures depends upon local interest and expertise but are seldom required in the management of lung cancer.

### Side-effects of narcotic analgesics

Patients frequently react badly to the prospect of being prescribed strong opioid analgesics, fearing that such treatment will 'drug them up' and render them incapable of all normal activity. They can be reassured on this count but should be warned that they may feel some drowsiness for the first 3 days or so. Effects on cognition are minimal once patients have been established on a stable dose and such patients should be permitted to drive should they so wish [24]. However, they should not drive when morphine is being started or increased in response to worsening pain [25].

Nausea or vomiting should be anticipated and may occur at the onset of treatment in up to two-thirds of patients. This can be prevented by the use of cyclizine 50mg or metaclopramide 10mg, each taken three times a day before meals. Haloperidol 1.5mg at night or twice daily may also be effective. These symptoms often subside spontaneously so that it is possible to withdraw the antiemetic within a few days.

Constipation is an inevitable consequence and the main nuisance of opioid analgesics. It should always be anticipated, whenever these are used, by the use of regular laxatives and patients should be forewarned. This aspect of

management is important and is dealt with below in more detail.

### Cough

A cough causing distress in terminal lung disease requires symptomatic treatment and, in addition, an explanation of the cause of the cough, coupled with reassurance that it is not going to cause choking or suffocation; a description of how it can be dealt with does much to help the patient's flagging morale. Assuming that the patient is not already taking morphine, codeine linctus 30mg three or four times daily can be tried initially. Patients in whom this is ineffective may be started on morphine, which can be titrated against response in the manner described above for pain. Methadone may be effective for night-time cough as it has a relatively long half-life.

There are a number of other symptomatic remedies that may be tried for additional relief. These include inhalations of benzoin tincture, one teaspoonful of which is put in a pint of hot water and the vapour breathed in by the patient from a Nelson's inhaler. The sensation of warm moist aromatic air is comfortable and may assist difficult expectoration. Sometimes the patient may feel the presence of viscid sputum that has great trouble in breaking free and, if a moist inhalation is ineffective, carbocysteine or another mucolytic agent sometimes produces symptomatic relief, although the cost of such preparations may outweigh their benefit. Simple change of posture and physiotherapy may also help these patients, who may be advised to try lying with the affected lung uppermost in order to facilitate the drainage of obstinate bronchial secretions. Advanced bronchioloalveolar cell carcinoma may unusually produce extremely copious and salty-tasting sputum, the sheer volume of which provides the patient with an exhausting and unbearable problem that is best dealt with by regular and increasing doses of morphine.

Inhalations of nebulized solutions of local anaesthetic may prove effective in intractable cough where other measures have failed. They suffer from the disadvantage of anaesthetizing the mouth and pharynx so that fluids or food may be inadvertently aspirated if taken within 1 h of the dose. Lidocaine (lignocaine) up to 5mL of 2% solution every 6 h may be used; alternatively, bupivacaine 0.25% solution has been recommended at a dose of up to 5mL every 8 h [26,27].

### Dyspnoea and associated symptoms

As with other respiratory symptoms in the terminally ill, the advice that treatment for shortness of breath is available and effective and that support is at hand may provide reassuring comfort. Relaxation techniques and simple measures such as the provision of a fan may increase

comfort. Sometimes breathlessness in advanced malignancy may be treated by attention to the cause, such as those listed below.

1 Obstruction of a large central airway by tumour that may be responsive to radiotherapy, laser treatment or stenting (see Chapter 41). Stridor in this situation may also be temporarily relieved by breathing a commercially available mixture of helium and oxygen (4:1). Dexamethasone 16 mg daily may also help.

2 Restriction of the movement of the affected hemithorax by the presence of a pleural effusion, in which case relief may be obtained by thoracentesis (see Chapter 43). In both these cases the clinician has to make a judgement on whether active intervention will improve the patient's comfort. If the end is seemingly very close, then invasive measures are probably unwarranted. Sometimes surprisingly large effusions may occur in the absence of symptoms, in which case they should be left alone. At other times simply changing the posture of a recumbent patient with unilateral lung disease so that the 'good lung' is dependent improves oxygenation [28].

When reaccumulation of a symptomatic effusion occurs, further aspiration is merited; if the reaccumulation has been rapid, some form of sclerosant such as 500 mg tetracycline added to 50 mL of normal saline and 10 mL 1% lidocaine in a 60-mL syringe can be introduced intrapleurally after drainage, left overnight and any residual fluid removed the next day [29,30]. A slurry of talc in saline may be similarly used. Even with lidocaine and other analgesia, this procedure is often painful and a useful outcome not always forthcoming.

Sometimes dyspnoea may result from associated disease such as pneumonia or an exacerbation of chronic bronchitis; symptomatic relief using nebulized bronchodilators may be achieved in the latter case. The giving or withholding of antibiotics depends on the physician's assessment of whether the symptoms of infection are causing distress and whether further prolongation of life is likely to be wished for by either the patient or close relatives. It may sometimes be important to gain some extra time if, for example, a close relation is travelling from afar or if legal or other affairs need settling. At other times pneumonia may provide a welcome release to all concerned.

Frequently in terminal respiratory malignancy, treatment cannot usefully be addressed to the cause of breathlessness, which may be diffuse neoplastic spread, and remedies are directed to the symptom of dyspnoea itself. Once again a strong opioid analgesic such as morphine is required and can be used in similar doses to those already described for the relief of pain. This has the advantage of suppressing respiratory drive centrally and of decreasing anxiety and distress. It also relieves any associated chest pain, which may itself be making breathing difficult and uncomfortable. The association of chronic obstructive

airways disease with advanced malignancy is not a contraindication to the use of morphine in a patient whose life is drawing to its close and who is experiencing significant dyspnoea.

Nebulized morphine or diamorphine has been used in attempts to control dyspnoea. Reports of its efficacy in cancer have been based on uncontrolled observations and are therefore open to question [13,31,32]. As might be expected, doses used vary widely, from 5 mg morphine added to 5 mL of normal saline to as much as 50 mg diamorphine. Conflicting results have been reported when this form of treatment has been used in other patient groups, including those with dyspnoea due to severe chronic lung and heart disease [33–35]. Benzodiazepines such as diazepam starting with a small dose such as 2 mg three times daily may also help to alleviate the anxiety associated with breathlessness and are worth trying. Sublingual lorazepam 2.5–5 mg has a rapid onset of action and a short half-life, lending itself to self-administration for the management of more acute dyspnoea that may be associated with panic.

Although the provision of oxygen may have little to offer in a physiological sense, the availability of an oxygen cylinder to a person who feels the need for 'more air' may be a source of some comfort to both the patient and family. This having been said, the proper provision of morphine is likely to reduce such feelings of need for what is often a psychological crutch.

As a dying patient weakens to the extent that coughing is no longer easy, loose secretions may be heard to rattle in the larger airways during respiration. By this time the patient's conscious level may be sufficiently depressed for the sensation to go unnoticed and it may be a greater source of distress to those about the bed who have to listen to it. Repositioning of the patient may help in this respect. The traditional remedy is the atropine-like substance hyoscine hydrobromide, given at a dose of 400–600 µg every 4 h subcutaneously as necessary or infused subcutaneously at a dose of 1.2–2.4 mg over 24 h. The rationale for this is that it dries bronchial secretions and that it is less likely than atropine to cause central nervous system stimulation. The extent to which it is effective is somewhat doubtful.

## Dehydration

Whereas it is good practice to keep patients who still have a chance of recovery well hydrated and nourished when they are too ill to swallow, this line of action makes little sense in a patient who is dying; indeed there is a strong body of opinion among hospice workers that dehydration is symptomatically beneficial in terminal patients, reducing the problems of urinary incontinence and also those of loose bronchial secretions referred to in the previous section [36]. It is sensible to avoid intravenous or nasoga-

tric tube rehydration in such circumstances. Attention can instead be paid to mouth care [37], keeping the patient's mouth moistened with 2-mL aliquots of cool water by syringe or with chips of ice.

### Haemoptysis

The small haemoptyses that occur commonly in association with lung cancer are a source of anxiety to the patient and firm reassurance that they do not presage a major bleed may be all that is required. If the haemoptysis persists and is of sufficient volume to continue to cause the concern, palliative radiotherapy may very well be helpful and should be requested (see Chapter 41). In the mean time, an oral haemostatic agent such as tranexamic acid or etamsylate (ethamsylate) that tends to reduce capillary bleeding can be tried, although there are no published controlled trials to support the clinical impression that they may help in this situation. A major haemorrhage is rare, but should one occur and if the patient survives and remains conscious, an immediate intravenous injection of 5–10 mg morphine is advisable and may if necessary be followed by a similar dose of diazepam by the same route in order to reduce fear and awareness. The patient should not be left alone and blood stains on the bed linen should be covered with red or green towelling to reduce further alarm [31].

### Constipation

Constipation is an inevitable consequence of any terminal illness that is protracted and is a cause of considerable anxiety to patients unless dealt with adequately. It is best to anticipate it and treat from an early stage with laxatives, particularly in patients taking narcotics or other constipating drugs. Opioids are one of the major causes of constipation in terminal illness, tending to increase smooth muscle tone with suppression of peristalsis while also increasing sphincter tone and reducing the awareness of rectal distension. Other factors contributing to constipation are anorexia, leading to a poor intake, dehydration, inactivity and general debility. Hypercalcaemia or the use of tricyclic antidepressants may also be contributory and the possibility of spinal cord compression should not be forgotten.

It is routine to combine a stool-softening laxative with a bowel stimulant, since a single agent of either class may produce an inadequate effect. There are numerous laxatives available, the liquid preparations being referred to by some patients as 'engine oil'. It is best to become familiar with a few but to be prepared to make some adjustments according to patient preference.

Although liquid paraffin is avoided in other longer-term situations because of its propensity to cause lipoid pneumonia, it is a suitable stool softener for use in patients

with terminal conditions, a dose of 10–30 mL being taken on retiring (as combined with magnesium hydroxide in Milpar). Other agents that have stool-softening effects include the bulking agents methylcellulose, which may produce bloatedness, and lactulose, which draws water into the bowel osmotically and which has a sickly taste. Examples of bowel stimulants include senna taken in tablets or as granules 15–30 mg or bisacodyl tablets 10 mg, both taken on retiring. These preparations have effect within the following 10–12 h [38]. Another very useful alternative is the stimulant dantron (danthron), combined with a stool softener such as poloxamer (i.e. codanthramer) or the surfactant docusate (i.e. codanthrusate), both being available as capsules (two at night or up to three four times daily) or as a suspension usually to be taken at night.

If the patient remains constipated for more than 2 days and examination reveals formed stools in the rectum, then two glycerol suppositories may be used for their stimulant effect, an alternative stimulant suppository being bisacodyl 10 mg which may produce rapid results. Both of these should act within an hour or so. If examination shows the rectum to be empty then a high phosphate enema, delivered via a soft catheter inserted 20 cm into the rectum to prevent immediate expulsion, may be used. Unusually an impacted rectum requires manual evacuation combined with some form of sedation. High soap and warm water enemas are sometimes required for gross constipation that has been neglected but this is also unusual.

### Miscellaneous symptoms

#### Anorexia

Anorexia and weight loss are frequent accompaniments of advanced malignant disease. The mechanism is obscure but is likely to be multifactorial, apparently being related to the production of cytokines and to tumour type rather than size. Some predisposing factors are readily identifiable and can be dealt with appropriately.

#### Nausea

Nausea resulting from opiates may be controlled with an antiemetic such as cyclizine (50 mg) or metoclopramide (10 mg), each to be taken three times a day before meals. Haloperidol 1.5 mg at night or twice daily may also be effective. Mouth care should be meticulous. Nausea and vomiting occurring as a result of chemotherapy may be effectively prevented by a selective serotonin receptor antagonist such as ondansetron [39]. This drug, as well as granisetron and tropisetron, acts by antagonizing 5-HT<sub>3</sub> receptor-mediated activation of afferent gastrointestinal neurones before they can trigger the brainstem centres

that initiate vomiting. Prednisolone 15–30mg daily frequently improves the appetite as well as having a mild euphoriant effect but does not result in lost weight being regained [40]. An alcoholic drink before meals may also be helpful. Dexamethasone reduces vomiting due to raised intracranial pressure from brain metastases (see below).

### Dysphagia

Dysphagia may be caused by a sore or dry mouth and may be managed with regular mouth rinses. If the patient is too weak to drink, 2 mL of water can be placed in the dependent side of the mouth with a syringe every 30 min or small pieces of ice may be used for the same purpose. Nystatin suspension 200 000 units four or five times daily may be used if oral thrush is present; alternatively amphotericin lozenges may be sucked. Ketoconazole 200 mg daily for 5 days is effective in difficult cases and fluconazole 50 mg daily for 1–2 weeks may be taken if oesophageal candidiasis is suspected or confirmed by barium swallow. The latter drug may be taken long term in patients with recurrent candidiasis associated with AIDS. Oesophagitis occurring following irradiation of the mediastinum may be treated with the proprietary antacid Mucaine, which contains a local anaesthetic oxetacaine (oxethazaine), and patients can be reassured that the discomfort will resolve completely in a week or two. Extrinsic oesophageal compression may result from mediastinal lymph node metastases or direct extension of a tumour into the mediastinum, the diagnosis being confirmed by a radiographic contrast swallow examination. How this is managed depends not only on the general fitness of patients but also on their views about what they would like to be done. When symptoms are mild, a blender may produce food of the right consistency to pass the obstruction, but eventually dysphagia and regurgitation for liquids including saliva will occur and aspiration pneumonia will supervene. If the patient wishes for nothing further to be done, then heavy sedation with morphine is appropriate in order to relieve their inevitable distress. However, if the patient is sufficiently fit, a thoracic surgical opinion can be obtained concerning the insertion of a palliative oesophageal tube, or palliative radiotherapy may be considered.

### Hiccups

Hiccupping is occasionally very persistent and troublesome in a small minority of patients with thoracic cancer. There are a large number of both central and peripheral causes, including gastric distension and mediastinal invasion by tumour. Physical stimulation of the back of the pharynx with a nasal catheter, iced water or the like may stop it and is worth trying [41]. Gastric

distension may be caused by gross hepatomegaly ('squashed stomach syndrome') and patients may be helped by practical advice to take small meals followed by 10 mg metoclopramide, which promotes normal gastric emptying. Activated dimeticone (dimethicone), an antifoaming agent, may also be used as a deflatulent in such cases, 10 mL being taken after meals. Chlorpromazine may be necessary for a severe episode of hiccups but is sedating and may cause postural hypotension, particularly in the elderly. It can be tried orally at first at a dose of 10–25 mg three times daily followed by a single slow intravenous dose of 25 mg if necessary. Other treatments sometimes used include carbamazepine, nifedipine, baclofen, haloperidol, ketamine, phenytoin and, in extreme cases, intravenous lidocaine [42,43].

### Sleeplessness

Sleeplessness may be due to a readily identifiable cause such as pain, in which case appropriate analgesia can be given. Where no such cause is evident, a benzodiazepine such as temazepam 10 mg may be given. Alternatively, nitrazepam 5 mg at night may provide some anxiolytic effect the next day as this has a longer half-life. Benzodiazepines may produce confusion in elderly patients in whom clomethiazole (chlormethiazole) two capsules at night is a useful alternative.

### Symptoms due to cerebral metastases

Nausea, vomiting and pain are dealt with as outlined in earlier sections of this chapter. The decision about whether to treat more actively using steroids and/or radiotherapy must take account of the patient's general situation as well as the attitude of any close family. No particular benefit may be seen in achieving a temporary respite in a patient who is clearly in the terminal phase of the disease. In other circumstances, more active management might be considered to be in their best interests. Dexamethasone 16 mg daily for 1–2 weeks is given in order to reduce oedema around metastases. If there is no response, the drug can be rapidly tailed off. If response does occur, the dose may be reduced by 2 mg per week to a 'maintenance' dose of about 4 mg daily. Recurrent symptoms sometimes respond to an increase in the dose to its original level. A response to dexamethasone may encourage the radiotherapist to treat with palliative cranial irradiation. The opposite usually deters them from intervening.

### Epileptic seizures

Epileptic seizures are treated in conventional manner with an oral anticonvulsant such as phenytoin 150–600 mg



daily. If the parenteral route is required, diazepam 10 mg may be given intravenously over 2 min to control a persistent fit and may be repeated if necessary. An emulsified form, Diazemuls, is best used to avoid thrombophlebitis. Another option if intravenous access is difficult is to give diazepam as a rectal solution, also at a dose of 10 mg. Phenobarbital (phenobarbitone) may then be given twice daily intramuscularly if the oral route remains unavailable. When the patient is in the terminal phase, fits may be controlled by subcutaneous midazolam, given by syringe driver at a dose of 20–40 mg per 24 h. This is also suitable for very restless patients (see below) and is compatible with diamorphine.

### Confusion, restlessness and delirium

Confusion in elderly ill patients is often attributed to their inability to adapt to changed circumstances or an altered environment. Whether or not this is true, it is worth spending some time thinking through possible physical causes of confusion that might be amenable to treatment. Psychotropic drugs, including narcotic analgesics, benzodiazepines and corticosteroids, should all be suspected. Metabolic disturbances, such as uraemia, hypercalcaemia or a low blood glucose due to regular oral hypoglycaemic therapy, may be responsible for disturbances of consciousness. Confusion or agitation may also arise as a result of systemic infection, hypoxaemia or urinary retention. Sedative drugs are required if confusion cannot be settled by identification and treatment of any such cause (provided that there is no response to simple reassurance) and if it is causing distress or if it is likely to result in physical injury to the patient or anyone else. In mild cases of confusion and restlessness, haloperidol 1.5–5 mg at bedtime may be sufficient. For severe delirium, haloperidol 5–10 mg may be given subcutaneously or intravenously, being repeated hourly until the patient is settled, after which it may be continued orally if necessary. Alternatives are thioridazine 25 mg three times daily, which has to be taken orally, and chlorpromazine 50 mg intramuscularly or orally followed by 25–50 mg three times daily, the latter drug being useful if more sedation is required. Levomepromazine (methotrimeprazine) is a more heavily sedating alternative for restlessness and confusion in the terminal stage, being infused subcutaneously at a dose of 20–100 mg per 24 h. When necessary this can be combined with diamorphine in the same syringe driver. A good nursing technique is invaluable in dealing with such patients and every attempt should be made to understand and calm them. It should never be assumed that patients cannot understand what is being said in their presence and the relatives feel better if they can be given a physical explanation for the disturbance rather than be left with the impression that the doctors and nurses do not know what is going on.

## Psychological aspects

Attempts to unravel the psychology of dying are beyond the scope of this chapter. Suffice to say that the journey may be charged with many strong emotions and that appropriate action on the part of those in a position of care may work strongly to diminish the unpleasantness and to provide comfort and support in the face of suffering [44]. It is dangerous to generalize about the nature of an individual's response to the revelation that life will shortly end, but nevertheless such generalizations have been made and are widely quoted.

Kübler-Ross [45] describes five stages: first denial and isolation, then anger followed by bargaining, then depression and finally acceptance, the passage through these stages representing a gradual process of realization. In reality many reactions are encountered and they do not necessarily occur in any particular sequence. Initial incomprehension is almost invariably followed by apprehension and various mental acrobatics that are apparently performed to avoid the perception of unpleasant reality. Bargaining is said to occur if patients 'do deals' with their own conscience to behave in a certain manner in order to improve the chances of a more successful outcome. Denial may be tested by asking patients whether they have times when they feel that they may not 'beat' the illness after all. Patients are likely to experience sadness, depression or despair but may also display hopefulness and optimism and may slip in and out of these different emotions from day to day as they seek to cope with their illness. It is to be hoped that the inevitability of new circumstances is eventually accepted and that this acceptance brings with it an inner tranquillity. Certainly this peace of mind is the major objective of terminal care, as it brings comfort to the patient and is a source of strength to the family, whereas anger and resentment does the reverse. As has been previously emphasized in this chapter, it is generally thought that kindly, open and supportive discussion helps the patient to achieve acceptance.

## Organization

Most patients with terminal cancer die in hospital in the UK, and the type of terminal care that they receive is influenced not only by the training and attitudes of those who look after them but also by the other demands inevitably placed upon the staff of busy acute wards. One of the achievements of the hospice movement has been to promote discussion and to disseminate a greater understanding of the needs of the dying [46]. Whereas the acute hospital ward cannot produce the same physical environment, nevertheless it should be possible to transpose some of the organizational practices and the general ethos of the hospice or 'continuing care' unit to the management of terminal patients in any hospital. Such care depends upon

good liaison between the senior nurse on the ward, the medical team and the social worker, and time spent talking not only to the patient but also to the family and the general practitioner is in itself therapeutic. Physiotherapists and occupational therapists also play an important role in helping the patient to remain as independent as practicable. The family should be allowed to come and go as they please and should be made to feel welcome on the ward, rather than being restricted to predetermined visiting hours. Their anxieties should be listened to and an attempt should be made to deal with them in a well thought out manner. When practicable, home visits or excursions with the relations should be allowed and whenever possible the patient should be discharged with the provision of adequate social support and district nursing care. Specialized care such as that given by Macmillan nurses may be made available and provision should be made for readmission if the need arises.

The anxieties of patients should be appreciated; many fear separation from their family and home and are happier in their own surroundings if this can be arranged. A fear of dependence on others is also common and this may be alleviated by avoiding an impatient or patronizing attitude, so that care is delivered as though it was a privilege rather than a chore. Concerns about how the surviving relatives will cope may be prominent and if voiced are best dealt with in a practical manner, sometimes with the help of a sympathetic social worker, hospital chaplain or other minister of religion. A study that asked patients from whom they most wanted emotional support and from whom they most got it indicated that their first choice was their doctor and that senior doctors were perceived as providing more emotional support than junior colleagues, leading to the conclusion that this form of comfort stemmed from what was thought to be the provision of accurate and authoritative information [47,48].

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# MEDICOLEGAL ASPECTS OF LUNG DISEASE

ANTHONY SEATON

At its simplest, the law exists to protect citizens, their property and the environment within which they exist from harm due to the actions or omissions of others. Doctors may become involved in legal processes in their role as citizen, as when they are sued by an aggrieved patient or, fortunately rarely, accused of a criminal offence such as unlawful killing, or in their role as medical expert when asked to give evidence about the causation and consequences of disease. This chapter is concerned with the latter role, relating particularly to lung disease.

The great majority of cases in which a medical expert is likely to be involved occur under the civil, as opposed to the criminal, law. The difference is important with respect to the legal definition of proof, a matter not always appreciated by doctors. In criminal law, in which a crime is alleged to have been committed, it is necessary for the prosecution to prove a case 'beyond reasonable doubt'. This form of proof is similar to that with which we are familiar in our clinical role, in which we pursue the investigation of a patient until fairly certain that we know the diagnosis. In contrast, in civil proceedings it is only necessary for the litigant (sometimes referred to as the plaintiff or pursuer) to prove the case 'on the balance of probabilities', i.e. greater than 50% likelihood or more likely than not. This test applies to all matters in contention, such as the presence of a particular disease, the likelihood of something having caused it and whether appropriate measures were taken to prevent it. In most jurisdictions, civil cases are argued before a judge, both parties being represented by lawyers who examine their own witnesses and cross-examine those called on behalf of the other side. The judge arrives at a verdict and decides the amount of the award in damages. In contrast, in the USA all cases are argued before a jury, which is responsible not only for the verdict but also for assessing the amount of the award. In general the award of damages takes account of all financial losses, both actual and likely future ones, in terms of earnings, expenses and so on, and of pain and suffering. Again, in the USA an additional sum is often added by the

jury, so-called punitive damages, often adding considerably to the award.

A further difference between the USA and most other jurisdictions is the method of obtaining the services of a lawyer. In most countries, the transaction involves a fee for service, usually calculated on the basis of guidelines issued by the relevant professional body. This means that the costs of litigation are considerable and, as has been found by many who have sued unsuccessfully for libel, ruinous. The costs may be recovered if the action is successful, at the discretion of the judge, but if the litigation is unsuccessful they fall upon the litigant. Thus only the very wealthy can usually afford to embark on legal action unsupported by some other agency. In the USA this problem has been overcome by the introduction of a system of contingency fees, lawyers agreeing to act for a client on a speculative basis with an agreement that they will pay the costs if unsuccessful but will take a percentage of the damages if successful. The introduction of a similar system is likely in the UK, and has already been introduced by some law firms. From the experience in the USA it seems to be associated with inflationary pressures on court settlements and acts as a stimulus to an ambulance-chasing form of legal behaviour. However, it does ensure that anyone with a reasonable case can obtain legal representation. In the UK, most injured workers manage at present to obtain support from their trade union, a powerful reason for being a member of one, or from the state through legal aid. Legal aid is means-tested and is likely to be available to fewer people in future as part of an effort to control government expenditure.

## Compensation

### No-fault benefits

It is not uncommon for a doctor to be asked by a patient if he or she is entitled to compensation for some work-related lung disease. In these circumstances, it is wise to advise the patient to consult a lawyer, preferably through

the trade union. If the patient is not a member, limited advice may be obtained from the Citizens' Advice Bureaux or similar organizations. However, there is some useful advice that a doctor can give. Most importantly, doctors should be aware of the system of no-fault benefits available in their country or state. In the UK there is a state-funded system of industrial injuries benefits available to all employed people (but not self-employed, who have to make their own insurance arrangements) who suffer an injury or illness as a result of their work, funded from the social security budget. While any work-caused injury is potentially eligible for compensation, benefits for illnesses are only available if the illness is prescribed, i.e. on a list agreed by Parliament. This list is updated regularly as a result of the recommendations of an independent committee of experts, the Industrial Injuries Advisory Council, who base their advice on the medical, mainly epidemiological, evidence relating diseases to work. The lung diseases currently prescribed on this list are shown in Table 61.1.

Before advising a patient to seek industrial injuries benefit, the doctor should ensure first that the patient is or was employed as opposed to self-employed. It is also the case that this system of compensation is not available to

members of the armed services, who may however be able to obtain war pensions instead. Secondly, it is necessary to be reasonably sure that the disease was caused, and not simply made worse, by work. Thirdly, the illness must be one that is on the list of prescribed diseases and the patient must have been working in a trade in which a relevant exposure is likely to have occurred. Alternatively, if the illness occurred as a consequence of an accidental exposure, say to a toxic gas or fume, benefits may be claimable for an industrial injury rather than for a prescribed disease. If these conditions are fulfilled, the patient should be told that it is worth applying for benefits and an explanation of the process given. Application must be made by the patient to the local branch of the Department of Social Security (DSS), where a form needs to be completed, indicating the disease being claimed for and the work that the patient has been doing. There then follows an interview with an insurance officer, whose job is simply to ensure that the applicant has indeed been employed and is eligible for benefits if the prescribed disease is present. The papers are then sent to the regional panel of DSS doctors specializing in respiratory diseases, whose role is to determine, on the balance of probabilities, whether the patient has the prescribed disease and to determine the extent of disablement ascribable to it. This determination is expressed in terms of loss of faculty, i.e. loss of the functional abilities of a healthy person of the same age and sex, account being taken of the employability of the individual as a result of the illness. A percentage figure for loss of faculty is arrived at and this is usually applied by the insurance officer to calculate the benefit payments. A sum for 100% disability is agreed by Parliament each year. In some circumstances, a lump sum payment may be made to the claimant, but more usually an annual pension is awarded and this may be adjusted after further medical assessments in the light of improvement or deterioration in the patient's condition. Such reviews usually take place every 2 years. If a patient is unsuccessful in claiming benefit, there is a mechanism for appeal to a Medical Appeals Tribunal, chaired by a lawyer and including doctors with special experience of lung disease.

This system of state benefits was introduced at a time when injured workers were effectively unable, because of the costs of litigation and lack of a system of social security, to obtain any compensation and were often rendered indigent. It remains in force now despite a comprehensive system of sickness benefits available to those unable to work for whatever cause, and therefore provides people injured at work with benefits additional to those available to someone injured, say, in a domestic accident or suffering from some illness as a result of ill-fortune. It may therefore be regarded as something of an anomaly, and in recent years there has been a progressive erosion of the value of the benefits payable. At one time it served to limit the numbers of people seeking redress through the courts, but

**Table 61.1** Prescribed occupational lung diseases in the UK.

Disease	Prescribed occupation
Anthrax	Contact with animals or their products
Tuberculosis	Medical or laboratory contact
Extrinsic allergic alveolitis	Agriculture, malt work, mushroom growing, bird handling, bagasse handling
Asthma	Exposure to a sensitizing agent
Byssinosis	Contact with cotton or flax dust
Various poisonings	Exposure to mercury, cadmium, nickel carbonyl, beryllium, nitrogen oxides
Pneumoconiosis	Mining, quarrying, ceramics, foundry work, asbestos handling, etc.
Mesothelioma	Asbestos handling
Lung cancer	Nickel refining, asbestos handling (if asbestosis or diffuse pleural fibrosis is also present), and in the presence of silicosis
Nasal cancer	Nickel refining, woodwork, shoe manufacture
Bilateral pleural fibrosis	Asbestos handling

For full details, see *Notes on the Diagnosis of Occupational Disease* (1979) HMSO, London; and leaflets published by the Department of Social Security: NI 3 (pneumoconiosis) and NI 238 (asthma).

more recently an award of benefits is often taken as an indication that a claim in civil law is likely to be successful; this is far from always the case, since in civil litigation it is necessary not only to show that the disease is present and was caused by the work but also to prove that it occurred as a consequence of the employer's negligence. If a patient is successful in obtaining damages in a civil case, any state benefits paid in respect of the illness are repayable.

### Civil litigation

When patients wish to sue their employer, the main role of the doctor is in advising them whether they have a work-related disease or not, and it is then up to patients to seek advice from a lawyer. The date at which this advice is given should be recorded, since in most jurisdictions there is a limited time available from the moment the patient became aware that the illness was caused by work for the lawyer to lodge a claim against the employer(s). This so-called time bar sometimes becomes an issue when a patient only decides to see a lawyer after hearing of a successful claim by a colleague, most commonly for a relatively trivial condition such as pleural plaques.

The process of civil litigation involves the issue of a writ, or a statement that the litigant is suing the employer for a stated sum in compensation for suffering and loss incurred as a result of illness caused by the negligence of the person sued. The negligence is defined in terms of the defender's failure to comply with the law as it obtained at the time the injury occurred. This is then answered by the lawyers acting for the defender, who generally enter a robust denial of any negligence or of any knowledge that the litigant has indeed suffered any injury. These documents appear to represent irreconcilable views but can be taken to be opening moves in a prolonged game in which evidence is obtained and challenged, leading in most cases to an agreement between the parties prior to appearing in court. Occasionally, however, the case actually reaches the courts and is argued before a judge, witnesses being examined and cross-examined by advocates. This outcome should always be anticipated by any doctor writing a report for a lawyer.

Lawyers, like doctors, specialize and some firms are particularly effective in the area of work-related illness. The good lawyer seeks the opinion of a doctor recognized as an expert in the field of lung disease as to what the illness is, what is likely to have been the cause, to what extent the patient is disabled and the likely prognosis. In general, advice is not sought from a chest physician as to whether or not the person being sued was negligent, since this is a legal matter. However, the lawyer may require advice about the state of medical knowledge at the time the injury is alleged to have occurred in order to determine whether the defender could reasonably have foreseen the consequences of the alleged negligence. Both parties to the

litigation seek advice independently from experts, both in respect of diagnosis and disability and often also in relation to conditions in the workplace. Having obtained such evidence as they require, they usually consult with a trial lawyer (barrister in England, advocate in Scotland) and decide how to proceed. The costs of a court hearing are considerable, and in most cases settlement can be arrived at by a process of discussion (or a game of cat-and-mouse) between opposing lawyers, the decision often being reached shortly before the hearing and indeed sometimes on the first day. This settlement is usually reached on the basis of a payment, including costs, by the defender to the litigant without accepting responsibility for the injury. If after such an offer is made and refused the case proceeds to trial and the litigant is subsequently awarded a smaller sum in damages than that offered, the responsibility for costs of the action may fall on the litigant. There is thus a good incentive to accept a reasonable offer.

If the case proceeds to trial, the lawyers state their positions before the judge and call witnesses. All witnesses, whether giving evidence about conditions in the workplace at the relevant time or an expert opinion, are led through their evidence by the lawyer for whom they are acting and then cross-examined by the lawyer for the other side, whose job it is to discredit them. At this point, every word and opinion written in a report may be subject to the most detailed inquisition. Any papers quoted in support of statements by an expert may be dissected, and the opinions put forward by one doctor are likely to be challenged by those of another. The whole process requires not just a cool head but also an unshakeable ability to justify all one says and all one has already committed to paper. It is never an enjoyable experience and can be likened to an anatomy viva prolonged, sometimes, for a day or two! This possible outcome should be borne in mind by anyone writing a report for a lawyer. With the agreement of the judge, witnesses may be recalled to deal with matters brought up in subsequent evidence and some trial lawyers may ask experts to assist them through the course of the trial with informal medical advice. Once the evidence has been heard, the lawyers summarize their cases and the judge eventually delivers a decision and, if finding for the plaintiff, decides on an appropriate sum in damages and costs.

The system in the USA differs in several ways. The trial lawyer may often conduct both the investigative and trial parts of the action, and is likely to wish to maximize the chances of success by giving advice to the expert on such matters as how to address a jury, how best to present a case and so on. Witnesses are often required to make a deposition before the case comes to court; lawyers call this 'being deposed' and it involves being questioned for a prolonged period by the lawyer from the other side in order to find out what evidence will be given and just how knowledgeable the witness really is. If the case comes to trial it is

argued before a jury and all sorts of stratagems are used to convince the jurors of a witness's veracity and expertise. The process is undoubtedly less gentlemanly than the British version, and clearly the lawyers for the litigant, being on a contingency fee, have a lot more at stake than just professional pride. In both systems, however, when a case comes to court the arguments are usually finely balanced and the most important factors in determining the outcome are the expertise and skill of the advocate and the competence of the expert witnesses.

### **Role of the doctor as expert**

From what has been said above, a doctor should not agree to write an expert medical opinion unless he or she has a particular knowledge of the subject and should confine any opinions to those pertaining to these areas of expertise. There may be a temptation to overstep these limits in support, perhaps, of one's patient but this should be resisted for fear of having to justify them in the witness box in the face of conflicting evidence from a real expert and from the literature. A doctor is approached by lawyers from one or other side, and here again there is a temptation to slant one's evidence in favour of that side. While this is understandable and may indeed be encouraged by some lawyers, it is unwise since it leads to difficulties in justifying the opinion under cross-examination and possible loss of credibility as an expert. An expert should give as honest and impartial advice as possible and it is for the lawyers to act as advocates. It can be argued that good lawyers want to know the truth, even if it does not support their case, since this helps to decide on settlement and thus minimize costs. This does not mean that an expert should not point out possible defences or weaknesses in the other side's case, where such matters fall within his or her field of expertise. In an ideal world, the opinions of experts about an individual patient should differ little, and this in fact is frequently the case with respect to disease and its causation. There is often greater scope for disagreement with respect to prognosis, though even here agreement is usually possible by compromise. Exchange of medical reports prior to trial, in the expectation of being able to resolve relatively small differences, is becoming more common in British actions and is a desirable tendency.

### **Expert medical report**

A report is written in response to a letter requesting advice from a lawyer, and that letter should ask the questions that the lawyer wishes answered. In general there are four: what disease does the client suffer from, is it likely that the illness was caused by the client's work, how disabled is the client and what is the prognosis? If the doctor is an expert in occupational medicine, the lawyer may

in addition wish to know whether the precautions taken to prevent disease were reasonable in the light of knowledge at the time in question. The letter may ask the expert to examine the patient or it may simply request an opinion on various records, statements by others and radiographs.

The format of the report is of course a matter for the individual doctor, although it is sensible to have one's personal style and stick to it in order to avoid neglecting any important matters. It is usual to head it with a note of the case and a statement of what was done and when. If the doctor has not previously worked for the lawyer requesting advice, it may be helpful to state one's qualifications, both formal and in respect of one's expertise in the case at hand, and it is usual to provide the lawyer with a short curriculum vitae. Clinical and research experience with respect to the alleged condition are relevant, as are any personal publications on the subject. However, it is worth noting that any such publications can appear in court at a later stage if they appear to contradict any part of the evidence given in the report or orally in court, and may result in dramatic loss of credibility! The author has come across a report written by an expert denying the existence of a condition that he himself had described some two decades previously, an act of carelessness that destroyed his case.

The report should then detail the findings from the history and examination of the litigant, from careful reading of any written material provided or from both. It is usually sensible to seek corroboration of the clinical history, which may be imperfect on account of forgetfulness or deliberate deceit, from hospital and general practice notes. The lawyer should be asked to obtain these prior to seeing the client if at all possible and they should normally be reviewed prior to writing a definitive report. Particular care should be taken over the occupational history, since this is crucial to determining if work was likely to have been responsible for the condition. If the illness is thought to have been caused by an acute exposure to toxic gas, full details of the episode are necessary together with their temporal relationship to the onset of symptoms. All available evidence as to what gases or fumes were involved, where the exposure took place and for how long, and what were the likely concentrations should be considered. Lawyers are often able to provide data sheets and witness statements in such circumstances and should be asked to obtain them if they are not available. It is of course essential to form an opinion on the health of the client prior to the accident and how it has changed as a result. In the case of illness thought to be due to longer exposure, as in the case of mineral dust diseases, a lifetime occupational history is essential, again making particular note of possible levels and duration of exposure to harmful substances. This information on likely exposures is often disputed in actions that reach the court, and



it is crucial to convince oneself that the individual's history is consistent with the disease that is present.

It is usual as part of the process of examination to include certain tests, depending on what has been done before. A chest radiograph is clearly essential in many cases, as are lung function tests. However, in the case of occupational asthma it is useful to remember that the legal test of proof is on the balance of probabilities, and such tests as serial peak flow rates and challenge with suspected antigen are rarely necessary. Indeed, challenge testing has potential hazards and should only be considered as part of a clinical rather than medicolegal investigation.

Having recorded the findings, it is usual to provide a commentary written in non-technical language. This is conveniently set out under headings corresponding to the questions asked by the lawyer. Thus, the first section might be headed 'What does the client suffer from?', the next 'What are the likely causes?', then 'How disabled is the client?' and finally 'What is the prognosis?'

In assessing disablement, a particular problem commonly arises when the litigant has two or more conditions. A sensible balanced judgement should be made as to which are the main contributors to disability. For example, it is not uncommon to see people whose disability has been attributed to pleural fibrosis when they have normal lung function but clear evidence of ischaemic heart disease. The author has seen patients with breathlessness due not only to this condition but also undiagnosed atrial septal defect and motoneurone disease, in all of whom an expert had confidently attributed the symptom to pleural disease. The patient with atrial septal defect was actually cured of his symptom as a result of entering the process of litigation, having missed this benefit from the normal medical process.

In discussing disablement, it is important to differentiate between impairment, disability and handicap. An abnormality of lung function is a measure of *impairment*, and is convincing evidence of lung disease if the tests have been done carefully and reliably. In this respect it is always wise to check the original traces if the tests were not done personally. However, it does not of itself provide a measure of *disability*, which takes account of the expected activity levels of a person of the same age and sex. A person with abnormal lung function may be free of disability because the impairment does not interfere with normal activities, while someone with normal lung function may be disabled because of psychological breathlessness due to anxiety about, for example, a spurious diagnosis. The level of disability is assessed from the history and its likely cause is judged by considering the results of the lung function tests. *Handicap* is a measure of the amount to which individuals are prevented from pursuing their normal lives and therefore takes account of their work. Thus someone with occupational asthma due

to spraying isocyanate paints may no longer show any impairment of function or disability but may be severely handicapped in the job market because of an inability to work in the paint-spraying trades. All these points and the subtle distinctions between them need to be considered in writing that part of the report that answers questions about level of disability.

The question of prognosis is often critical if the disease is proved, since it is an important factor in determining the level of damages. If available, serial lung function tests and radiographs from the client's records are invaluable in determining prognosis and should never be ignored. It is common for doctors to take unduly optimistic or pessimistic views, depending on which side they are appearing for. This is unwise, since cases often take years to come to court and it can be embarrassing to see someone hale and hearty whom one confidently predicted would be on his last legs, or vice versa. If possible, one's prognosis should be based on epidemiological and clinical studies in the literature as well as one's own experience. The prognosis should cover not only the disease or diseases in question but also any other disease that may follow in the future as a complication of the present illness or its causes. This is particularly relevant with respect to asbestos, where damages paid to people with benign pleural plaques takes account of the future possibilities of developing mesothelioma.

This section discussing the findings and their implications should then be followed by a succinctly expressed opinion that the writer would have no difficulty defending under cross-examination. There is the likelihood of challenge in all these parts of the report; the diagnosis and the cause are usually contested and there is plenty of scope for debate on level of disability and prognosis. This opinion should state in simple terms the views arrived at on each of these points. If there is insufficient evidence on which to arrive at a conclusion, even on the balance of probabilities, this should be stated and a recommendation for further medical or legal investigation should be made. In these circumstances it is usual to offer to write a supplementary report when the further information has been produced.

### Appearing in court

Receipt of a carefully argued report should assist a lawyer to decide whether the case is worth pursuing, abandoning or settling out of court. Whichever side the report is written for, a clear, honest and straightforward opinion is of much greater value than an equivocal one, even if it does not support the side who have requested it. If it is decided to pursue the case, nothing is likely to be heard for a year or two as various legal procedures are followed and further evidence obtained. The most likely outcome is agreement to settle, usually just before the hearing. Before

this, it is usual for the lawyer to have a conference, and if the medical evidence is in dispute the doctors who have written reports are usually asked to attend. This helps the trial lawyer to prepare the case and courtroom tactics and is an opportunity to test the strength of the expert evidence. Thereafter the expert is summoned to court, and it is usually possible to negotiate a time within fairly tight limits. Evidence is given under oath and commences with a benign examination by the lawyer on the same side. It is usual to be asked to describe one's qualifications and position and the lawyer also asks some questions designed to demonstrate to the judge one's unique and unrivalled expertise, in comparison to the experts on the other side. The written report is likely to be discussed and the opinions expressed therein reiterated. The fun then begins with the cross-examination, when the other side's lawyer tries to show, albeit politely at first, that one's expertise is insubstantial and that the report was written on the basis of a poor appreciation of the facts of the case; in short, that one's opinion is of no value compared to that of the other experts. In the course of this there may be detailed discussion of papers from the literature that have been included as evidence and which have to be interpreted for the judge. It is as well to have read these papers carefully beforehand. After the cross-examination, the original lawyer has a chance to re-examine the expert in order to correct any false impression that may have been given and to direct the judge's attention back to the essentials of one's evidence.

All one's evidence in British civil courts is addressed to the judge, who should be spoken to with due deference and addressed by the proper title, usually 'my lord/lady'. The judge often intervenes with questions and requests for clarification or explanation. In courts in the USA, one gives one's evidence to the jurors, and this should be given at an appropriate level of comprehensibility. Again, the judge also intervenes from time to time for clarification. It is unusual to be asked to attend court throughout a hearing, although occasionally a lawyer might value an expert's comments on the evidence of other witnesses, and wish to hold conferences during the course of the trial. Generally, however, it is possible to arrange to attend simply to give evidence and then disappear.

## Trends in litigation

The respiratory disease medicolegal industry in the USA has been built on asbestos, though there is substantial activity also with respect to coal, quartz and chronic airflow obstruction. In the UK, there has been and continues to be much asbestos litigation, most concerned with benign pleural disease and mesothelioma. However, occupational asthma and acute lung disease due to inhalation of toxic substances are common conditions, as

discussed in Chapters 34, 36 and 54, and there is a rising trend of litigation in these areas. Chronic airflow obstruction in groups of workers where epidemiological evidence suggests an increased risk, such as coal-miners and welders, has also been an increasing cause of litigation. Changes in the value of, and access to, disability benefits and reduction in regulation of industry as part of British government policy is likely to lead to a rising trend both of litigation and of the diseases that provoke it.

## Postscript

Books such as this are not written overnight and, since this chapter was originally drafted, new Civil Procedure Rules have been introduced for actions in the English and Welsh (but not Scottish) courts. These respond to a report by Lord Justice Woolf which took a refreshing look at the waste of public money on much of this litigation. The Rules are happily consistent with the advice given above and should eliminate much of the unsatisfactory behaviour of doctors and other self-styled 'experts' taking on the role of advocate. They should also reduce the likelihood of busy and expensive doctors having to appear in court. With respect to experts, the Rules indicate that:

- 1 Evidence should be confined to that which is reasonably required to resolve the proceedings.
  - 2 It is the duty of an expert to *help the court*.
  - 3 This duty overrides any obligation to the person from whom the expert has received instruction.
- The court will approve the appointment of experts and may direct that only one such be appointed, to be agreed by the two parties. The Rules set down the form and content of the report, as follows. It must:
- 1 be addressed to the court;
  - 2 give details of the qualifications of the expert;
  - 3 give details of the literature relied upon;
  - 4 state who carried out any tests and give that person's qualifications;
  - 5 where there is a range of opinion, summarize that range and give reasons for the expert's own opinion;
  - 6 contain a summary of the conclusions reached;
  - 7 contain a statement that the expert understands his/her duty to the court;
  - 8 contain a statement setting out the written and oral instructions received; and
  - 9 state as follows: 'I believe the facts I have stated in this report are true and that the opinions I have expressed are correct'.

This last statement may form an appropriate note on which to end this book. It is our hope that the facts stated herein mostly turn out to be true and that the opinions which we have expressed are sensible and ultimately benefit our patients.

# INDEX

## Note:

### Abbreviations:

- ARDS Adult respiratory distress syndrome
- BAL Bronchoalveolar lavage
- COPD Chronic obstructive pulmonary disease
- SLE Systemic lupus erythematosus

Page numbers in **bold** refer to pages on which tables are located. Page numbers in *italics* refer to pages on which illustrations are found.

This index is in letter-by-letter order whereby hyphens and spaces in index headings are ignored in the alphabetization.

*vs* denotes differential diagnosis or comparisons.

Volume 1 pp. 1–828; Volume 2 pp. 829–1542.

- abdomen
  - 'doughy' 537
  - paradoxical movement 108, 710
- abdominal diseases, pleural effusions 1161
- abdominal distension, ventilation
  - complication 1506, 1507
- abdominal pain, tuberculosis 537
- abdominal swelling, tuberculosis 536
- abietic acid 950
- Abrams pleural punch 183, 183
- abscess
  - actinomycosis 463, 575
  - amoebic 605, 606, 1160
  - cerebral *see* cerebral abscess
  - cervicofacial 575
  - chest wall 1227
  - cold *see* cold abscess
  - liver *see* liver, abscess
  - lung *see* lung abscess
  - mediastinal 1300, 1301, 1302
  - peritonsillar (quinsy) 340
  - psoas 537
  - retropharyngeal 340
  - subphrenic 1239–40
  - tuberculous 529
- Absidia* 598
- acclimatization to altitude 55
  - loss 58
- acetazolamide 281–2
  - adverse effects 282
  - high-altitude pulmonary oedema 788
- acetylators
  - isoniazid metabolism 548
  - slow 98
- acetylcholine 250
  - antagonists 250
  - bronchial tone and 250
  - receptors 1280, 1282
    - antibodies 710, 1282
    - release, tetanus 711
- N-acetylcysteine, bronchiectasis 819–20
- Achilles tendon, non-traumatic rupture 270
- aciclovir (acyclovir) 234–6, 235
  - adverse effects 235
  - uses/indication 235
  - in VZV and HSV infections 234–6
- acidaemia
  - hypercapnia of respiratory failure 698
  - respiratory failure 709
- acid–base diagram, respiratory failure
  - diagnosis 699, 699
- acid–base status 38
  - COPD 656
  - respiratory failure 699
- acid-fast bacteria 476
  - in CSF 530
- acid glycoprotein 13
- acidification of water 324
- acid maltase deficiency 98
- acidosis *see* metabolic acidosis; respiratory acidosis
- Acinetobacter* pneumonia 409–10
  - hospital-acquired 371
- acini (acinus)
  - number 15
  - obstruction 800, 800
  - structure 9, 15–18
- acrolein 284
- acrylonitrile (vinyl cyanide) 1445
- ACTH *see* adrenocorticotrophic hormone (ACTH)
- actin, myosin interaction 938
- Actinobacillus actinomycetes* 575
- Actinobacillus actinomycetem comitans* 576
- Actinomyces* 573
  - empyema 448, 452, 454
  - pleural effusions 1160
  - species 575
- Actinomyces israeli* 463, 575
- actinomycetes 573
  - classification 574
  - farmer's lung due to 1011
- actinomycosis 575–6
  - chest wall 1228
  - clinical manifestations 575–6
  - lung abscess and 463, 470, 575
  - management 576
  - treatment 454
- actinomycotic diseases 573–603
- activated partial thromboplastin time (APTT) 736–7
- activated protein C 97
- acute mountain sickness 57–8, 788
  - prevention 282
  - symptoms and management 788
- acute respiratory distress syndrome (ARDS) 770
  - see also* adult respiratory distress syndrome (ARDS)
- acyclovir *see* aciclovir
- adamantanes 242–3, 350
  - see also* amantadine
- Adamkiewicz, artery 1278
- adeno-associated virus vectors 866
- adenocarcinoma
  - lung *see* lung cancer
  - paranasal sinuses 5
- adenoid cystic carcinoma (cylindroma) 1135–6, 1136
- adenosine deaminase
  - deficiency 97
  - in peritoneal fluid 537
- adenoviruses 337
  - bronchiectasis aetiology 799
  - common cold 335–6
  - pneumonia 415–16
  - serotypes 416
  - vaccines 416
  - vector for cystic fibrosis gene therapy 866
- adenyl cyclase 245
- adhesion molecules 910
  - asthma pathogenesis 928
  - granulocytes 917, 917

- adhesion molecules (*Continued*)
  - late asthmatic response 917
  - neutrophil-endothelial 779
- adolescents, cystic fibrosis 866–7
  - holistic care 867–8
- adrenal cortical insufficiency 272, 275, 582
- adrenaline *see* epinephrine
- adrenal suppression, corticosteroid effects 272–3, 275
- $\beta$ -adrenergic receptors
  - agonists interaction 938
  - in asthma 938
  - $\beta_2$  agonists *see*  $\beta_2$ -agonists
  - $\beta_2$  receptors 244, 245
    - downregulation 246
  - glucocorticosteroid effects 262–3
  - types 1 and 2 244
- adrenoceptor stimulants *see*  $\beta_2$ -agonists
- adrenocorticotrophic hormone (ACTH) 272
  - ectopic secretion 1111
  - suppression by glucocorticosteroids 263
  - therapy 266
    - asthma 984
- adult respiratory distress syndrome (ARDS) 31, 41, 85, 766, 770–87
  - at-risk groups 773–4
  - causes 772, 772
    - direct 772, 772
    - indirect 772, 773
  - chest radiography 770, 771, 783
  - clinical features 770, 783
  - clinical spectrum 771, 772–3
  - complications 784
  - definition 770, 771–2
    - lung injury score and 772, 772
  - diagnosis 783
  - epidemiology 773
  - iceberg concept 773, 773
  - incidence 773
  - malaria 608
  - management 783–6
    - drug therapy 784–6, 785
    - mechanism-based therapy 785, 785–6
    - non-respiratory support 784
    - respiratory support 697, 783–4
  - miliary tuberculosis 514
  - mortality 786–7
    - causes 787
  - nosocomial infections 784
  - outcome, natural history 786–7
  - pathogenesis 776–82
    - mediators 777–8
    - neutrophils and inflammatory cells 776–81
    - repair of injury 782
    - resolution of inflammation 781–2
  - pathology 775, 775–6
  - pathophysiology 782–3
  - pneumothorax in 1188
  - predisposing/predictive factors 773–5
  - pulmonary hypertension in 783
  - recovery phase 776
  - sequelae 787
  - tuberculosis complication 523
- aegophony 1154
- Africa, tuberculosis 490
- age
  - airways obstruction in COPD 626, 626
  - asthma epidemiology 895
  - empyema and 448
  - postprimary pulmonary tuberculosis 515, 515
- sarcoidosis 1037–8
- AIDS 1351–61
  - antiretroviral agents 236–40
  - classification 1354
  - co-trimoxazole use 210
  - cryptococcosis 580, 581
  - definition 1356
  - fibreoptic bronchoscopy 166
  - invasive aspergillosis 593–4
  - itraconazole use 231
  - Kaposi's sarcoma 1137–8, 1138, 1358, 1359, 1360
  - lung biopsy in 180
  - mortality 1361
  - see also* HIV infection
- air
  - conditioning in nose 5, 53, 54
  - conduction route 53
  - humidification 5, 53
  - quality standards 333, 333
  - volume breathed 52–3, 83
  - warming in nose 5, 53
- airborne transmission, droplet nuclei in tuberculosis 478
- air bronchogram 128, 130
- air conditioner lung 1013
- air conditioning 1013
  - Legionella* contaminated 387
- air embolism 722
  - cutting-needle biopsy complication 176
  - diving and 1485
  - management 1163–4
  - percutaneous fine-needle biopsy complication 174–5
  - pleural aspiration causing 1163–4
- air filter respirators 479
- airflow
  - laminar 41, 45
  - rates, bronchiole obstruction 829
  - turbulent 42, 45, 114
- airflow limitation
  - barotrauma during diving 1483
  - drug management 244–59
    - see also* bronchodilators
  - reversibility, bronchiectasis 808
- airflow obstruction
  - assessment 58
  - asthma 76, 951, 955, 956, 957
  - breathlessness 108
  - chronic bronchitis with 616
  - COPD 626, 626, 642
    - persistence 619–20
  - crackles 116
  - diffuse panbronchiolitis 832
  - extra-/intra-thoracic 44
  - leucocyte elastase levels and 637
  - low-frequency fatigue 49, 1235
  - prevention of weaning from ventilation 1511
  - reversible 43, 58, 1441
  - rheumatoid disease 1388
  - sarcoidosis 1053
  - small airways, test 10
  - terminal care 1530
  - tests 10, 43–5
  - upper airways 44
  - variability, asthma 76
  - wheezes and 115
  - see also* bronchial obstruction
- airflow resistance 14
  - large airways 10
  - nose 4
- see also* airway resistance
- air pollutants 325–9
  - carbon monoxide 327, 331
  - carcinogens 328–9, 331
  - combinations 331–2
  - lead 329
  - nitrogen oxides 327, 330, 1447
  - ozone 327–8, 331, 1448
  - particles 325–7, 327
    - chemical composition 326
    - clearance from lung 1406–8, 1407
    - COPD 622
    - cryptogenic fibrosing alveolitis 878
    - daily counts and sizes 326
    - deposition in lung 325, 325, 1406–8, 1407
    - fine 622
    - health effects 329–30, 330
    - PM<sub>10</sub> 325, 326
    - size and deposition 1407
    - sulphur dioxide 327, 330, 622, 1448
- air pollution 324–34
  - advice to patients 332–3
  - asthma and 898, 947, 1479
  - causes 324
  - control 333
  - COPD risk factor 622–3, 947
  - ecological problem 324
  - fossil fuels and 664
  - health effects and mechanisms 329–32
  - indoor 332
  - lung cancer aetiology 1079
  - mortality and 324, 325, 329
  - reduction, COPD prevention 664
  - response to aeroallergens increased 947
  - rural 331
  - seasonal 331, 332–3
  - types 324
  - UK air quality standards 333
  - urban 324, 325, 330
- air sacs 9
- airspace 766, 767
  - elastase activity 637
  - enlargement in emphysema 629
  - glycoprotein in 1334
  - normal size 631
  - wall destruction in emphysema 632
- airspace wall per unit lung volume (AWUV) 631, 631
- airway(s)
  - anastomosis, lung transplant complication 1521
  - attachments, loss in emphysema 632, 633
  - closure in COPD 641
  - crackles and causes 115–16
  - cross-sectional area 10, 10
  - development 1–2
    - postnatal 3
  - dynamic compression 45
  - epithelium, ion transport 844–5
  - fetal 712
  - fibrocartilaginous layer 13–14
  - inflammation
    - chronic bronchitis 628
    - ciliated epithelial cell role 12
  - microscopic anatomy 11–14
  - mucosa 11–13
  - obstruction *see* airflow obstruction
  - oedema, asthma 907, 929
  - overdistension in asthma 925
  - pain, causes 106
  - secretions 14–15

- see also* bronchial secretions;
  - respiratory secretions
- smooth muscle *see* airway smooth muscle
- submucosal layer 13
- upper 1251, 1251
  - control by mechanical ventilation 1501
  - muscles 1251, 1251, 1252
  - neuromuscular control 1251–2
  - pacing 1261
  - sleep-induced hypotonia 1252
  - see also* upper respiratory tract
  - see also* bronchi; bronchioles
- airway access
  - mechanical ventilation 704
  - see also* endotracheal tubes;
  - tracheostomy; *specific methods*
- airway diseases
  - breathlessness 108
  - mechanical ventilation 705–6
  - obstructive, decompression sickness 1486
  - small airways 628, 632
- airway hyperresponsiveness
  - $\beta$ -adrenoceptor agonists effect 625
  - COPD risk factor 625–6
  - pathogenesis 918–19
  - smoking-induced increase 625, 898
  - see also* asthma
- airway narrowing 13
  - arousal from sleep terminating 1252
  - consequences 1252–3, 1253
  - intrathoracic 110
  - mechanisms (upper airway) 1251, 1251–2, 1253
  - site in asthma 956
  - site in sleep 1251
- airway resistance 41–3, 45
  - after smoking 622
  - asthma 42, 930, 956
  - factors affecting 42
  - increased, pressure–volume loop 48
  - measurement 43
  - nasal passages 53
  - sites 42, 42
  - see also* airflow resistance
- airway smooth muscle 13–14
  - asthma 918
  - hypertrophy, asthma 907, 927, 928
  - relaxation by  $\beta$  agonists 976
  - upper airway narrowing and 1251, 1252
- airways obstruction
  - bronchiectasis 800–1, 808
  - scoliosis 1218
  - ventilation complication 1506
  - see also* bronchial obstruction
- Ajellomyces dermatitidis* 577
- Alaska, tuberculosis 488, 490, 498
- albendazole, strongyloidiasis 609
- albuterol *see* salbutamol
- alcohol, cephalosporin interaction 200–1
- alcoholism, tuberculosis reactivation 515
- alfentanil 152
- aliphatic amines 951
- allergens
  - asthma 897, 942–6, 961
  - atopic 907–8
  - occupational 949
  - avoidance 975
  - birds 945
  - cat 897, 945
  - cockroaches 945
  - in homes 897, 943
  - house dust mites 943
  - late asthmatic response 917
  - pollen 897, 943–4
  - seasonal 897, 944
  - soybean 897, 898
- allergic alveolitis, extrinsic 586, 588, 1003
- antigens 1008, 1009
  - removal/exposure prevention 1009, 1010
- bronchoalveolar lavage 162, 1006, 1007, 1009
- causes 889, 1011–16, 1012
  - animal 1014–16
  - chemical 1016
  - domestic 1014
  - feathers 1008, 1009
  - microbial 1011–14
- challenge tests 1009, 1010
- chest radiography 1003, 1004, 1005, 1009
- chronic 1003
  - management 1011
- clinical features 108, 1002–3
- episodic dyspnoea 889, 1003
- diagnosis and investigations 1008–10, 1011
  - lung biopsy 180, 1009
  - lung function 1003–5
  - management 1010–11
  - pathogenesis 1005–8
  - pathology 1005, 1006
  - periodicity of symptoms 1003
  - see also* hypersensitivity pneumonitis
- allergic bronchopulmonary aspergillosis 586, 587–90, 1013–14, 1023–4
- asthma and 953–4, 991
- bronchiectasis association 803
- chest radiography 589, 591, 959, 960
- chronic persistent 588, 590
- computed tomography 590, 960
- in cystic fibrosis 855
- diagnosis/diagnostic criteria 953–4, 1023, 1023
- radiology 958–9
- treatment 231, 991
- allergic bronchopulmonary mycosis, fungi causing 590, 954
- allergic granulomatosis *see* Churg–Strauss syndrome
- allergic reactions
  - cephalosporins 200
  - cows' milk 1333, 1334
  - drug-induced alveolitis 1461–2
  - feathers 943, 1008, 1009
  - fungal 945
  - HLA and 95
  - latex rubber 951
  - meat 946
  - peanut 946
  - penicillins 193, 194, 369, 370
  - testing, penicillin reaction avoidance 194
  - see also* atopy
- allopurinol 286
- almitrine bimesylate 282–3
- alopecia, chemotherapy causing 284, 1107
- alteplase, pulmonary embolism 738
- altitude *see* entries beginning high-altitude
- aluminium 1439
- alveolar air 1195
  - equation 28
- alveolar airspaces *see* airspaces
- alveolar–arterial  $P_{O_2}$  difference 28, 33
- respiratory failure 696
- alveolar basement membrane 15, 20
- antibodies 1330–3
- antigens 1330–1
- alveolar capillaries 15, 19–20
- structures 19–20, 766, 767
- see also* pulmonary capillaries
- alveolar capillary membrane
  - forces acting across 30, 30
  - permeability 30–1
- alveolar cells *see* pneumocytes
- alveolar dead space 27
  - type II respiratory failure 698–9
- alveolar disease
  - mechanical ventilation 706
  - prevention of weaning from ventilation 1511
- alveolar ducts 9
- alveolar epithelium 15, 766
- cryptogenic fibrosing alveolitis 878, 879, 880
- alveolar haemorrhage 1330–4
- antiglomerular basement membrane antibody disease 1330–3
- barotrauma causing 1483
- causes 1330, 1331
- idiopathic pulmonary haemosiderosis 1333–4
- alveolar hypoventilation
  - acute severe asthma 986
  - causes 697, 752, 752
  - cervical cordotomy causing 712
  - drug-induced 709
  - pulmonary hypertension due to 752
  - in sleep, diaphragmatic paralysis 1238
  - type II respiratory failure 697
  - see also* respiratory failure, type II
- alveolar hypoxia
  - COPD 633
  - hypoxic pulmonary hypertension 752
- alveolar interstitial space
  - fluid accumulation 766–7, 782
  - fluid clearance 767
- alveolar interstitium 766, 767
- alveolar macrophage 16–17, 87–90, 88
- activation
  - cryptogenic fibrosing alveolitis 881
  - in smokers 54
- as antigen-presenting cells 89
- asthma pathogenesis 908–9
- cryptogenic fibrosing alveolitis 878, 881
- functions 16, 54, 86, 87–8, 88
- immune response initiation/control 89
- inflammatory response
  - initiation/control 89
- lipoid pneumonia 428
- microorganisms resisting 89
- movement/distribution 1407
- numbers 16
- origin 16, 54, 87
- particle removal 1407
- phagocytosis 87, 88–9
- production 16
- receptors 87, 88
  - substances binding 88
- sarcoidosis 1042–3
- scavenging activity 16
- secretory products 16, 54, 89, 89
  - cytokines 881, 908–9
- Sp-A effect/action 85
- in sputum 54
- structure 16, 18
- tissue modelling and repair 90

- alveolar microlithiasis 1339–40  
 alveolar proteinosis *see* pulmonary alveolar proteinosis  
 alveolar sacs 15  
 alveolar ventilation 15, 27–8, 28  
   mechanical ventilation 1501–2  
 alveolar wall 15–16  
   cells *see* pneumocytes  
   thickening  
     cryptogenic fibrosing alveolitis 878, 879  
     silicosis 1422  
 alveoli 15  
   anatomy and physiology 766–7  
   collapse  
     neonatal respiratory distress syndrome 712  
     pulmonary embolism 722  
   destruction in COPD 642  
   development 3  
   exudate, radiation pneumonitis 427  
   number 3, 9  
   rupture 1205  
   structure 9, 15  
   total surface area 15  
 alveolitis  
   asbestosis 1429  
   cryptogenic fibrosing *see* cryptogenic fibrosing alveolitis  
   drug-induced 1460–5  
     clinical features 1460–1  
     drugs causing 1462, 1462–5  
     mechanisms 1461–2  
   fibrosing *see* fibrosing alveolitis  
   hypersensitivity type 1465  
   lymphocytic, radiation pneumonitis 1471  
 Alzheimer's disease 1439  
 amantadine 242–3  
   influenza 242, 243, 349  
   prophylaxis 243  
   structure 242  
 ambroxol 1337  
 amenorrhoea 516, 862  
 American Thoracic Society  
   antimycobacterial drugs susceptibility testing 567  
   COPD definition 617  
   lung sounds 116  
   opportunistic mycobacterial disease 567  
   pneumonia treatment guidelines 369, 370–1  
   questionnaires 75, 76  
   severe pneumonia definition 373  
   theophylline doses 254  
   tuberculosis chemoprophylaxis 499–500, 500  
 amfebutamone 317  
 amikacin 213, 216  
   tuberculosis 551, 551  
 aminoglycosides 212–16  
   administration, distribution and excretion 213  
   adverse effects 213–14, 214  
   ototoxicity 864  
   choice and uses 214  
   in cystic fibrosis 864  
   drug interactions 214  
   nebulized 216  
   spectrum of activity 212–13  
   *see also* gentamicin  
 aminopenicillins 196–8  
   pneumonia 368  
 aminophylline 252, 253, 255  
   acute severe asthma treatment 987  
   administration 254  
   diaphragmatic fatigue 1236  
   rectal administration 255  
   uses/indications 256  
 aminorex, primary pulmonary hypertension after 755  
 amiodarone, side-effects 1463  
 amitriptyline 1528  
 ammonia fumes 1446  
 amniotic fluid embolism 722  
 amniotic membranes, premature rupture 1315  
 amoebiasis 604–6  
   empyema 449  
   hepatic 1160  
   thoracic 604–6  
 amoebic liver abscess 605, 1160  
 amoebic lung abscess 605, 606  
 amosite 1174, 1424  
 amoxicillin 196–7  
   administration and dose 197  
   adverse effects 197  
   bronchiectasis 817  
   epiglottitis 340  
   pneumonia 365  
   prophylactic, pneumonia prevention 383  
   resistance/susceptibility 196–7  
   sinusitis 344  
 amoxicillin–clavulanate (co-amoxiclav) 197–8  
 amphiboles 1424, 1431, 1432  
 amphotericin 228–30  
   administration, distribution and excretion 228–9  
   adverse effects 229, 1350  
   blastomycosis 578  
   coccidioidomycosis 580  
   dosage 229  
   lipid formulations 229  
   spectrum of activity 228  
   structure 228  
   uses/indications 229–30, 1350  
 ampicillin 196–7  
   administration and dose 197  
   adverse effects 197  
   bronchiectasis 817  
   *Moraxella catarrhalis* pneumonia 411  
   pneumococcal pneumonia 380  
   resistance/susceptibility 196–7  
 ampicillin–sulbactam (sultamicillin) 197  
 amylases 1164  
 amyloidosis 1291, 1337–9, 1338  
   bronchiectasis complication 823  
   classification 1337, 1337  
   generalized and localized types 1337, 1337  
   mediastinal 1291  
   primary 1337  
   secondary 1337  
   tuberculosis complication 523  
 anaemia  
   aplastic 228  
   iron deficiency 1331, 1333  
   megaloblastic 210  
   zidovudine causing 237  
 anaerobes  
   antibiotic sensitivity 468, 472  
   culture and specimens for 468  
   in saliva 460  
   sputum culture 413  
 anaerobic infections  
   acute sinusitis 342  
   bronchiectasis and 809  
   empyema 447, 448  
   hospital-acquired pneumonia 372  
   management 453–4  
     clindamycin 219  
     metronidazole 217–18  
 anaerobic threshold 55  
 anaesthesia  
   percutaneous fine-needle biopsy 173  
   topical  
     complications 168–9  
     fibreoptic bronchoscopy 153–4  
 anaesthetic agents, local, cough reflex inhibition 84, 1529  
 analeptic drugs 280  
 analgesia/analgesics *see* pain relief  
 anaphylactic reactions  
   amphotericin 229  
   cephalosporins 200  
   early asthmatic response 908  
 anaphylaxis  
   immunotherapy for asthma and 991  
   management 195, 249  
   penicillin reaction 195  
 anatomical dead space 13–14, 26–7, 27, 1501  
   measurement 27, 27  
   type II respiratory failure 698–9  
 anatomy  
   airways 11–14  
   alveoli 766–7  
   bronchi 9, 11  
   bronchioles 829  
   endothelial cells 20, 21  
   left recurrent laryngeal nerve 19  
   lung 10, 10–11  
   lymphatic ducts 1165–6  
   mediastinum 1269  
   nose 342  
   paranasal sinuses 341, 342  
   pleura 23, 1152, 1182  
   pulmonary artery and arterioles 19, 20  
   in pulmonary oedema 766–8  
   thoracic duct 1165–6  
   thymus gland 1278–9  
   turbinates 342  
*Ancylostoma braziliense* 1022  
*Ancylostoma duodenale* 608  
 aneurysm  
   aortic *see* aortic aneurysm  
   carotid arteries 1298  
   pulmonary arteriovenous 1322–6  
 angitis, pulmonary lymphocytic *see* pulmonary lymphocytic angitis  
 angina pectoris 248, 992  
 angiofollicular hyperplasia 1342  
 angiogenesis, asthma 918  
 angiography *see* pulmonary angiography  
 angioma, pulmonary and pulmonary cavernous *see* arteriovenous malformations  
 angioneurotic oedema 709  
 angioplasty, superior vena cava obstruction 1114  
 angiosarcoma (Kaposi's sarcoma) *see* Kaposi's sarcoma  
 angiotensin-converting enzyme (ACE) inhibitors, cough 104, 1460  
   serum levels in sarcoidosis 1055–6  
 angiotensin I 20  
 angiotensin II 20

- animal dander 943
- animal models
  - COPD 634
  - sarcoidosis 1039
- animals
  - allergic alveolitis due to 1014–16
  - asthma aetiology 897, 945
  - high-altitude 752
  - occupational asthma causes 949, 949, 950
- anistreplase, pulmonary embolism 738
- ankle oedema 1253
- ankylosing spondylitis 108, 1218–19, 1220, 1395–6
  - lung involvement 1396
  - upper lobe fibrosis 1396, 1397
- anorexia, terminal care 1531
- antenatal screening, cystic fibrosis 850–1, 1476
- anterior horn cell disease 1237
- anthrax 425–6
- anthrax sore 426
- antibiotics
  - acute COPD 674–5
  - alveolitis due to 1462, 1462
  - antagonistic effect on oral contraceptives 863
  - asthma 986
  - bronchiectasis 816–18
    - choice 816–17
  - bronchoconstriction due to 1459, 1460
  - cystic fibrosis 864–5
  - empyema 453–5
  - glycopeptide 219–21
  - influence on empyema 447
  - intravenous, cystic fibrosis 865
  - intravenous pulsed, bronchiectasis 818
  - lung abscess 470–2
  - nebulized 216
    - bronchiectasis 818
  - penicillins *see* penicillin(s)
  - pneumonia treatment *see* pneumonia
  - poor penetration 816
  - in pregnancy 863
  - prophylactic, after lung transplantation 1520
  - resistance
    - in bronchiectasis 816
    - mechanisms 99
    - penicillin *see* penicillin(s), resistance
    - pneumonia treatment 365, 366
    - S. pneumoniae* cross-resistance 384
  - sinusitis 344
  - see also individual antibiotics/antibiotic groups/infections*
- antibodies
  - allergic alveolitis pathogenesis 1008
  - deficiency 97, 1384
  - monoclonal, CMV detection 1349
  - see also individual antibodies*
- anticholinergic bronchodilators 249–52, 250
  - administration, absorption and metabolism 250–1
  - adverse effects 251
  - asthma treatment 979, 987
  - $\beta_2$ -agonists with 251–2
  - COPD 664, 665
  - mode of action 250
  - onset of action 250, 251
  - uses/indications 251–2
  - see also ipratropium bromide*
- anticholinesterase drugs
  - myasthenia gravis 710
  - overdose 710
- anticholinesterase inhibitors 250
- $\alpha_1$ -antichymotrypsin 87
- anticoagulants
  - acute exacerbation of COPD 676
  - acute pulmonary embolism 736
  - natural proteins 719
  - oral
    - duration of course 738
    - induction steps 738
    - pulmonary embolism 737–8
    - venous thrombosis prevention 742
  - radiation pneumonitis 427
- anticonvulsants, alveolitis due to 1462, 1462–3
- antidiuretic hormone (ADH; arginine vasopressin)
  - in COPD 650, 651
  - syndrome of inappropriate secretion (SIADH) 1111
- anti-DNA antibodies, interstitial lung disease 890
- antielastases, cystic fibrosis 865
- antiemetics 1531–2
- antifungal agents 228–34
  - aspergilloma 592, 592
  - aspergillosis 588, 590
  - asthma 991
  - blastomycosis 578
  - candidiasis 595
  - coccidioidomycosis 580
  - histoplasmosis 586
  - paracoccidioidomycosis 582
  - Pneumocystis carinii* pneumonia 596–8
  - pulsed therapy 991
- antigen challenge, asthma 931–2
- antigenic drift 347–8
- antigenic shift 347–8
- antigen-presenting cells, alveolar macrophage as 89
- antigens
  - inhaled, asthma mechanisms 931–2, 932
  - pneumococcal, detection 363
- antiglomerular basement membrane
  - antibody disease 1330–3
- antihelmintics 611, 612, 613
- anti-inflammatory therapy
  - ARDS 785
  - see also non-steroidal anti-inflammatory drugs (NSAIDs)*
- antileucoprotease (ALP) 639
- antileukotrienes 259
- $\alpha_2$ -antimacroglobulin 86, 87
- antimicrobial drugs 193–228
  - antibacterial *see* antibiotics
  - fungal infections 228–34
    - see also antifungal agents*
  - viral infections 234–44
    - see also antiviral agents*
- antimony 1439
- antimycobacterial drugs
  - resistance 567, 568, 570
  - susceptibility testing 567
  - see also antituberculosis drugs*
- antineutrophil cytoplasmic antibodies (ANCA) 1063–5, 1069, 1070, 1332
  - diffusely cytoplasmic (cANCA) 1064
  - perinuclear (pANCA) 1064
- antinuclear antibodies
  - bronchiectasis pathogenesis 802
  - interstitial lung disease 890
- antioxidants, asthma and 900
- antiphospholipid antibodies 1392
- antiproteases 86–7, 638–9
  - cystic fibrosis 866
  - decreased, emphysema pathogenesis 638–40
  - mechanisms reducing effectiveness 639
  - types 638–9
- antiproteinases 86–7
  - inhibitor *see*  $\alpha_1$ -antitrypsin
- antipsychotic drugs, pulmonary oedema due to 1465
- antiretroviral agents 236–40
  - HIV resistance 236
  - see also antiviral agents*
- antistaphylococcal penicillins 198, 198–9, 199
- antithrombin 97
  - deficiency 97
- antithrombin III 719, 736
- antithrombotic molecules 718
- $\alpha_1$ -antitrypsin ( $\alpha_1$ -proteinase inhibitor) 87, 95, 623, 634–6, 779, 797, 1380
  - functions 635
  - genes 635
    - mutations 95, 635–6
    - polymorphism 635, 639, 1380
  - levels and emphysema risk 635
  - nebulized 865
  - oxidation effect 638, 639
  - PiM and PiZ 623, 635, 1380
  - variants 623, 635, 1380
  - Z variant 95, 96, 635
- $\alpha_1$ -antitrypsin deficiency 623, 634–6, 638, 1380
  - bronchiectasis aetiology 797
  - COPD risk factor 623
  - emphysema pathogenesis 636
  - emphysema risk 95, 1380
  - genetics 95–6
  - incidence 623
  - life expectancy 636
  - PiMM 636
  - PiSZ 1380
  - PiZZ 95, 96, 623, 635–6, 636, 1380
  - pulmonary manifestations 1380
  - smoking and 623
  - therapy 95
- antituberculosis drugs 223–5, 500, 546–52
  - activity/effectiveness 545–6
  - combined formulations 553
  - first-line agents 546–50
    - dosages and adverse effects 547
  - generalized reactions to 552–3, 553
  - new agents 552
  - recently added drugs 551, 551–2
  - reserve drugs (second-line) 550–1
    - dosage and adverse effects 550
  - resistance 544, 556, 557, 559
  - see also tuberculosis (TB), chemotherapy*
- antiviral agents 234–44
  - after lung transplantation 1520
  - common cold 338
  - resistance 234
  - see also antiretroviral agents*
- antrostomy 823
- anxiety, hyperventilation and 1264, 1265, 1267
- aorta 19, 1319
  - aberrant lung supply 2, 3, 19
  - coarctation 1221
  - thoracic, anomalous systemic arteries to lungs 1321



- aortic aneurysm 1298–300, 1299  
 rupture 1298, 1299–300  
 thoracic 1298, 1299–300
- aortic arch  
 aneurysm 1298, 1299  
 development 2
- aortic body tumours 1272, 1277
- aortic dissection 127, 1299, 1300
- aortic valve prosthesis 1300
- apex beat, deviation 114
- aphonia, hysterical 7
- aplastic anaemia 228
- apneustic centre 50
- apnoea  
 postoperative 709  
 sleep *see* sleep apnoea/hypopnoea syndromes (SAHS)
- apoproteins, in surfactant 18
- apoptosis, neutrophils 782, 786
- appetite suppressants, primary pulmonary hypertension after 755
- aprotinin 1518
- APUD cells 13, 1133  
 mediastinal tumours 1278
- APUDomas 1278
- arachidonic acid 258, 261  
 storage and release 933  
 synthesis, inhibition by glucocorticosteroids 260–1
- Arachnia* 573
- Arachnia propionica* 575
- arginine vasopressin *see* antidiuretic hormone (ADH)
- Armillifer* 614
- arterial blood gases  
 control during mechanical ventilation 1500  
 COPD 644, 648, 656, 698  
 improvement by long-term ventilation 1512  
 pneumonia 364  
 pneumococcal 380  
*Pneumocystis carinii* 1368  
 pulmonary embolism 729  
 respiratory failure 696, 699, 699  
 tensions, measurement 37–8  
*see also* carbon dioxide; oxygen
- arterioles  
 in mitral valve disease 759  
*see also* pulmonary arterioles
- arteriovenous malformations (fistula), pulmonary 33, 1140–1, 1266, 1322–6  
 clinical features 1323–4  
 definition and pathology 1322  
 genetics 97  
 hyperventilation in 1266  
 radiography 1141, 1142, 1323, 1324–5  
 treatment 1326  
 types 1324
- arthralgia  
 erythema nodosum 511  
 pyrazinamide causing 549
- arthritis  
 in cystic fibrosis 862  
 rheumatoid *see* rheumatoid disease  
 sarcoid 1052  
 septic, chest wall 1227
- arthropathy, in cystic fibrosis 862
- arthropod parasites 605, 614
- Arthus phenomenon 510
- articular cartilage, drug-induced damage 226
- arytenoid cartilage 6
- asbestos 1404, 1424–5  
 exposure link to disease 1425–6  
 lung cancer and 1079, 1080, 1424, 1425, 1426, 1432  
 measurement 1426  
 mesothelioma association 80, 1173–4  
 pleural adhesions due to 142–3  
 pleural effusions associated 1161, 1162  
 pleural fibrosis due to 142–3, 1170, 1171  
 pleural plaques due to 142, 1167, 1167, 1169, 1427, 1429  
 regulations 1432, 1433  
 removal regulations 1432  
 smoking synergy 311, 1426  
 uses 1424–5
- asbestos bodies 1176, 1430, 1430
- asbestos fibres 1424–5, 1431  
 detection 1429–31
- asbestosis 1424–33  
 chest radiography 1427, 1427–8  
 clinical features 1427–8  
 CT 142, 1427, 1428  
 epidemiology 1424–6  
 lung function 1429  
 management 1432  
 mortality 1425, 1425  
 pathogenesis 1431–2  
 pathology 1429, 1429–31, 1430, 1431  
 prevention 1432–3  
 silicosis with 1429
- asbestos workers, management 1432
- ascariasis 608, 609
- Ascaris lumbricoides* 608  
 life cycle 1022  
 Loeffler's syndrome (simple pulmonary eosinophilia) 1022
- ascites, tuberculosis 536, 537
- Asian flu 347
- aspartate aminotransferase, rifampicin effect 548
- aspergilloma 587, 591–2, 592, 954  
 ankylosing spondylitis 1219  
 bleeding 106  
 imaging 138–9, 139  
 management 592, 592  
 tuberculosis complication 517, 523, 523  
*see also* mycetoma
- aspergillosis 586–94  
 aetiology 1013–14  
 allergic bronchopulmonary *see* allergic bronchopulmonary aspergillosis  
 bronchiectasis complication 823  
 chronic necrotizing 231  
 invasive 592, 593, 593–4  
 mixed syndromes 594  
 treatment 229
- Aspergillus* 586–94, 594  
 allergens 587–8  
 antifungal agents 228  
 antigens 945  
 asthma association 587–90  
 cystic fibrosis 855  
 diseases 586–7  
 mixed syndromes 594  
*see also* aspergilloma; aspergillosis
- empyema 448, 454  
 lung abscess 463  
 pathogenicity and factors associated 587  
 precipitins 803  
 sources 575  
 species and characteristics 586
- Aspergillus clavatus* 1013
- Aspergillus fumigatus* 586, 587, 590
- allergic bronchopulmonary aspergillosis 1023–4
- bronchiectasis association 803
- bronchocentric granulomatosis 1073–4
- fiberoptic bronchoscopy 166
- hypersensitivity 954
- mycetoma 591
- spores, asthma 944–5  
 in sputum in asthma 953, 954
- Aspergillus niger* 586
- Aspergillus terreus* 586, 588
- asphyxiant gases 1444–5, 1445
- asphyxiation 1444–5
- aspiration  
 chemical lung injury 412, 465  
 fatty material *see* lipid pneumonia  
 food  
 prevention 5  
 recurrent, cough 104  
 massive 465  
 mineral oil 428, 1465, 1467  
 oesophageal contents, tracheo-oesophageal fistula 1309  
 oropharyngeal contents 359  
 oropharyngeal flora 460–1, 461, 465  
 pleural 1163–4  
 pneumothorax 1196–7, 1197  
 of saliva 460
- aspiration biopsy 172, 173  
 needles 172, 172  
 technique 173, 174
- aspiration pneumonia 412–14  
 empyema pathogenesis 446  
 hospital-acquired 413, 414  
 pathogenesis 359  
 systemic sclerosis 1394  
 treatment 414
- aspiration pneumonitis, metronidazole use 217
- aspirin 338  
 adverse effect 1458  
 bronchoconstriction due to 1458, 1459, 1459–60  
 effects in asthma 935, 946, 1459–60  
 intolerance reduction 1525  
 pain relief in terminal care 1525  
 poisoning 1266  
 in pregnancy and pulmonary hypertension in neonate 1319  
 pulmonary oedema due to 1465  
 Reye's syndrome and 349  
 sensitivity 946, 1459  
 tolerance induction 1467  
 venous thrombosis prevention 742
- asplenia  
 pneumococcal pneumonia 377  
 pneumococcal vaccines 383  
 vaccinations needed 383
- assist control ventilation 1497–9
- assisted ventilation *see* ventilation, mechanical
- asteroid bodies 1041, 1041
- asthma 894–997  
 acute severe 952–3  
 spontaneous resolution 953  
 acute severe, management 985–8  
 anticholinergics 987  
 $\beta_2$ -agonists 986–7  
 corticosteroids 987–8  
 general 985–6  
 oxygen 986  
 ventilation 705, 988, 1510  
 xanthine derivatives 987

- advice on air pollution 332  
aetiology and provoking factors 894, 897–900, 908, 922–3, 941, 942–51  
air pollution effect 329, 331, 898, 947, 998, 1479  
allergen exposure 897, 942–6, 961  
avoidance 974–6  
childhood 1479  
exercise *see* asthma, exercise-induced  
gastro-oesophageal reflux 948  
infections 898–9, 946–7  
occupational 949–51  
psychological factors 948  
smoking 897–8, 942, 947–8, 951  
strongyloidiasis 609  
weather 948–9  
age and sex differences 895  
age of onset 952  
airflow obstruction variability 76, 951, 955, 957–8  
airway resistance 42, 930, 956  
allergen avoidance 975  
allergic 'extrinsic' 924, 933  
*see also* asthma, atopic  
aspirin effects 935, 946, 1459–60  
atopic 907–8, 910, 933, 945–6  
clinical course 951  
genetics 95  
bronchial biopsy 926–7  
bronchiectasis association 803  
bronchoalveolar lavage 928  
bronchopulmonary aspergillosis 953–5  
management 991  
cardiac function 957, 992  
cellular/humoral mechanisms 907–19, 933, 934  
cell types 907, 908–12, 927, 933  
circulating leucocytes 910–12, 934  
mediators 912–16, 931, 933, 935–7  
orchestration 916–19  
resident cells 908–10, 933  
challenge tests 895, 932–3, 961–3  
children 923, 952, 1479  
management 979  
chronic  
definition 923  
severe 953  
chronic, management 976–85  
anticholinergics 251, 252, 979  
anti-inflammatory properties (preventers) 979–84  
 $\beta$ -agonists 976–8, 985  
corticosteroids 902, 953  
delayed treatment effect 980  
first-line therapy 980  
general principles 984–5  
guidelines 980–1  
H<sub>1</sub>-receptor antagonists 979  
inhaled corticosteroids 980–3, 985  
leukotriene antagonists 983  
nedocromil sodium 979  
relief/suppression of symptoms (relievers) 976–9  
sodium cromoglycate 256–7, 979  
stepwise approach 984–5  
systemic corticosteroids 983–4  
theophylline 978–9  
*see also*  $\beta_2$ -agonists; corticosteroids  
Churg–Strauss syndrome presenting with 1028  
classification 907  
clinical course 951–5  
clinical features 922–72  
history-taking 940–8, 940–51  
clinical presentation 894–5, 940–2  
complications 955  
computed tomography 960  
COPD differentiation 616  
cor pulmonale 955  
corticosteroid-resistant 953, 981  
definition 894–5, 907, 922  
dehydration 985–6  
diagnosis and investigations 960–3  
bronchodilator test 895  
confirmation 958, 961, 962  
methods in surveys 894–5, 895  
variations 894–5  
diet and 899–900  
differential diagnosis 961  
diurnal variations 952, 960  
diving and 1492  
early response 908, 916, 931  
pathogenesis 916  
electrolyte abnormalities 986  
environmental determinants 923–4, 930  
epidemiology 894–906  
childhood 1479  
distribution 895–6  
ethnic groups 895–6  
reasons for increased prevalence 939–40  
time trends 896  
exercise-induced 5, 931, 941, 948  
leukotriene modifier therapy 259  
mechanism and model 930–1, 931  
nedocromil sodium therapy 258  
treatment *see* asthma, chronic;  
epinephrine  
exercise testing 958  
fiberoptic bronchoscopy and 169, 170  
forced expiratory volume in 1 s (FEV<sub>1</sub>) 924  
gas exchange 956–7  
genetic factors 94–5, 923–4, 930, 939  
growth delays and 276, 955, 983  
histology 928–9, 930  
historical aspects 922  
hospital admission trends 896  
hyperventilation 930–1, 956, 985  
'intrinsic' 924  
late response 908, 916–19, 931  
cell recruitment 916–17  
effector mechanisms 917–19  
lung function 955–8  
prognosis and 900–1  
variability 957–8  
lung function tests 957–8  
management 973–97  
aims and principles 973  
British guidelines 976, 984–5  
compliance problems 992  
delivery devices *see* inhalers; spacers  
drug treatment 976  
evaluation by bronchial biopsy 927  
immunotherapy 990–1  
leukotriene modifiers 259  
non-steroidal prophylactic drugs 256–9  
patient compliance 976  
patient participation 973–6  
peak flow monitoring 974  
in pregnancy 991  
*see also* asthma, acute; asthma, chronic  
mortality 901–2, 924–5, 946  
age-specific 925, 926  
 $\beta_2$ -agonists causing 248–9, 901–2, 925  
corticosteroids effect 981  
seasonal variation 897  
trends 896, 901, 925  
mucociliary clearance 85  
natural history 923–5  
nocturnal 941, 952  
management 978  
occupational *see* occupational asthma  
overtreatment, mortality 901–2  
ozone pollution effect 331, 947  
parasympathetic control 937–8  
pathogenesis 930–9  
antigen challenge 931–2, 932  
bronchial muscle 938–9  
IgE 916, 933  
immunological *see* asthma,  
cellular/humoral mechanisms  
mediators, challenge 932–3  
models of mechanisms 930–3  
neural mechanisms 937–8  
pathology 907, 925–30  
peptidergic control 938  
persistent, occupational 949  
physical findings 955–8  
predictors in early life 896–7  
prevalence 923, 924  
prognosis 900–2  
provoking factors *see* asthma, aetiology  
radiology 958–60, 959, 960  
risk reduction, by early infections 899, 934, 940  
secondary spontaneous pneumothorax 1185  
self-management plans 973–4  
sensitivity 1460  
severity assessment 952  
social status and 896  
sputum 927–8  
susceptibility, factors 940, 941  
sympathetic control 931, 938  
symptom periodicity 941  
trigger factors 908  
avoidance 974–6  
undertreatment 902  
undiagnosed in elderly, cross-sectional study 68  
ventilation 705, 988  
indication 1510  
asthmatic pulmonary eosinophilia *see*  
allergic bronchopulmonary  
aspergillosis  
asthmatic state 908  
ataxia telangiectasis 97  
atelectasis  
cystic fibrosis 856  
linear, SLE 1392  
round 142–3, 143  
theory/mechanism 804  
atheroma, in COPD 633  
atherosclerosis, smoking and 313  
atmospheric pressure 1188, 1481  
diving and 1187, 1481–2  
atopic asthma *see* asthma  
atopy 94–5, 625  
BCG inverse relationship 899  
bronchiectasis association 803  
COPD risk factor 625–6  
'Dutch hypothesis' 625, 626, 894  
evolutionary theory and 934  
genetic locus 922–3, 939  
genetics 92, 94–5  
measles inverse relationship 899, 940  
predictors in early life 896–7

- atopy (*Continued*)  
   *see also* allergic reactions  
 atovaquone 222–3, 1372  
 atrial natriuretic peptide (ANP), elevation in COPD 650, 651  
 atrial septal defect 760–1, 761  
 atrium, diastolic collapse 532  
 atropine 249  
   COPD 665  
   fiberoptic bronchoscopy 152  
   structure 250  
 atropine-like bronchodilators *see* anticholinergic bronchodilators  
 attapulgite 1435  
 auscultation, chest 114–16  
 autoantibodies  
   Wegener's granulomatosis 1063–5  
   *see also specific autoantibodies*  
 autocrine growth stimulation, lung cancer 1084, 1085  
 autogenic drainage, in cystic fibrosis 864  
 autoimmune diseases  
   bronchiectasis association 802–3  
   primary pulmonary hypertension with 753  
 autonomic nervous system 23  
   asthma pathogenesis 937–8  
   dysfunction in COPD 650  
   lung 22  
   mediastinal tumours 1276–8  
 auto-PEEP (intrinsic PEEP) 706, 1497, 1513  
 avascular necrosis of bone 269  
 aversion therapy, smoking cessation 317  
 axillary lymphadenitis, tuberculous 532  
 azathioprine 285–7  
   administration and excretion 286  
   adverse effects and precautions 286–7  
   cryptogenic fibrosing alveolitis 887  
   dosage 286  
   lung transplantation 858  
   mode of action 286  
   uses/indications 285–6  
   Wegener's granulomatosis 1070  
 azidothymidine (AZT) *see* zidovudine  
 azithromycin 206–7  
   pneumonia 365, 368  
 azole antifungals 228  
 azoospermia 844, 862  
   idiopathic obstructive 796  
 azotaemia, amphotericin causing 229  
 aztreonam 203–4  
   pneumonia 371  
 azygos lobe 10, 1315, 1316  
 azygos vein 10  
   invagination 1315, 1316
- Bacille Calmette–Guérin (BCG) *see* BCG vaccination  
*Bacillus*, empyema 448  
*Bacillus anthracis*  
   pneumonia 425–6  
   *see also* anthrax  
*Bacillus cereus*, empyema 448, 454  
 Bactec system 519, 530  
 bacteraemia  
   pneumococcal 375–6, 377, 384  
   pneumonia pathogenesis 359–60  
   *Pseudomonas pseudomallei* 423, 424  
   staphylococcal 405  
   *Staphylococcus aureus* 403, 405, 406  
   tuberculous 541  
 bacteria  
   colonization, in cystic fibrosis 853  
   occupational asthma 950, 950  
   persistence, cystic fibrosis 854  
   sputum culture 361–2  
   *see also specific genera*  
 bacterial infection  
   corticosteroid-induced susceptibility 271  
   pneumonia *see* pneumonia  
*Bacteroides fragilis*  
   antibiotics 217  
   lung abscess 462  
   pneumonia 412  
*Bacteroides melaninogenicus* 412, 462  
 bagassosis 1002, 1013  
 BALT *see* bronchial-associated lymphoid tissue (BALT)  
 bambuterol 247  
 bare lymphocyte syndrome 798  
 barium, toxicity 1439  
 barium swallow 127  
 barotrauma, pulmonary 1187–8, 1483–6  
   diving and 1188, 1483–6  
   effects on lung 1483  
   lung compliance impairment after 1492  
   mechanical ventilation complication 708  
   pneumomediastinum 1188, 1188, 1205, 1484, 1485  
   pneumothorax 1187–8, 1202  
   prevention 1485  
   respiratory disorders caused 1485  
   tension pneumothorax 1484, 1485  
 barotrauma, thorax 1486  
 basal cells 11, 13  
 basement membrane 15, 766  
   alveolar *see* alveolar basement membrane  
   glomerular, antibodies 1330–3  
   thickening, asthma 926, 928, 929  
 basophils 14  
   asthma pathogenesis 910, 933  
 B cells  
   asthma pathogenesis 912  
   cryptogenic fibrosing alveolitis 878, 881  
   deficiency 97  
   follicles 878, 881  
   functions 912  
 BCG 481  
   as antitumour agent 1465  
 BCG vaccination 497–8  
   administration techniques 498  
   atopy inverse relationship 899  
   complications 498  
   developing countries 500  
   efficacy and evidence 497–8, 500  
   healthcare staff 496  
   indications 498  
   vaccine types 497  
 beclomethasone dipropionate 276, 277  
   asthma 980, 982  
   COPD 667  
   structure 274  
 behavioural breathlessness 1264, 1265–7  
   causes 1264, 1265  
   clinical features 1265  
   diagnosis 1265–6  
   differential diagnosis 1266  
   management 1266–7  
 Behçet's syndrome 1396  
 belladonna 249, 251  
 bends, the 1486  
 benzathine benzylpenicillin (benzathine penicillin) 196  
 benzene, as carcinogen 328, 331  
 benzocaine, fiberoptic bronchoscopy 153  
 benzodiazepine  
   cryptogenic fibrosing alveolitis 887  
   fiberoptic bronchoscopy 152  
   terminal care 1532  
   withdrawal reactions 153  
 benzylpenicillin 195–6  
   administration and doses 195  
   aspiration pneumonia 414  
   indications 195–6  
   lung abscess 471, 472  
   meningococcal pneumonia 420  
   pneumococcal pneumonia 380, 381  
   resistance 195, 471  
   structure 195  
   susceptible organisms 195  
 Bernoulli effect 110, 115  
 Bernoulli equation 649  
 berylliosis 1404, 1436–8, 1437  
   chronic 1436, 1437  
   clinical features and pathology 1437  
   diagnosis and management 1438  
   pathogenesis 1437–8  
 beryllium 1436, 1437, 1438  
   exposure effects 1436  
 $\beta_2$ -agonists 244–9  
   anticholinergic bronchodilators with 251–2  
   asthma deaths due to 248–9, 901–2, 925  
   asthma management 938, 976–8, 985  
   acute severe asthma 986–7  
   corticosteroids with 978  
   inhaled short-acting 976–7  
   COPD 664–5  
   inhalation 246–7, 249, 664  
   long-acting 665, 977–8  
   mechanism of action 976  
   metabolism and excretion 247–8  
   nebulized, acute severe asthma 986–7  
   non-bronchodilator effects 245  
   receptor interaction 938  
   safety concerns 664–5  
   short-acting, dangers of regular treatment 977  
   side-effects 925, 978  
   stereoisomers 246  
   toxicity 925  
   *see also* sympathomimetic bronchodilators  
 beta-blockers, bronchoconstriction due to 1459, 1459  
 $\beta$  receptors *see*  $\beta$ -adrenergic receptors  
 betamethasone 264  
   parenteral 266  
   structure 265  
 bias 65, 66  
   measurement 66  
 bicarbonate 37, 38  
   increased in metabolic alkalosis 38  
   reduced in metabolic acidosis 38  
   retention, type II respiratory failure 698  
 bicycle ergometer 54  
 bile, reduced production 860  
 biliary disease, extrahepatic, cystic fibrosis 861  
 biliary scintigraphy 860  
 biliary sludge 202  
 biochemistry  
   empyema 452–3  
   pneumococcal pneumonia 378  
   tuberculosis 521  
 biocides 1444  
 biopsy

- aspiration *see* aspiration biopsy
- bronchial *see* bronchial biopsy
- endobronchial 158
- Hodgkin's lymphoma 1125
- lung *see* lung biopsy
- nasal, asthma 926
- non-Hodgkin's lymphoma 1128
- peritoneal, tuberculosis 537
- pleural *see* pleural biopsy
- sample fixation 158
- sarcoidosis 1055, 1057
- biopsy forceps, transbronchial lung biopsy 158, 159, 160
- Biopsy gun 176, 177
- Birbeck bodies 1130
- bird allergens 945
- bird fanciers, *Chlamydia psittaci* pneumonia 397
- bird fancier's lung 889, 1002, 1014–16
  - diagnosis and management 1015–16
- bisphosphonates 269
- blackfat tobacco-smokers' lung 1467
- bladder cancer, smoking and 313
- blastoma 1144–5
- Blastomyces dermatitidis* 577–8
  - empyema 448, 454
- blastomycosis 577–8
  - acute and chronic 578
  - aetiology and predisposing factors 577–8
  - South American (paracoccidioidomycosis) 581–2
    - treatment 230, 231, 234, 454
- blebs, pulmonary 1183, 1184
- bleeding diathesis, lung biopsy
  - contraindication 172, 175
- bleomycin, alveolitis due to 1464, 1464
- Blesovsky's syndrome 1169, 1172
- blood cultures
  - empyema fluid 452
  - in immunosuppressed patients 1348–9
  - lung abscess 467
  - pneumococcal pneumonia 380
  - pneumonia 363
- blood dyscrasias, penicillins causing 194
- blood flow
  - at high altitude 57
  - pulmonary *see* pulmonary blood flow
- blood gases *see* arterial blood gases
- blood pressure, increase
  - arousal from sleep 1253, 1255
  - sleep apnoea/hypopnoea syndrome 1254–5
- blood supply
  - lung sequestration and 1317
  - pleura 23
- blood tests
  - hypersensitivity pneumonitis 1008–9
    - see also* haematology
- blood transfusions, massive, adult
  - respiratory distress syndrome after 773
- blood vessels, lung 19–21
  - development 1–2
- blue bloaters 51, 643, 646, 653
- B-lymphocytes *see* B cells
- Bochdalek hernia 1242–3, 1300
- body cell mass (BCM), in cystic fibrosis 861
- Boerhaave's syndrome 1300
- Bohr effect 36
- Bohr equation 27
- bombesin, lung cancer development 1084
- bone
  - avascular necrosis 269
  - cysts, chest wall 1224–5
  - formation in hypertrophic pulmonary osteoarthropathy 1111–12, 1112
  - metastases 1223–4, 1225
    - lung cancer 1095, 1095
  - mineral density 269
    - corticosteroid effects 276
    - increased, chest radiography 121
    - reduction, smoking effect 313
  - pain 1111
    - relief 1528
  - remodelling, corticosteroid-induced
    - osteoporosis 269
  - sarcoidosis 1052
  - scans, metastases 1095, 1095
  - trauma, fat embolism 721
  - tuberculosis 533–6, 556
- bone marrow suppression 1107
  - azathioprine 286
  - chloramphenicol 228
  - cyclophosphamide 284
  - doxorubicin 289
  - etoposide 292
  - ganciclovir causing 241
  - ifosfamide 285
  - lomustine 291
  - vinca alkaloids causing 291
  - zidovudine causing 237
- bone marrow transplantation
  - autologous with high-dose chemotherapy 1106
  - bronchiectasis association 803
  - infective complications 1347–8
  - obliterative bronchiolitis aetiology 833
- Bordetella pertussis* 351
- Borg scale 651
- Bornholm disease 106, 1153
- Borrelia vincenti* 339
- botromycosis, lung abscess 464
- boutonneuse fever 421
- bowel stimulants 1531
- Boyle's law 1187, 1481
- brachytherapy, tracheobronchial
  - narrowing 151
- bradykinin
  - ARDS pathogenesis 778
  - asthma pathogenesis 913, 937
- brain abscess *see* cerebral abscess
- brain metastases *see* intracranial metastases
- brainstem, breathing control 50
- branchial arches 1, 2, 1319, 1320
- Branhamella catarrhalis* *see* *Moraxella catarrhalis*
- breast, tuberculosis 539–40, 540
- breast cancer 121
  - lung metastases 1146, 1147
  - radiation pneumonitis 1470, 1470, 1471
  - thoracic cage metastases 1223
- breast-feeding 899, 946
- breath, shortness *see* dyspnoea
- breath-hold diving 1482, 1483, 1490
- breathing
  - active cycle technique 864
  - adaptations in COPD 645
  - awareness and control 1266–7
  - bronchial 115
  - control 50–2, 53, 108, 1264
    - chemoreceptors 50–1, 1264
    - disordered 1266
    - involuntary 1264
    - vagal reflexes 51–2
  - voluntary 1264, 1266–7
- controlled techniques, COPD
  - rehabilitation 673
- energy requirements/costs 48, 48
- fetal 4
- frequency, normal 26
- hypercapnic drive 647
- hyperventilation explanations to patients 1266–7
- hypoxic drive 647
  - removal by oxygen therapy 700
    - see also* respiratory drive
- infants 53
- noise 109
- normal sound 114
- paradoxical abdominal movement 108, 710
- pattern 109–10
  - in COPD 652
- pursed-lipped 652, 673
- quiet, noise during 109
- rate 110
  - see also* tachypnoea
- tidal *see* tidal breathing
- T-piece spontaneous 1511
- wheezy 110
- work of 47–8
  - in cystic fibrosis 861
  - see also* respiration; ventilation
- breathing apparatus, underwater *see* diving
- breathlessness 107–9, 1264
  - see also* dyspnoea
- breath sounds 114–15
  - added 115–16
  - classification 116
  - COPD 652
  - intensity 115
  - pneumococcal pneumonia 378
  - terminology 115, 116
- British comparative thromboplastin (BCT) 737
- British corrected ratio (BCR) 737
- 'British hypothesis,' chronic obstructive bronchitis 616, 624
- British Society of Haematology 738
- British Thoracic Society
  - asthma management 976, 984–5
- COPD
  - definition 616, 617
  - diagnostic guidelines 617, 653, 654
  - treatment guidelines 616, 667, 675
- oral anticoagulants for pulmonary embolism 738
- smoking cessation and 316
- tuberculosis chemotherapy 553, 554
- Brock's syndrome 801
- bronchi
  - anatomy 9, 11
  - branching 9, 9
    - abnormal 1311, 1311–12
  - development 2
  - in emphysema 632, 632
  - left 9
  - pus in 464
  - right main 9
  - rudimentary 1313
  - segmental 9, 9
  - structure 9–14
  - supernumerary right upper lobe 1311
    - see also* airway(s)
- bronchial adenoma 1136–7
- cylindroma 1135–6, 1136

- bronchial angiography 127
- bronchial arteries 19, 23, 1319
  - aberrant 2, 3, 19
  - development 1
  - persistence of primitive arteries 1–2, 3
- bronchial artery embolization 127
  - in bronchiectasis 822–3
  - in haemorrhage due to mycetoma 592
- bronchial-associated lymphoid tissue (BAL) 86
  - tumours 1133
- bronchial atresia 1312
  - lobar emphysema with 677
- bronchial biopsy
  - asthma 926–7
  - COPD 628–9
- bronchial brushings 160, 927
- bronchial carcinoma *see* lung cancer
- bronchial cartilage, atresia 677
- bronchial casts 105, 927, 927
- bronchial challenge tests 49–50
  - asthma 895
  - see also* challenge tests
- bronchial circulation 19
  - development 1–2
- bronchial cyst *see* bronchogenic cysts
- bronchial dilatation
  - chest radiography 146, 810, 811
  - mechanisms 804–5
  - see also* bronchiectasis
- bronchial diseases, genetics 93–5
- bronchial epithelial cells
  - damage in asthma 907
  - see also* epithelial cells
- bronchial glands 937
- bronchial isomerism 1311–12
- bronchial melanoma 1136
- bronchial mucus *see* mucus
- bronchial obstruction 800, 800
  - bronchiectasis pathogenesis 800–1
  - central 800–1
  - empyema pathogenesis 446
  - extramural compression 800–1
  - intraluminal occlusion 800
  - pressure of secretions theory 805
  - small peripheral bronchi 800
  - see also* airflow obstruction
- bronchial papilloma 1136
- bronchial reactivity, asthma definition 922
- bronchial responsiveness
  - lung function relationship 900–1
  - sodium-induced increase 900
- bronchial sarcoidosis 1049
- bronchial secretions 14, 15, 53
  - protective proteins in 15, 85–7, 86
  - see also* mucus; respiratory secretions; sputum
- bronchial smooth muscle 13
  - asthma 907, 927
  - pathogenesis 931–2, 938–9
  - contractile mechanism 938, 939
  - resting tone 13, 250
- bronchial tumour
  - asthma *vs* 961
  - see also* lung cancer
- bronchial veins 19
- bronchial walls, thickening
  - asthma 958
  - COPD 658
- bronchial washings 160
  - infection detection 161
  - see also* bronchoalveolar lavage (BAL)
- bronchiectasis 794–828
  - aetiology and pathogenesis 794–806, 795
    - bronchial dilatation mechanisms 804–5
    - infections 798–800
    - inflammation 801–4
    - mucociliary clearance 794–8
    - obstruction 800–1
    - theories 804–5
  - allergic bronchopulmonary aspergillosis 588, 803
  - atelectatic 806
  - atopy and asthma association 803
  - autoimmune diseases associated 802–3
  - breath sounds 116, 807
  - bronchography 812–14, 814
  - chest radiography 145–6, 804, 810–12, 811, 812, 813
  - children 807, 822
  - classification 806
  - clinical features 116, 806–8
  - complications 822–3
  - computed tomography 142, 147, 794, 804, 814–15, 821
  - high-resolution (HRCT) 123, 794, 804, 815
  - congenital 797, 1313
  - cor pulmonale 750, 806, 822
  - cystic 806, 815
  - cystic fibrosis 794, 796–7, 851
  - definition 794
  - 'dry' and 'wet' 805, 807
  - follicular 806
  - functional impairment 808–9
  - investigations 809–15
  - microbiology 809–10
  - mortality 822
  - 'old-fashioned' 799–800
  - pathology 805, 805–6
  - pertussis complication 352, 799
  - predisposing conditions 794–8
  - prevalence 794
  - primary pulmonary tuberculosis 509, 517, 799
  - prognosis 821–2
  - rheumatoid disease 1389
  - saccular (cystic) 806, 815
  - sites 806
  - sputum 104, 806, 809
  - traction 142, 143
  - treatment 815–21
    - antibiotic choice 816–17
    - antibiotic dose/duration and route 817–18
    - end-stage 821
    - medical 816–20
    - postural drainage 818–19
    - surgical 820–1, 823
- bronchiolar disease 829–38
  - classification 829–30, 830
  - physiological aspects 829
  - syndromes 829–36
  - see also* bronchiolitis
- bronchiolar emphysema 880
- bronchiolar inflammation, smoking and 625
- bronchiole–alveolar communications 15
- bronchioles 9, 829
  - anatomy 829
  - development 2–3
  - emphysema 632, 632
  - microscopic structure 14, 829
  - obstruction 829
- bronchiolitis
  - acute, in children 1478
  - constrictive 830
    - see also* obliterative bronchiolitis
  - cystic fibrosis 855–6
  - diffuse panbronchiolitis 831–2
  - infective 829, 830
  - localized, unilateral emphysema due to 677–9
  - mineral dust 831, 832
  - non-obliterative 830–1
  - obliterative *see* obliterative bronchiolitis
  - 'respiratory bronchiolitis causing interstitial disease' 831
  - respiratory syncytial virus (RSV) 899, 1478
  - smokers' 830–1, 831
  - toxic 830, 836
  - transplant-associated 833, 836
- bronchiolitis obliterans *see* obliterative bronchiolitis
- bronchiolitis obliterans with organizing pneumonia (BOOP) 830, 832, 833
  - chest radiography 833, 834
  - clinical course and management 835–6
  - connective tissue diseases 1396
  - CT 833, 834
  - HIV infection 1360
  - pathology 835, 836
  - see also* obliterative bronchiolitis
- bronchioloalveolar carcinoma 1080, 1082, 1083
  - chest radiography 1089, 1092
  - sputum 1529
- bronchioloalveolar tumour, intravascular 1137
- bronchitis
  - acute 345–7
    - seasonal variations 345
  - acute-on-chronic 345
  - localized, unilateral emphysema due to 677–9
  - occupational 1441
  - 'purulent' 814
  - spasmodic in tropical pulmonary eosinophilia 1024
- bronchitis, chronic 616
  - airways obstruction with 616
  - antibiotics 208, 210
  - 'British hypothesis' 616, 624
  - classification 616
  - coal dust association 1414–15
  - death rates 621
  - definition 616
  - intraluminal airspace inflammation 624
  - mechanical ventilation indication 1510–11
  - metabolic alkalosis 38
  - mucopurulent 616
  - obstructive 616
  - pathology 628
  - in silicosis 1422
  - simple 616
  - smoking and 312, 313
  - symptoms 651
  - see also* chronic obstructive pulmonary disease (COPD)
- bronchitis obliterans 805, 808, 814
  - see also* bronchiectasis
- bronchoalveolar lavage (BAL) 150, 160–2
  - allergic alveolitis 1006, 1007, 1009
  - asthma 928
  - cell counts and findings 162, 1043
  - clinical approach 160–1

- COPD 628–9  
 cryptogenic fibrosing alveolitis 886  
 elastolytic activity and 638  
 eosinophils 928  
 IgG in cryptogenic fibrosing alveolitis 881  
 in immunosuppressed patients 1349  
 indications 161  
 interstitial lung disease differential diagnosis 890  
 large-volume 161–2  
 normal cell numbers 162, 1043  
*Pneumocystis carinii* pneumonia 1368–9  
 research 161–2  
 respiratory secretion collection 362  
 sarcoidosis 162, 1035, 1043, 1056  
 specimen management 161, 162  
 volume of fluid 160, 161  
 bronchocentric granulomatosis 588, 954, 1072–4, 1074  
 bronchoconstriction  
   acetylcholine-mediated 250  
   asthma 907, 918  
   by cysteinyl leukotrienes 259  
   drug-induced 1458–60  
     drugs causing 1458, 1459, 1459–60  
     mechanisms 1458–9  
   exercise 5  
   histamine and dusts causing 250  
   neurokinin A 938  
   paradoxical  
     after  $\beta_2$ -agonists 248  
     anticholinergic bronchodilators causing 251  
   parasympathetic control and 937  
   prostaglandins involved 935–6  
   reduction by bronchodilators 246  
   transient in workplace 949  
   vagal-mediated 250  
 bronchodilators  
   anticholinergic (atropine-like) 249–52  
     *see also* anticholinergic bronchodilators  
   asthma  
     acute severe 986  
     chronic *see* asthma  
     diagnostic test 895  
   bronchiectasis 819  
   COPD 664–6  
     acute exacerbation 675  
     reversibility assessment 655, 667  
   effect in divers 1492  
   long-acting 249  
   magnesium as 900  
   nebulized  
     acute COPD 675  
     terminal care 1530  
   sympathomimetic *see*  $\beta_2$ -agonists;  
   sympathomimetic bronchodilators  
 bronchogenic carcinoma  
   in cryptogenic fibrosing alveolitis 882  
   phrenic nerve involvement 1236  
 bronchogenic cysts (bronchial cysts) 1293, 1312–13  
   infected 1312  
   lung abscess *vs* 469  
   pathological and clinical features 1312, 1314  
 bronchographic contrast media,  
   pulmonary reactions 428  
 bronchography 151  
 bronchiectasis 812–14, 814  
   difficulties 814  
   lung sequestration 1318–19  
     technique 812–13  
 broncholith, primary pulmonary  
   tuberculosis 509–10  
 bronchomalacia (Williams–Campbell  
   syndrome) 797  
 bronchomediastinal trunk 1166  
 bronchopancratic fistula 1247  
 bronchopathia osteoplastica 1338–9  
 bronchopleural fistula 446, 1158–9  
   empyema with 457, 468–9  
 bronchopneumonia 356  
   *see also* pneumonia  
 bronchopulmonary aspergillosis  
   asthma 953–5  
   *see also* allergic bronchopulmonary  
   aspergillosis  
 bronchopulmonary dysplasia 19, 41, 714, 1477  
   clinical features and treatment 714  
 bronchopulmonary infections *see*  
   respiratory tract infections  
 bronchopulmonary lavage, alveolar  
   proteinosis 1335–7  
 bronchopulmonary nodes 21  
 bronchopulmonary reactions, irritative,  
   questionnaires 75–6  
 bronchorrhoea 104  
   lung cancer 1086  
   management 105  
 bronchoscopes  
   fiberoptic 156  
     cleaning and disinfection 170–1  
     contamination 170–1  
     protection/handling 170  
   rigid 171  
 bronchoscopy  
   after closed drainage of empyema 456  
   allergic bronchopulmonary aspergillosis 954  
   lung abscess 468, 473  
   massive haemoptysis 473  
   respiratory secretion collection 362–3  
 bronchoscopy, fiberoptic 148–72  
   appearances/interpretation 155–8  
   trachea 155  
   tracheobronchial mucosa 156, 158  
   complications 166–9  
   contraindications 169, 169–70  
   diagnostic indications 148–51, 149  
   diffuse lung disease 149–50  
   infections 150  
   lung cancer 148–9  
   diagnostic methods 151  
   diagnostic yield 163–6  
   elderly 152  
   equipment 153  
   forceps 158, 159, 160  
   infection control 170–1  
   morbidity 167–9  
   mortality 167  
   procedure 151–7  
     advancement of instrument 155  
     passing bronchoscope 153, 154–5  
   report sheet 157  
   respiratory secretion collection 362  
   sample handling 170  
   sampling procedures 158–63  
     *see also* bronchoalveolar lavage (BAL)  
   sedation for 152–3  
   staff co-ordination 161  
   ‘surveillance’ 150  
   therapeutic applications 149, 151  
   topical anaesthesia 153–4  
   tuberculosis diagnosis 520  
 bronchoscopy, rigid 171–2, 172  
   in bronchiectasis 823  
*Brucella* 420  
   antibodies 420  
   pneumonia 420–1  
*Brucella melitensis*, empyema 448–9, 454  
 brucellosis 420–1  
   transmission 420  
   treatment 420–1  
 bruising, steroids causing 268  
 bruit, arteriovenous malformation 1324  
 brush cells 13  
 Bruton’s agammaglobulinaemia 798  
 bubbles  
   lung as filter 1486, 1491  
   *see also* gases  
 bubo 425  
 budesonide 276, 277  
   COPD 667  
   high-dose 277  
   inhaled 955  
     asthma 980, 982  
   structure 278  
 budgerigar antigen 1002, 1009, 1010  
 antigen removal/exposure prevention 1010  
 budgerigars 1014–16  
 ‘buffalo hump’ 239  
 bullae 630  
   classification and origins 630  
   definition 661  
   emphysematous *see* emphysematous  
   bullae  
   infected, lung abscess *vs* 469, 470  
 buprenorphine, in terminal care 1527  
*Burkholderia cepacia* 407  
   cystic fibrosis 854–5  
   empyema 449, 455  
 burns, *Pseudomonas aeruginosa* infections 408  
 busulfan (busulphan), alveolitis due to 1464  
 1,3-butadiene, as carcinogen 328, 331  
 byssinosis 1441–3  
   acute effects of cotton 1441–2  
   chronic effects of cotton 1442–3  
   pathogenesis 1443  
   prevention and management 1443  
   WHO grading 1442, 1442  
 cadmium 1448  
   COPD and 624  
*café-au-lait* spots 1273  
 caffeine 252  
   diaphragmatic fatigue 1236  
 Calabar swellings 609  
 calcification  
   eggshell, of nodes 1418, 1419  
   hilar lymph nodes *see* hilar lymph nodes  
   lung *see* lung  
   mediastinal teratoma 1286, 1287  
   paranasal sinuses 344  
   pleural 134, 1159  
   popcorn 138, 138  
 calcium  
   glucocorticosteroid actions 263  
   influx  
     allergic asthma 933  
     glucocorticosteroid action 260–1  
   role in smooth muscle contraction 939  
   supplements 269

- calcium channel antagonists  
 asthma 939  
 primary pulmonary hypertension 756  
 calcium folinate 222  
 Caldwell–Luc procedure 345  
 cancer  
 fluconazole ‘primary prophylaxis’ 233  
 genetics 98  
 pain relief 1525, 1525–9  
 thrombosis predisposition 720  
*see also specific cancers*  
*Candida* 594–5  
 lung abscess 463  
*Candida albicans* 594  
 fluconazole activity against 231  
 oral thrush 339  
 candidiasis 594–5  
 ampicillin and amoxicillin association 197  
 disseminated 595  
 fluconazole use 232  
 oral 339, 595  
 oropharyngeal, inhaled corticosteroids and 276, 981  
 pulmonary 595  
*see also thrush*  
 cannabis 1188  
 cannulas, intercostal tube drainage 1198  
 capillary haemangioma  
 mediastinal 1291  
 pulmonary 1141  
 capillary permeability 30–1  
 reduction by glucocorticosteroids 262  
 Caplan’s lesions 1411, 1412, 1414  
 Caplan’s syndrome 1386, 1411, 1412  
 capreomycin 550, 551, 558  
 carbamate poisoning 1229  
 carbamazepine 1528  
 carbamino compounds 37  
 carbapenems 204  
 carbon, particles as air pollutants 326  
 carbon anhydrase 37  
 carbon dioxide  
 alveolar ventilation 27  
 arterial partial pressure  
 respiratory failure 699  
 type II respiratory failure 697, 697, 701  
 asphyxiant 1444  
 chemoreceptor sensitivity 51  
 diffusing capacity, *P. carinii* pneumonia 1367–8  
 diffusion to CSF 51  
 dissociation curve 37  
 dissolved 37  
 excretion in type I respiratory failure 697  
 partial pressure ( $P_{CO_2}$ ) 26, 28, 28–9  
 abnormal  $V_A/Q$  ratios 32  
 alveolar 28–9  
 control during mechanical ventilation 1500  
 diving and 1482, 1483  
 high altitude 56  
 in hyperventilation 1265  
 raised in respiratory acidosis 38  
 regulation 51  
 transcutaneous monitoring 38  
 release from tissues 37  
 retention  
 oxygen therapy causing 700  
 scoliosis 1217  
 transport in blood 38  
 vasodilator properties 698  
 ventilatory response 51  
 carbon fibres 1435, 1439  
 carbonic acid 37  
 carbonic anhydrase, inhibition 281–2  
 carbon monoxide  
 affinity for haemoglobin 35, 36  
 asphyxiation 1444–5  
 diffusing capacity ( $D_{LCO}$ ) 34–5  
 alveolar haemorrhage and 1331  
 COPD 641, 643, 656  
 cryptogenic fibrosing alveolitis 886  
 pulmonary telangiectasia 1325  
 sarcoidosis 1053  
 scoliosis 1217  
 health effects and mechanisms 331  
 poisoning 331, 1445  
 as pollutant 327  
 transfer factor  
 allergic alveolitis 1003  
 asbestosis 1429  
 asthma 956  
 bronchiectasis 808  
 carbon monoxide transfer coefficient ( $K_{CO}$ )  
 alveolar haemorrhage 1331  
 COPD 627  
 carboplatin 292–3  
 Carborundum 1440  
 carboxyhaemoglobin 36, 1444–5  
 carbon monoxide effects 331  
 smoking and 313, 331  
 carboxypenicillins 199–200  
 carcinogens 98  
 as air pollutants 328–9, 331  
 carcinoid syndrome 1135, 1466  
 carcinoid tumours 1133–5  
 atypical 1133  
 clinical features 1134–5  
 endobronchial, fiberoptic bronchoscopy 156  
 histology 1133–4, 1134  
 lung 138  
 mediastinal 1278  
 metastases 1134–5  
 obliterative bronchiolitis aetiology 833  
 small-cell carcinoma with 1083  
 thymic 1283  
 treatment and prognosis 1135  
 carcinomatosis, nodular shadows 141  
 carcinomatous embolization 1146–7  
 carcinosarcoma 1144–5  
 cardiac arrhythmias, fiberoptic  
 bronchoscopy contraindication 169  
 cardiac asthma 894, 922  
 cardiac dextroposition 1321  
 cardiac failure *see* heart failure  
 cardiac function, asthma 957  
 cardiac massage, external 789  
 cardiac output  
 COPD 647–8, 650  
 high altitude effect 56  
 measurement method 749  
 pulmonary artery pressure response 30, 30  
 cardiac pain 106  
 cardiac stress, asthma 957  
 cardiopulmonary bypass 1518  
 cardiopulmonary resuscitation,  
 barotrauma causing pneumothorax 1188  
 cardiothoracic ratio 120  
 cardiotoxicity, doxorubicin 289  
 cardiovascular complications  
 fiberoptic bronchoscopy 169  
 hypereosinophilic syndrome 1031  
 risk in sleep apnoea/hypopnoea  
 syndrome 1255  
*see also heart disease*  
 cardiovascular examination, COPD 653  
 cardiovascular system, sarcoidosis 1052–3  
 carinae 11  
 carmustine, alveolitis due to 1464–5  
 Carney’s triad 1143, 1144, 1381  
 carotid arteries, aneurysms 1298  
 carotid bodies 50  
 high altitude effect 57  
 nerve discharge stimuli 50  
 carotid chemoreceptors 50–1, 56  
 cars and pollution *see* vehicles  
 cartilage  
 articular, drug-induced damage 226  
 bony in tracheopathia osteoplastica 1338–9  
 bronchial, atresia 677  
 in larynx 6  
 ‘napkin-ring’ 1320  
 case–control study 65, 70–1  
 end-point 70  
 caseous necrosis, tuberculosis 479, 480, 509, 544  
 Castleman’s disease 1283, 1342  
 casts, bronchial 105, 927, 927  
 cat  
 allergens 897, 945  
 asthma aetiology 897, 945  
 catalase 1467  
 cataplexy 1255  
 cataracts  
 corticosteroid-induced 270–1  
 smoking and 313  
 subcapsular 983  
 catarrhal symptoms 335, 336–7  
 catecholamines  
 paragangliomas producing 1277–8  
*see also epinephrine*  
 catechol-*O*-methyltransferase 245, 247  
 cathepsin B 638  
 cathepsin G 87, 638  
 cathepsin L 638  
 caveolae 16  
 caveolae intracellulares 20  
 cavernostomy 592  
 cavernous haemangioma, mediastinal 1291  
 cavernous lymphangioma 1222, 1223  
 cavernous sinus thrombosis 345  
 cavitation (lung)  
 blastomycosis 578  
 histoplasmosis 584  
 lung abscess 464  
 lung cancer 1088  
 opportunistic mycobacterial disease 567, 568  
 rheumatoid disease 1387  
 tuberculosis 517, 518  
 cavity, definition 630  
 CD4 T cells  
 asthma 908, 912, 926  
 count in *Pneumocystis carinii* pneumonia 1367  
 HIV infection 236, 1351  
 in sarcoidosis 1042  
*see also T cells*  
 CD8 T cells, HIV infection 1352  
 CD11/18, neutrophil–endothelial interactions 779  
 CDKN2 gene, lung cancer and 1085  
 cefaclor 202



- cefadroxil 202
- cefalexin 202
- cefamandole 202
- cefazolin 202
- cefibuten 202
- cefipirome 202
- cefixime 202
- cefodizime 201
- cefotaxime 202
- cefoxitin 202
  - empyema 453–4
  - lung abscess 472
- cefpodoxime proxetil 202
- ceftazidime 202
  - meliodosis 424
- ceftizoxime 202
- ceftriaxone 202
- cefuroxime 202, 203
  - pneumococcal pneumonia 381
- cell-mediated immunity
  - asthma *see* asthma
  - defects in HIV infection 1351–2
  - tuberculosis 481
  - see also* T cells
- cement 1434
- Centers for Disease Control and Prevention (CDC) 349
  - Chlamydia* pneumonia 396
  - HIV infection staging 1352
- central nervous system (CNS)
  - breathing control 50
  - effects of hypercapnia 698
  - hypoxaemia effect 698
  - sarcoidosis 1051–2
  - tuberculosis *see* tuberculosis (TB)
  - Wegener's granulomatosis 1069
- central nervous system (CNS) depressants,
  - respiratory failure due to 709
- 'cepacia syndrome' 855
- cephalosporins 200–3
  - adverse effects 200–1
  - antipseudomonal 203
  - aspiration pneumonia 414
  - classification 201, 201–2
  - empyema 453–4
  - first-generation 201, 201–2
  - lung abscess 472
  - mechanism of action 200
  - overuse 203
  - pneumococcal pneumonia 381
  - resistance 203
  - second-generation 201, 202
  - spelling standardization 201
  - structure 200, 200
  - susceptible organisms 200
  - third-generation 201, 202, 203
  - uses 202–3
- ceramic fibres 1435
- cerebellar ataxia 1113
- cerebral abscess 823, 1324
  - tuberculous 529
- cerebral cortex, breathing control 50
- cerebral metastases *see* intracranial metastases
- cerebral oedema 530, 788, 1532
- cerebrospinal fluid (CSF)
  - carbon dioxide diffusion 51
  - culture in tuberculous meningitis 530
  - examination in CNS tuberculosis 529–30
  - protein and glucose levels 529–30
- cerebrovascular accidents 1324
- cerebrovascular disease
  - arteriovenous malformations 1324
  - risk in sleep apnoea/hypopnoea syndrome 1255
  - see also* stroke
- cervical carcinoma, smoking and 313
- cervical cordotomy, respiratory failure 712
- cervical lymph nodes 21
- cervical ribs 1212, 1213
- cervicofacial abscess 575
- cestodes 610, 612–14
- CFC-free inhalers 279, 989
- C fibres 84
- Chagas' disease 604
- challenge tests
  - allergic alveolitis 1009, 1010
  - asthma *see* asthma
  - bronchial 49–50
  - drug-induced lung disease 1466
  - histamine 50, 932
  - methacholine 50, 932–3, 999
- chancre, tuberculous 539, 539
- chaperones, new cystic fibrosis treatment and 865
- charcoal haemoperfusion 1469
- Charcot–Leyden crystals 105, 910, 929, 954, 1020, 1021
- cheesewormer's disease 1014
- chemical pleurodesis 1199–200
- chemicals
  - allergic alveolitis due to 1016
  - alveolar haemorrhage due to 1330
  - household, indoor air pollution 332
  - occupational asthma 950, 950
- chemodectoma 1143, 1272, 1277
- chemokines 778, 913, 915–16
  - ARDS pathogenesis 778
  - asthma pathogenesis 915–16
  - C-C group 778, 913, 915
  - cells secreting 909
  - C-X-C group 778, 913, 915–16
  - receptors 915–16
- chemoreceptors
  - breathing control 50–1, 1264
  - abnormal in COPD 646
  - carotid 50–1, 56
  - central 32, 51
  - paraganglioma site 1277
- chemotactic factors
  - eosinophils 917, 935, 1020
  - leucocytes 935
  - monocytes 917
  - neutrophils 637, 912, 917, 931, 935
- chemotherapy 1103
  - complications 1107
  - 'gentle' (palliative) 1107–8
  - high-dose
    - seminoma 1290
    - small-cell lung cancer 1106
  - lung cancer 1103, 1103, 1103–4
  - palliative 1107–8
  - radiotherapy with 1104, 1108
  - small-cell 1104–8
  - surgery with 1103–4
  - malignant mesothelioma 1177
  - non-Hodgkin's lymphoma 1129
  - Pneumocystis carinii* pneumonia with 1363
  - pulmonary complications 1346, 1347
  - scheduling 1106–7
  - seminoma 1290
  - side effects 1107
  - superior vena cava obstruction 1113–14
  - thymoma 1280
  - see also* cytotoxic drugs
- chest
  - auscultation 114–16
  - barrel-shaped 652
  - discomfort, lung cancer 1086
  - funnel (pectus excavatum) 110–11, 1213–14
  - movement, pneumothorax 1190
  - overinflation 110, 1235
    - COPD 653
    - see also* lung, overinflation
  - palpation 114
  - percussion 114, 819
  - physiotherapy, cystic fibrosis 864
  - pigeon (pectus carinatum) 110–11, 1212–13
  - solitary lesions, imaging 134–9
- chest cage *see* thoracic cage
- chest pain 106–7
  - ankylosing spondylitis 1219
  - causes 106, 106
  - central anterior 107
  - COPD 652
  - corticosteroid-induced osteoporosis 269
  - diaphragmatic tumours 1240–1
  - differential diagnosis 889, 1192
  - interstitial lung disease 889
  - malignant mesothelioma 1175
  - mediastinal tumours/cysts 1271
  - pneumomediastinum 1205
  - pneumothorax 1189
  - pulmonary embolism 727
  - radiation pneumonitis 427
  - tuberculosis 516
- chest radiography 119–22
  - abnormal, bronchoscopy indication 148
  - adult respiratory distress syndrome 770, 771, 783
  - after percutaneous fine-needle biopsy 173–4
  - allergic bronchopulmonary aspergillosis 589, 591, 959, 960
  - amoebic lung abscess 606
  - amyloidosis 1338
  - ankylosing spondylitis 1397
  - anterior views 119–21
  - anteroposterior (AP) view 119
  - aortic aneurysms 1299
  - arteriovenous malformations (fistulae) 1141, 1142, 1323, 1324–5
  - asbestosis 1427, 1427–8
  - aspiration pneumonia 413, 413
  - asthma 958–60, 959, 960
  - atrial septal defect 761
  - atypical pneumonia 141, 141
  - azygos lobe 1316
  - barotrauma 1483, 1484
  - 'bat's wing' appearance 768, 769
  - bowed/bulging fissure sign 407
  - brochioloalveolar carcinoma 1089, 1092
  - bronchial branching anomalies 1311
  - bronchiectasis 145–6, 804, 810–12, 811, 812, 813
  - plain film usefulness 812
  - bronchogenic cyst 1314
  - Caplan's syndrome 1412
  - chickenpox pneumonia 416, 417
  - Chlamydia psittaci* pneumonia 398
  - chondrosarcoma 1226, 1226
  - chronic eosinophilic pneumonia 1025–6, 1027
  - Churg–Strauss syndrome 1029, 1030
  - coal-workers' pneumoconiosis 1409–11, 1410, 1411

- chest radiography (*Continued*)  
 COPD 657–9, 658  
 cor pulmonale 661, 751  
 cryptogenic fibrosing alveolitis 883, 883, 884  
 cryptogenic mediastinal fibrosis 1303  
 cryptogenic pulmonary eosinophilia 1025–6, 1027  
 cystic fibrosis 812, 857  
   scoring system 851–2  
 diaphragm 120, 1234–5  
 diaphragmatic paralysis 1237, 1238  
 diffuse lung disease 140–7  
 diffuse shadowing 144  
   before diving 1491  
   ‘double cardiac shadow’ 469  
   D-shaped shadow 450  
   emphysema 658, 658  
   emphysematous bullae 658, 658, 661–2  
   empyema 449–51, 451  
   eventration of diaphragm 1241, 1242  
   extrapulmonary lesions 134–6  
   extrinsic allergic alveolitis 1003, 1004, 1005, 1009  
 farmer’s lung 1003, 1004, 1005  
 foregut cysts 1294, 1294  
 ‘gloved finger’ shadows 810, 812, 959  
 Goodpasture’s syndrome 1331, 1332  
 ground-glass appearance 883, 1004  
 guidelines on use 119  
 in haemoptysis 106  
 hamartoma 1144, 1144  
 hiatus hernia 1244  
 high-pressure pulmonary oedema 768, 769  
 hilar lymphadenopathy 1046, 1047, 1048  
 hilar shadows 139  
 histoplasmosis 583, 584  
 HIV infection 1353  
 Hodgkin’s lymphoma 1124–5, 1126, 1127  
 ‘holly leaf’ shadows 1167, 1168  
 honeycomb lung 181, 883, 884, 1427  
 hyalinizing granuloma 1341  
 hydatid disease 612, 613  
 hydropneumothorax 1157, 1193  
 hypersensitivity pneumonitis 1003, 1004, 1005, 1009  
 idiopathic hilar fibrosis 1341  
 ILO classification 77–8, 78, 78–9  
 in immunosuppressed patients 1348, 1349  
 indications 119  
 interstitial lung disease differential diagnosis 890  
 intrapulmonary solitary lesion 134  
 Kaposi’s sarcoma 1137, 1138, 1359  
 Kartagener’s syndrome 810, 812  
*Klebsiella pneumoniae* 407  
 Langerhans’ cell histiocytosis 1132  
 lateral view 121, 122  
 Legionnaires’ disease 389, 389  
 lobar collapse 130, 131, 132  
 lobar consolidation 127–30, 129, 379  
 Loeffler’s syndrome 1023  
 lung abscess 462, 466, 466, 467  
 lung cancer 136, 136–7, 469, 1088, 1088–9, 1089, 1090, 1091, 1092  
 lung hypoplasia 1315  
 lung metastases 1145, 1146  
 lung sequestration 1318–19, 1319  
 lung volume loss 810  
 malignant mesothelioma 1176  
 mediastinal abscess 1301, 1302  
 mediastinal seminoma 1289, 1289  
 mediastinal teratoma 1285, 1286  
 metastases 1225  
 mitral valve disease 759, 760  
 Morgagni hernia 1245  
*Mycobacterium avium-intracellulare* infection 1357  
*Mycoplasma pneumoniae* 393, 394  
 near-drowning 1488  
 nodular shadows 140–1  
 obliterative bronchiolitis 833–5, 834  
 observations and interpretations 119–22  
 parallel lines 810, 811  
 pectus excavatum (funnel chest) 1214, 1215  
 pericardial tuberculosis 532  
 pleural effusions 130–4, 1154–5, 1155, 1163, 1355  
 pleural fibrosis 1170, 1171  
 pleural plaques 1167, 1168  
*Pneumocystis carinii* pneumonia 596, 1358, 1365, 1365, 1365–7, 1366, 1367  
 pneumomediastinum 1205–6, 1206, 1484  
 pneumonia 129, 364  
   pneumococcal 378–80  
 pneumothorax 1190–2, 1191, 1192  
 posteroanterior (PA) view 119, 120  
 pulmonary alveolar proteinosis 1335, 1336  
 pulmonary embolism 728–9, 730, 731  
 pulmonary fibrosis 1387, 1388  
 pulmonary hypertension 649, 661, 751, 754, 758, 760, 761, 810  
   primary 754  
 pulmonary nodules 1386  
 pulmonary opacity distributions 890  
 pulmonary telangiectasia 1140, 1141  
 pulmonary veno-occlusive disease 758, 758  
 radiation pneumonitis 427, 1470, 1470, 1471  
 reticular shadowing 141–4  
 reticulonodular shadows 141–2  
 retrosternal goitre 1297, 1297  
 ring shadows 145–6, 810, 811, 959  
 sarcoidosis 1045, 1046, 1047, 1048  
 silicosis 1418–21, 1419, 1420, 1421  
 SLE 1390  
 solid tubular opacities 810, 812  
 solitary lung masses 134, 137–9  
 standardization of studies 77–9  
 ‘straight edge effect’ 427  
 systemic sclerosis 1394  
 techniques 119–20  
 tension pneumothorax 1483, 1484  
 thoracoplasty 1228  
 thymic cysts 1284  
 thymoma 1281, 1282  
 thymus gland 1279  
 tramline shadows 810, 811, 959  
 tuberculosis  
   in AIDS 1354, 1355  
   miliary 512–13, 513, 1354  
   postprimary pulmonary 516–18, 517, 518  
   primary pulmonary 508, 508  
   screening 494–5  
 unilateral hypertransradiancy in McLeod’s syndrome 677, 678, 678  
 Wegener’s granulomatosis 1068  
*see also other specific conditions*  
 chest wall  
   acquired abnormalities 1214–28  
 actinomycosis 1228  
 appearance 110–11  
 bleeding, percutaneous fine-needle biopsy complication 174  
 cold abscess 1227  
 compliance 39–40  
   improvement by ventilation 1513  
 congenital abnormalities 1212–14  
 disorders 1212–33  
   breathlessness 108  
 echinococcosis 1228  
 fractures 1214–16  
 fungal infections 1228  
 infections 1226–8  
 lesions, chest radiography 135  
 movements 114  
 osteomyelitis 1226–7  
 pain 106  
 septic arthritis 1227  
 swellings 111  
 syphilitic gumma 1227–8  
 tuberculosis 1227  
 tumours 1221–6, 1222  
   metastases 1223–4, 1225  
   soft tissue 1221–3, 1222  
   thoracic cage 1222, 1223–6  
 unilateral changes, differential diagnosis 678  
 Cheyne–Stokes breathing 110  
 Chiba needle 172  
 chickenpox  
   pneumonia 235, 416–18  
   treatment 416, 418  
 children  
   asthma 923  
   BCG vaccination 498  
   bronchiectasis 807, 822  
   common colds 336  
   corticosteroid adverse effects 271  
   cystic fibrosis *see* cystic fibrosis  
   epiglottitis 340  
   growth retardation 276  
   infective bronchiolitis 830  
   influences on adult lung diseases 1476–80  
   lung disease 1477  
   lung transplantation 1518  
   passive smoking effect 313, 1478  
   respiratory tract infections 1478  
   sensitivity to toxins 1478  
   smoking by 314, 319  
   tuberculosis 483, 508  
     CNS involvement 528–9  
     treatment 557, 558  
   wheeze 900  
   wheezy illness 923, 923  
   whooping cough 351  
 Chinese avian influenza 348  
*Chlamydia* 396  
   antibiotic susceptibility 204  
   lipopolysaccharide antigen 398  
   pneumonia 396–400  
*Chlamydia-like microorganism Z* 400  
*Chlamydia pneumoniae*  
   coronary artery disease 400  
   culture 400  
   pneumonia 399–400  
   serological variant IOL-207 399  
*Chlamydia psittaci*, serotypes 398  
*Chlamydia psittaci* pneumonia 396–9  
   chest radiography 398  
   clinical manifestations 397–8  
   complications 398–9

- epidemiology and transmission 396–7
- incidence 397
- incubation period 397
- investigations 398
- pathology 397
- treatment and prognosis 398
- Chlamydia trachomatis* 396, 400
- chlorambucil 288–9
- chloramphenicol 227–8
  - adverse effects 228
  - empyema 454
  - lung abscess 472
  - uses/indications 228
- chloride
  - in sweat 844, 849, 849
  - sweat test 848–9
  - transport 844
- chloride channels
  - abnormal function, CF gene mutations 843
  - CFTR function 93, 841
  - cyclic AMP-activated 840, 844
  - outward rectifying (ORCC) 841, 844
- chlorine exposure 999, 1446–7
- chlorofluorocarbons 279
- chloroquine, amoebiasis 606
- chlorpromazine, hiccup relief 1239, 1532
- cholera, epidemics 63
- cholestasis, in cystic fibrosis 860
- cholestatic jaundice, erythromycin causing 205
- cholesterol, crystals 1385
- cholinergic crisis 710
- choline theophyllinate 252, 253
- chondroma 1224
- chondrosarcoma 1226, 1226
- choriocarcinoma 1284
- choroidal tubercles 512, 540
- chromolipid 1382
- chronic disease, history-taking 102
- chronic fatigue syndrome 1265
- chronic granulomatous disease 97
- chronic lung disease
  - GP consultations 618
  - paediatric 1477
- chronic obstructive airways disease (COAD) *see* chronic obstructive pulmonary disease (COPD)
- chronic obstructive pulmonary disease (COPD) 616–95
  - acute exacerbation 674
    - assessment of recovery from 676
  - acute exacerbation, management 674–6
    - antibiotics 197, 203, 674–5
    - anticoagulants 676
    - bronchodilators 675
    - diuretics 675–6
    - physiotherapy 676
  - aetiology 619–26
  - airflow obstruction
    - age effect 626, 626
    - persistent 619–20
  - animal models 634
  - breathing adaptations 645
  - 'British hypothesis' 616, 624
  - bronchoalveolar lavage 628–9
  - carbon monoxide transfer coefficient ( $K_{CO}$ ) 627
  - cardiovascular examination 653
  - clinical features 650–3
    - occupation/smoking history 652
    - presentation types 653
    - signs 652–3
  - symptoms 650–2
  - coal dust association 1414–15
  - definitions and terminology 616–17
  - differential diagnosis 616
  - domiciliary oxygen therapy 627, 668–72
    - criteria 670–1
    - portable 671
    - prescribing criteria 670
    - 'Dutch hypothesis' 625, 626, 894
  - epidemiology 617–19
    - prevalence 617–18
    - social class 619
  - exercise tolerance improvement
    - drug and oxygen therapy 665, 668
  - exercise training 672, 673
  - forced expiratory volume in 1 sec (FEV<sub>1</sub>) 617, 619, 624, 627, 651, 654
    - as measurement of choice 655
    - oxygen therapy effect 669
    - smokers *vs* non-smokers 620–1, 621
    - smoking and 620, 626–7
    - smoking cessation effect 621, 621, 662–3
    - 'tracking effect' 626–7
  - hypersecretion of mucus 617, 619–20, 628
  - influenza complications 348
  - influenza vaccination 674
  - long-term management 664–8
    - anticholinergics 251, 252, 664, 665
    - approach to patients 667–8
    - $\beta$ -agonists 664–5
    - bronchodilators 251, 252, 664–6
    - combination therapy 665–6
    - corticosteroids 666–7
    - drug-delivery devices 666
    - theophyllines 256, 664, 665
  - lung function 'escalator' 668
  - lung mechanics 640–3
  - lung transplantation 676–7, 1517
  - lung volume reduction surgery 679
  - mild 654
    - lung mechanics 640–1
    - management 667
  - moderate 654
    - lung mechanics 641–3
    - management 667
  - morbidity and use of health resources 619, 619
  - mortality 618, 618–19, 620, 709
  - natural history 626–7
  - non-physiological assessments 657
  - nutritional supplementation 646, 673–4, 707
  - oedema and cause 648–9, 650, 653
  - pathogenesis 634–40
    - see also under* emphysema
  - pathology 627–33
    - bronchial biopsy 628–9
    - severe COPD 632–3
  - pathophysiology 640–3
  - physiological assessment 653–7
    - arterial blood gases 644, 648, 656, 698
    - exercise tests 656–7
    - flow-volume loops/curves 641, 641, 654
    - gas transfer for carbon monoxide 656
    - lung volumes 654–5
    - peak expiratory flow 654
    - reversibility to bronchodilators 655, 667
    - reversibility to corticosteroids 656
    - sleep studies 657
    - spirometry 654
  - pressure-volume curves 641, 642
  - prevention 662–4
    - pollution reduction 664
    - smoking cessation 662–3
  - prognosis 627
  - pulmonary gas exchange 643–4
    - ventilation-perfusion mismatching 643, 643, 644
  - pulmonary hypertension and haemodynamics 647, 647–50, 648
  - pulmonary rehabilitation 672–4
  - radiology 657–62
    - chest radiography 657–9, 658
    - CT 659, 659–61, 660
  - respiratory failure 697, 700–1, 701
    - management 701–2
  - respiratory muscle function 644–6, 706
    - drug therapy 646
    - therapeutic interventions 645–6
    - training 645–6, 673
  - right ventricular function 649–50
  - risk factors 620–6
    - air pollution 622–3, 947
    - $\alpha_1$ -antitrypsin deficiency 623
    - atopy and airway hyperresponsiveness 625–6
    - chronic bronchopulmonary infections 624
    - growth and nutrition 624–5
    - occupation 623–4
    - passive smoking 621–2
  - severe 654
    - lung mechanics 641–3
    - management 667
  - smoking and 312, 619–20, 620–1, 634, 636
    - cessation effect 627
    - history and level of smoking 651
    - prevention/cessation 662–3, 668
  - structure-function relationships 627, 633–4
  - tuberculosis complication 523
  - vaccinations 674
  - ventilation control 646–7
  - ventilation in 701–2, 705
    - indication 1510
    - weaning 708
- chrysotile 1174, 1424, 1426
  - asbestosis pathogenesis 1431–2
  - concentration allowed 1433
- Churg–Strauss syndrome 1028–9
- chest radiography 1029, 1030
- treatment 286, 288
- chyle 1164, 1166
- chylomicrons 1166
- chylothorax 1165–7
  - clinical features and aetiology 1166
  - traumatic 1166
- chymotrypsin, faecal 849
- ciclacillin (cyclacillin) 196
- ciclosporin *see* cyclosporin
- cidofovir 241–2
- cigarettes
  - advertising bans 314
  - lower-nicotine 311, 663
  - safer 318–19
  - tar content 621
  - tar yields 318–19
    - sputum volume 312
  - see also* smoking

- cigarette smoke
  - air pollution due to 327
  - composition 313
  - indoor air pollution 332
  - see also smoke
- cigar smokers 311, 619, 620
- lung cancer 1077–8
- cilia 11, 84
  - beat
    - mechanism 11, 11, 14
    - rate and frequency 84
  - bending 12, 795
  - function 5
    - saccharin screening test 4, 84–5
  - inhibition by bacteria 809
  - loss, common cold 336
  - radial spokes 11, 12
  - shaft 11
  - structure 84
  - ultrastructure 11, 12
- ciliary dyskinesia, primary 85, 94, 794–6
  - investigations 809
- ciliary dyskinesia syndromes 794–6
  - cystic fibrosis and 796–7
  - Young's syndrome 796
- ciliated columnar epithelium, in chronic sinusitis 342
- ciliated epithelial cells 4, 11–12, 53, 84
  - development 2
- ciprofloxacin 225–7
  - administration, excretion and dosage 226
  - adverse effects and interactions 226
  - hospital-acquired pneumonia 372–3
  - Legionnaire's disease 391
  - Pseudomonas aeruginosa* pneumonia 408
  - resistance 226
  - spectrum of activity 225–6
  - tuberculosis 551, 551
  - uses/indications 226–7
- circulation
  - adaptations to high-altitude 56–7
  - development 1–2
  - see also bronchial circulation; pulmonary circulation
- cirrhosis, in cystic fibrosis 860
- cisplatin 292–3
- cisterna chyli 1165–6
- civil litigation 1536, 1538–9
- Clara cells 11, 12, 639
- clarithromycin 205–6
  - COPD 674
  - drug combinations 206
  - Legionnaire's disease 390
  - Mycobacterium avium-intracellulare* complex disease 569, 570
  - pneumonia 365, 368
- clavicles, hyperostosis 1219
- clavulanic acid 197
  - lung abscess 472
- clays 1416, 1433–4, 1434
- Clean Air Act (1956) 324, 622
- clear-cell tumour 1136
- clicking rib syndrome (slipping rib syndrome) 1219
- clinafloxacin 225, 227
- clindamycin 218–19
  - adverse effects 218
  - aspiration pneumonia 414
  - lung abscess 471–2
  - Pneumocystis carinii* pneumonia treatment 223
- clindamycin–primaquine
  - adverse effects 1372
  - Pneumocystis carinii* pneumonia 1372
  - clinical examination 114–16
  - clinical history 102
  - clofazimine 569
    - tuberculosis 552
  - cloning of organs 1522
  - 'closing volume' 46–7, 47
  - COPD 641
  - clostridia, empyema 448, 454
  - Clostridium difficile* 218
  - Clostridium tetani* 711
  - cloxacillin 198–9
    - administration and dosage 198, 199
  - clubbing, finger 111, 111–12
    - arteriovenous malformations 1324
  - asbestosis 1428
  - bronchiectasis 807
  - causes 112
  - COPD 652
  - cryptogenic fibrosing alveolitis 882
  - idiopathic pulmonary haemosiderosis 1333
  - interstitial lung disease 889
  - lung abscess 465–6
  - lung cancer 1086
  - rheumatoid disease 1387
  - theories on 112
  - tuberculosis 516
- coagulation
  - anticoagulation balance 719
  - cascade 721
  - in lung, cryptogenic fibrosing alveolitis 880
  - tests 737
- coagulation factors 719
  - secretion by macrophage 89
- coal 1408, 1409
- coal dust 1408, 1413, 1414
  - smoking additive effect 1414–15
  - suppression and control 1415
- coal macule 1413, 1413
- coal miners 1408
  - coal dust exposure 1408–9
  - COPD 623
  - forced expiratory volume in 1 s (FEV<sub>1</sub>) 73, 73
  - risks of massive fibrosis 74
- coal-workers' pneumoconiosis 1408–16
  - bronchitis and emphysema 1414–15
  - cavitated lesions, lung abscess vs 469
  - chest radiography 1409–11, 1410, 1411
  - clinical features 1409–12
  - complicated 1410–11
    - see also progressive massive fibrosis
  - epidemiology 1408–9, 1409
  - lesion classification 1409–10
  - longitudinal (cohort) study 73–4
  - lung function 1412–13
  - management and prevention 1415–16
  - pathogenesis 1414
  - pathology 1413, 1413–14, 1414
- co-amoxiclav 197–8
- coarctation
  - aorta 1221
  - pulmonary artery (stenosis) 1320
- cobalt 1440–1
  - allergic alveolitis due to 1016
  - occupational asthma 951
- Cobb's angle 1217, 1217
- Coccidioides*
  - spherules 579
  - spores 575
- Coccidioides immitis* 578–80
  - empyema 448
  - fluconazole activity against 231
- coccidioidin 579
- coccidioidomycosis 578–80
  - acute pulmonary 231
  - fibreoptic bronchoscopy 150
  - fluconazole use 232
  - treatment 230, 231
- cockroaches, allergens 945
- codeine linctus 104, 346
- cod liver oil 428, 900
- coeliac disease 1398
- coelomic cysts (pleuropericardial cysts) 1295–6, 1296
- coffee worker's lung 1016
- cohort study see longitudinal (cohort) study
- coin lesions 181
- cold, common see common cold
- cold abscess
  - bronchial 517
  - chest wall 1227
  - tuberculosis 534
- cold agglutinins 1333
  - Mycoplasma pneumonia* 364, 394, 396
- cold air, asthma 930
- cold exposure, diving 1489
- 'cold freon effect' 989
- coliforms 361
- colistin 216–17
  - bronchiectasis 818
  - nebulized, in cystic fibrosis 864
- collagen
  - increase in emphysema 632
  - type IV 1331
- collagen diseases
  - cryptogenic fibrosing alveolitis aetiology 878, 882
  - see also connective tissue diseases
- colon
  - strictures 859
  - tuberculosis 537
- colonopathy, fibrosing 859
- colophony (rosin), occupational asthma 950
- columnar cells 11, 39
- coma, in hypercapnia 698
- common cold 335–8
  - asthma after 941–2
  - causative organisms 335–6
  - clinical manifestations 336–7
  - complications 337, 338
  - diagnosis 337–8
  - epidemiology 336
  - pathology 336
  - recurrent, in tuberculosis 516
  - seasonal 336
  - spread 336
  - treatment 338
- common varied immunodeficiency (CVID) 798
- community-acquired pneumonia 356, 359
  - complication, empyema 447
  - costs 356
  - Haemophilus influenzae* 410
  - investigations 360
  - Legionella* causing 386
  - Moraxella catarrhalis* 411
  - Mycoplasma* 392
  - pneumococcal pneumonia 375–6
  - prevention 381–3
  - severity assessment 367–8

- treatment
  - antibiotics used 203, 205, 206
  - antimicrobial 365–6, 366
  - inpatient 366–71
  - in lung disease 370
  - older patients 370
  - severe infections 369–70, 370–1
  - young patients 368–70
- see also* pneumonia
- compensation, for industrial injuries 1536–9
- complement
  - C3 deficiency 86, 97
  - C3 role 86
  - C5a
    - ARDS 774, 778
    - neutrophil priming 780
  - Clq receptor, Sp-A interaction 85
  - deficiency 97
  - in lung secretions 86
  - secretion by macrophage 89
- complement fixation test
  - Chlamydia pneumoniae* 399
  - Chlamydia psittaci* pneumonia 398
  - Mycoplasma pneumoniae* 395
  - pneumonia 363
  - virus detection 337
- compliance, drug
  - see also* asthma; *specific disorders*
- compliance, lung 39–40
  - COPD 641
  - dynamic 40, 41
  - impairment after diving accident 1492
  - lung and thorax 39–41
  - measurement 39–40
  - reduced
    - ARDS 770, 771
    - cryptogenic fibrosing alveolitis 886
    - high-pressure pulmonary oedema 769
    - pressure–volume loop 48
  - scoliosis 1217
  - static 39–40, 41
  - total 39
- compressed gas cylinders 671
  - C-size and H-size 671
- compression Doppler ultrasound, deep
  - venous thrombosis 724–6
- computed tomography (CT) 122–3
  - allergic bronchopulmonary aspergillosis 590
  - alveolar proteinosis 1336
  - angiography
    - disadvantages 125
    - spiral 124–5, 125, 126
  - aortic aneurysms 1299
  - asthma 960
  - bronchiectasis 147, 794, 814–15, 821
  - chronic eosinophilic pneumonia 1026, 1027
  - COPD 659, 659–61, 660
  - cryptogenic fibrosing alveolitis 883–5, 885
  - diffuse lung disease 142, 143
  - empyema 450, 452
  - high-resolution (HRCT) 123, 814
    - asbestosis 1427, 1428
    - bronchiectasis 123, 794, 804
    - bronchiectasis diagnostic criteria 815
    - COPD 657, 659, 659–61
    - cryptogenic fibrosing alveolitis 884–5, 885, 886
    - ‘density mask’ technique 659–60
    - diffuse panbronchiolitis 831
    - before lung transplantation 1517
    - obliterative bronchiolitis 833, 834
    - pleural fibrosis 1171
    - Pneumocystis carinii* pneumonia 1367
    - ‘signet-ring’ appearance 815
    - in immunosuppressed patients 1348
    - infected bulla 470
    - Langerhans’ cell histiocytosis 146, 147
    - lung abscess 466–7
    - lung cancer 1094, 1094, 1096–7
    - staging 137
    - lung density measurements 660, 660
    - neurofibroma 1275
    - pleural effusion investigation 1164–5
    - pleural fibrosis 1171
    - pulmonary embolism 734, 735
    - radiation dose 123
    - retrosternal goitre 1298
    - sarcoidosis 1045, 1047, 1049, 1049, 1056
    - seminoma 1289
    - sinusitis 343, 343–4
    - solitary lung metastases 137–8
    - spiral 123
    - spiral contrast-enhanced 734, 735
    - stop–start procedure 122–3
    - thymoma 1282
    - tuberculoma 530
  - conchoid bodies (Schaumann bodies) 1040–1
  - confounding 66
  - confounding factors 70
  - confusion, terminal care 1533
  - congenital abnormalities 1478
    - arteriovenous malformations 1140–1, 1141, 1142, 1322–6
    - diaphragm 1241–2
    - lungs *see* lung, developmental disorders
  - congenital adenomatoid malformation of lung 1313
  - congenital pulmonary lesions, infected 469
  - congenital pulmonary venolobar syndrome 1321–2
  - congenital X-linked agammaglobulinaemia 798
  - congestive heart failure 1156
  - conjunctivitis, sarcoidosis 1049–50
  - connective tissue diseases
    - classification 1384
    - cryptogenic fibrosing alveolitis aetiology 878, 882
    - interstitial lung disease due to 889
    - obliterative bronchiolitis aetiology 833
    - pleural effusions 1160–1
    - pulmonary hypertension with 756–7
    - pulmonary manifestations 1384, 1384–99
    - tumours in 1142–3
  - connective tissue tumours, mediastinal 1291–3
  - consciousness
    - impaired, aspiration and lung abscess due to 460
    - loss
      - underwater 1483, 1487
    - see also* coma
  - constipation
    - relief in terminal care 1531
    - side-effect of narcotic analgesics 1529, 1531
  - continuous hyperfractionated accelerated radiotherapy (CHART) 1101
  - continuous positive airway pressure (CPAP) 1495
  - COPD 673
    - efficacy in sleep apnoea 1260
    - nasal masks 1259
    - patient compliance 1260
    - principles and mechanism 1259, 1259–60
    - respiratory distress syndrome 713
    - side-effects 1260
    - sleep apnoea/hypopnoea syndrome 1257, 1259–60
  - contraceptive pill *see* oral contraception
  - contrast media
    - bronchoconstriction due to 1460
    - pulmonary reactions 428
  - convulsions, in divers 1486
  - Cooperman system, cystic fibrosis scoring 851
  - COPD *see* chronic obstructive pulmonary disease (COPD)
  - ‘core organisms,’ concept 371
  - corneal oedema 251
  - coronary artery disease
    - Chlamydia pneumoniae* and 400
    - smoking and 312
  - coronary blood flow, high altitude effect 57
  - coronaviruses 338
  - common cold 335
  - cor pulmonale 750–2
    - asthma 955
    - bronchiectasis 806, 822
    - chest radiography 661, 751
    - clinical signs and pathology 750–1
    - definition 648
    - hypoxic pulmonary hypertension 750–2
    - sarcoidosis 1052–3
    - schistosomiasis 611
    - tuberculosis complication 523
  - corticosteroids
    - adverse effects 268–73, 955
    - avoidance 273
    - allergic alveolitis 1010, 1011
    - allergic bronchopulmonary aspergillosis 588
    - anti-inflammatory actions 980, 984
    - ARDS 785
    - asthma resistance 953, 981
    - asthma treatment 902, 913, 980–3, 983–4
    - acute severe 987–8
    - β<sub>2</sub> agonists with, asthma 978
    - bronchiectasis 819
    - Churg–Strauss syndrome 1029
    - COPD 666–7
      - acute exacerbation 675
      - reversibility assessment 656
    - cryptogenic fibrosing alveolitis 887
    - cystic fibrosis 865–6
    - drug interactions 273
    - growth retardation 955, 983
    - inhaled 273–7, 274–5
      - asthma 980–3
      - bronchiectasis 819
      - COPD 656, 667
      - delayed asthma treatment effect 980
      - development 980
      - dose increase in asthma 985
      - high-dose 981, 982
      - local side-effects 981–2
      - mechanism of action 980
      - pulmonary sarcoidosis 1058
      - spacer use 989
      - specific drugs 277–9
      - systemic side-effects 982–3
    - see also* glucocorticosteroids

- corticosteroids (*Continued*)  
low-dose and high-dose differentiation 982  
metabolism 982  
oral 263–5  
asthma 984, 985  
COPD 666–7  
parenteral 265–6  
*Pneumocystis carinii* pneumonia 1372–3  
pneumonia 373  
radiation pneumonitis 427  
sarcoidosis 1057–8  
systemic  
adverse effects 984  
asthma treatment 983–4  
weaning 984  
withdrawal in asthma 980  
tuberculosis 539, 557, 560  
intracerebral tuberculoma 530  
primary pulmonary 509  
Wegener's granulomatosis 1069–70  
*see also* glucocorticosteroids;  
prednisolone
- corticotrophin-releasing hormone 272
- cortisol 260  
*see also* hydrocortisone
- cortisone 260, 264, 265  
structure 264  
*see also* hydrocortisone
- cor triatriatum 760
- Corynebacterium diphtheriae* 339
- Corynebacterium parvum*, pleurodesis 1165
- coryza, acute *see* common cold
- costal cartilages, swelling and pain 1221
- costal tuberculosis 1227
- costochondritis 1221
- costophrenic angle  
COPD 658  
pleural fluid collection 130, 134
- costs  
community-acquired pneumonia 356  
epidemiology studies 64  
lung transplantation 1522  
oxygen therapy 672  
pneumonia 356  
polysomnography 1258  
recombinant human DNase 865  
upper respiratory tract infections 335
- cot death (sudden infant death syndrome) 313, 1255
- co-trimoxazole 207, 208–9  
adverse effects 210, 1369, 1370–1  
dosages 209  
melioidosis 424  
*Pneumocystis carinii* pneumonia 208–10, 596, 1369, 1370–1  
prophylaxis 1373–4  
principal uses 210
- cotton 1441  
exposure *see* byssinosis
- cough 83–4, 103–4  
ACE inhibitors causing 1460  
acute bronchitis 346  
allergic bronchopulmonary aspergillosis 588  
anaesthesia for fiberoptic bronchoscopy 154  
asthma 941, 952  
bovine 7, 103  
bronchiectasis 796, 807  
causes 104  
chronic 103  
COPD 651  
depressed, pneumonia pathogenesis 359, 412  
droplet nuclei produced and TB transmission 478  
drug-induced 1460  
empyema 449  
inhaled corticosteroid side-effect 982  
lung cancer 103–4, 148, 1086  
management 104  
mechanism 84, 103  
mediastinal tumours/cysts 1270–1  
*Mycoplasma* pneumonia 393  
nocturnal 651  
paroxysmal, whooping cough 351, 352  
paroxysms 103  
patterns 103–4  
persistent 148  
sinusitis 341  
process 54  
psychogenic 103  
reactive airways dysfunction syndrome 998  
relief in terminal care 1529  
smoking and 312, 314  
smoking cessation effect 651  
tracheobronchomegaly 1310–11  
tuberculosis 508, 516  
wheezy 103  
cough fractures 955, 1216  
cough mixtures 104, 1529  
cough receptors 52, 103  
cough reflex 52, 54, 83–4, 103  
impairment, aspiration of saliva 460  
inhibition 84  
initiation 103  
mechanism 83–4, 103  
sensitivity in females 104  
cough suppressants 338, 1529  
cough syncope 103  
counterimmunoelectrophoresis (CIE), sputum 361  
court appearances 1540–1  
cows' milk allergy 1333, 1334  
*Coxiella burnetii* 400  
antibiotic susceptibility 204  
culture 401  
inflammatory pseudotumour 401  
transmission and reservoirs 400  
*Coxiella* pneumonia *see* Q fever  
Coxsackie A virus infection 1153  
pharyngitis 339  
Coxsackie B virus infection 106, 1153  
coxsackieviruses  
pneumonia 418  
upper respiratory tract infection 336  
crackles 115–16  
allergic alveolitis 1008  
asbestosis 1428  
bronchiectasis 807  
COPD 653  
hypersensitivity pneumonitis 1002, 1003  
cranial irradiation 1101–2, 1108–9  
cranial neuropathies, CNS tuberculosis 529  
creatinine clearance, estimation 214–15, 219  
C receptors 103  
Creola bodies 929  
crepitations 115, 116  
bronchiectasis 807  
cryptogenic fibrosing alveolitis 877  
interstitial lung disease 889  
tuberculosis 516, 521  
CREST syndrome 756–7, 1392, 1393  
pulmonary hypertension 1393–4  
cricoarytenoid muscles 6  
cricoid cartilage 6, 153  
cricothyroid membrane 153  
cricothyroid muscles 6, 7  
criminal law 1536  
crocidolite 1173–4, 1424, 1426  
Crohn's disease 1398  
smoking and 312  
tuberculosis *vs* 537  
cromoglicate *see* sodium cromoglycate  
cromolyn sodium *see* sodium cromoglycate  
cross-sectional study 65, 67–70  
aims 67–8  
controls in 68  
examples 68–70  
*Crotalaria* 755, 759  
croup 346  
cryotherapy probe 1529  
cryptococcal meningitis 230, 231, 529  
cryptococcosis 580–1  
in AIDS 580, 581  
pulmonary 580  
treatment 232, 454  
*Cryptococcus albidus* 580  
*Cryptococcus laurentii* 580  
*Cryptococcus neoformans* 580–1  
antifungal agents 228  
empyema 448, 454  
fluconazole activity against 231  
lung abscess 463  
cryptogenic fibrosing alveolitis 877–93  
aetiology 877–8  
bronchoalveolar lavage 162, 886  
chest radiography 883, 883, 884  
clinical features 882  
computed tomography 883–5, 885, 886  
desquamative interstitial pneumonitis 879, 879, 883, 885, 888  
diagnosis 886  
differential diagnosis 885, 888–90  
diseases associated 878, 882  
environmental causes 878  
epidemiology 878  
fiberoptic bronchoscopy 165  
gallium-67 lung scanning 885  
genetic causes 877  
investigations 886  
lung biopsy 150, 180, 878, 886  
lung cancer and 1080  
lung function 877, 886  
lung transplantation 887, 1517, 1518  
mortality 882  
pathogenesis 880–2, 881  
cell types 881–2  
pathology 878–80  
prognosis 887–8  
treatment 886–7  
failure to respond 887  
'usual' interstitial pneumonitis 879, 879, 883, 885, 888  
cryptogenic mediastinal fibrosis 1302–4  
*Cryptostroma corticale* 1002, 1013  
Cuirass ventilation 1238, 1509, 1509, 1510  
Curschmann's spirals 105, 929, 953  
cutaneous atrophy 268  
cutaneous blood flow, at high altitude 57  
cutis laxa syndrome 1382  
cyanides, poisoning 1445  
cyanmethaemoglobin 1445  
cyanosis 110  
central, in hypoxaemia in respiratory

- failure 698
- COPD 652
- cryptogenic fibrosing alveolitis 882
- pneumococcal pneumonia 378
- pulmonary telangiectasia 1140, 1324
- respiratory distress syndrome 712
- cyclic AMP 245, 252
  - $\beta_2$  agonist–receptor interaction 938
  - response failure, exercise-induced asthma 931
- cyclooxygenase 261
  - COX1 and COX2 913
  - products, asthma pathogenesis 913–14
  - products secreted by macrophage 909
- cyclooxygenase pathway 935, 936
- 8-cyclophenyl-1,3-dipropylxanthine 865
- cyclophosphamide 283–5
  - administration, excretion and dosage 284
  - adverse effects and precautions 284–5
  - cryptogenic fibrosing alveolitis 887
  - mode of action 284
  - small-cell lung cancer 1106
  - uses/indications 283–4
  - Wegener's granulomatosis 1069
- cycloserine 550, 550, 558, 569
- cyclosporin 287–8
  - adverse effects and precautions 288
  - azathioprine with 286
  - dosage 287–8
  - drug interactions 231, 232, 287
  - lung transplantation 858, 1516, 1520
  - pulmonary sarcoidosis 1058
- cylindroma 1135–6, 1136
- cyst(s) 630
  - bone, chest wall 1224–5
  - bronchogenic (bronchial) *see* bronchogenic cysts
  - in cystic fibrosis 856
  - dermoid 1143
  - foregut *see* foregut cysts
  - gastroenteric 1293
  - hydatid *see* hydatid cysts
  - lung, Langerhans' cell histiocytosis 1131
  - mediastinal *see* mediastinal cysts
  - mesothelial 1240
  - neurenteric 1293
  - oesophageal 1293
  - parathyroid 1298
  - pleuropelvic (coelomic; serosal) 1295–6
  - thoracic duct 1296
  - thymic 1282–3, 1284
- cysteinyl leukotrienes 259, 261
- cysticercosis 604, 613–14
- cystic fibrosis 93–4, 796–7, 839–76, 1476–7
  - arthropathy and vasculitis 862
  - bacterial colonization 853, 853
  - bronchiectasis 794, 796–7, 851
  - bronchiolitis 855–6
  - carriers 94, 839–40
  - evolutional advantage 839–40
  - testing 850–1
  - childhood management 851
  - childhood presentations 846–8
  - clinical decision-making 846
  - clinical features 796, 851
  - clinical presentation 846
  - cor pulmonale 750
  - diabetes mellitus and 861–2
  - diagnosis 797, 848–51
    - benefits of early detection 850
  - diagnostic tests 844
  - empyema in 449
  - epidemiology 845–6, 1476
    - estimated frequency 845, 845, 1476
    - incidence 93, 845
    - survival 845–6
  - fertility and pregnancy 862–3
  - gastrointestinal complications 858–60
  - gene 92, 839, 840, 840, 1476
    - processing 843
  - gene mutations 94, 94, 841–4, 842
    - antibiotic action against 865
    - CFTR mRNA alteration 841–3
    - classes 842, 843–4, 865
    - $\Delta F508$  92, 94, 841, 843, 865
    - frameshift 841
    - G551D 843, 846
    - new therapies 865
    - nonsense 841–2
    - phenotype 843–4
    - splice-site 842–3
  - gene therapy 94, 866–7
  - genetic counselling 94
  - genetics 93–4, 839, 840–4
    - CFTR promoter 840–1
    - gene 840
  - hepatobiliary complications 860–1
  - historical review 839–40
  - holistic care 867–8
  - imaging 147, 812
    - chest radiography 812, 857
  - inheritance 839
  - ion transport 844–5
  - lung function tests 808
  - lung transplantation 856–8, 1517–18
    - bilateral 856
    - complications and results 858, 1518
    - preparation 857–8
    - referral and waiting 856–7
  - management 863–7
    - antibiotics 227, 864–5
    - antiproteases 866
    - corticosteroids 865–6
    - DNase 865
    - immunotherapy for infections 854
    - nebulized antibiotics 216, 864–5
    - new therapies 866–7
    - NSAIDs 866
    - physiotherapy 864
  - microbiology 854–5
  - morbidity 846
  - mortality 845–6, 861
  - mucus 85, 845, 853
  - nutritional consequences/implications 858, 861
  - pathogenesis 863, 863
  - pathogens associated 810
  - pathophysiology of respiratory disease 852–4
    - bacterial colonization 853, 853
    - infection and inflammation 853–4
  - pneumothorax 1186, 1201
  - prognosis 845–6
  - respiratory complications 855–8
  - scoring systems 851–2
    - Northern score 852, 853
    - Shwachman–Kulczycki score 851, 852
  - screening 79, 848, 850, 1476
    - antenatal 850–1, 1476
  - severity range 846
  - survival 846, 847, 1476–7
- Cystic Fibrosis Foundation (US) 851
- cystic fibrosis transmembrane regulator (CFTR) 92, 93, 93, 796, 839
  - CF gene mutations effect 841–4, 842
    - abnormal processing and chloride channel function 843
    - mRNA changes 841–3
    - new therapies based on 866
  - function and gene expression 841
  - gene *see* cystic fibrosis, gene
  - localization 841
  - promoter 840–1
  - structure 840, 840
- Cystic Fibrosis Trust 851
- cystic hygroma 1222, 1223
  - mediastinal 1291, 1292, 1292
- cystic teratoma *see* teratoma
- cystitis, chemical 284, 285
- cytochrome P450 enzymes 98
  - genetic polymorphisms 98
  - induction 231
  - inhibition 226
    - protease inhibitors 239
  - P4501A1 and P4502E1 mutations 98
  - xanthine metabolism 253
- cytokines 260, 778, 909, 914
- ARDS 778, 786
  - mortality and 787
- asthma pathogenesis 914–15, 926
- bronchiectasis pathogenesis 801
- cryptogenic fibrosing alveolitis pathogenesis 880
- proinflammatory effects 915
- secretion by
  - alveolar macrophage 881, 908–9
  - eosinophils 882, 911
  - injured epithelial cells 918–19
  - macrophage 89
  - Th1 and Th2 T cells 912, 934
- silicosis pathogenesis 1423
- sources and functions 909
- see also* interferons; specific interleukins
- cytomegalovirus (CMV) infection 1348
- combined therapy 242
- diagnosis 1349, 1358
- drug treatment 240–2
- fibreoptic bronchoscopy 150, 166
- in HIV infection 1357, 1358
- pneumonia 418
  - prophylaxis 1351
  - treatment 1350
- retinitis, treatment 240–2
- transplantation complication 858, 1347
- cytoprotective mechanisms, ARDS therapy 786
- cytotoxic drugs 283–95
  - alveolitis due to 1464
  - carcinogenic effect 285
  - interstitial lung disease due to 889
  - neoplastic disease 283
  - non-neoplastic disease 283
  - pneumonitis 426, 427
  - small-cell lung cancer 1104–5
  - see also* chemotherapy; individual drugs
- Dactylaria constricta*, lung abscess 463
- Dalton's law 1481
- damp housing
  - allergic alveolitis and 1003
  - allergies 945
- dapsone 223, 1374
- dapsone–trimethoprim 597, 1371–2
- daytime somnolence 1218, 1230, 1252–3
  - differential diagnosis 1255–6



- dead space 1501  
in type II respiratory failure 698–9  
ventilation 1501  
*see also* alveolar dead space; anatomical dead space
- deafness, drug-induced *see* ototoxicity
- death  
truthful explanation 1524–5  
*see also* terminal care in respiratory disease
- death certificates  
asthma 901  
causes of death 358
- death receptors 782
- decompression, sudden  
pneumomediastinum 1205  
pneumothorax 1187
- decompression chamber 1485
- decompression illness 1483–6, 1486  
management 1485, 1487  
prevention 1486  
symptoms and pathogenesis 1486
- decortication, empyema 457–8
- ‘deep sulcus sign’ 1192
- deep venous thrombosis 723–7  
clinical assessment 723, 723–4  
compression Doppler ultrasound 724–6  
diagnostic strategy 726–7, 727  
formation 721  
high risk patients 742  
impedance plethysmography 724  
investigations 724–6  
in pregnancy 743  
length and attachment 721  
management 740  
prevention 741–2  
protocol 742  
symptoms and signs 723–4  
venography 724, 725
- defensins 86
- deflation reflex 52
- deflazocort 265
- dehydration  
asthma 985–6  
cystic fibrosis 844, 851  
management in terminal care 1530–1
- delavirdine 239
- delayed hypersensitivity, tuberculin  
reaction 493–4
- delirium, terminal care 1533
- demeclocycline 1111  
adverse effects 212
- dendritic cells 89  
asthma pathogenesis 909  
‘professional’ 89
- dental devices, sleep apnoea treatment  
1260
- dental drills, pneumomediastinum due to  
1205
- dental sepsis 342  
lung abscess pathogenesis 460
- deoxyhaemoglobin, carbon dioxide  
binding 37
- depression  
COPD 652, 673  
sleep disorders 1256
- dermatomyositis–polymyositis syndrome  
1396
- Dermatophagoides pteronyssinus* 942, 943
- dermoid cyst (tumour) 1143, 1285
- desensitization 1467  
antituberculosis drugs 552–3  
asthma 990–1
- deserts  
coccidioidomycosis 578, 579
- desmoid tumour, fibrous benign 1222
- desmosine 640
- desmosomes 11
- developed countries  
antituberculosis campaign 500  
tuberculosis  
case finding 494–7  
risk 488  
trends 488–9
- developing countries  
antituberculosis campaign 500  
sarcoidosis prevalence 1036  
smoking trends and lung cancer 1078  
tuberculosis 476  
case finding 497, 500  
HIV infection impact 490  
trends 489, 489–90
- developmental anomalies *see* congenital abnormalities
- devil’s grip (Bornholm disease) 106, 1153
- dexamethasone 265  
cerebral oedema 1532  
CNS tuberculosis 530  
high-dose 265  
palliative cranial irradiation and 1109  
parenteral 266  
structure 265
- dextran 70 742
- dextrocardia 795, 796
- dextropropoxyphene, pain relief in  
terminal care 1525
- diabetes insipidus 1051, 1131
- diabetes mellitus  
cystic fibrosis and 861–2  
reactivation of tuberculosis 515  
sibling-pair analysis 93  
type II, in cystic fibrosis 862
- diagnostic imaging *see* imaging
- dialysis, tuberculosis treatment with 558
- diamorphine (heroin)  
nebulized 1530  
pain relief in terminal care 1527  
syringe drivers 1527
- diaphragm 1234–9  
chest radiography 120, 1234–5  
contraction 1235  
duplication 1242  
‘duty cycle’ 645  
embryology 1234  
eventration 1241, 1241–2  
partial 1242, 1242  
fatigue 1235–6  
COPD 645  
‘low-frequency’ 49, 1235  
flattened, COPD 658  
function 1235  
assessment 1235  
disorders 1235–9  
infections 1239–40  
inversion 1234–5  
involuntary movements 1238–9  
lesions, chest radiography 135–6  
metabolic activity, COPD 644  
muscles fibres 1235  
paralysis 1235, 1236–8  
bilateral 48, 108, 1237, 1237–8  
imaging 136  
unilateral 48, 1236–7, 1237  
in pectus excavatum 1213  
in scimitar syndrome 1321  
structural disorders 1241–7
- tic (flutter) 1239
- tonic spasm 1239
- trichiniasis 1240
- tumours 1240, 1240–1  
metastatic 1240  
weakness 710  
*see also* hemidiaphragm
- diaphragmatic breathing, exercises in  
COPD 673
- diaphragmatic hernias 3, 1242–7, 1300, 1313  
Bochdalek 1242–3, 1300  
hiatus *see* hiatus hernia  
Morgagni 1243, 1245, 1300  
sites 1242, 1243  
traumatic 1246, 1247
- diaphragmatic plication 1237, 1242
- diarrhoea  
antibiotic-associated, treatment 218  
cephalosporins causing 200  
clindamycin causing 218  
in Legionnaires’ disease 388  
tuberculosis 536
- diazepam, fiberoptic bronchoscopy 152
- dicloxacillin 198–9, 199
- didanosine (ddI) 238
- diesel combustion 327
- diesel engine exhaust fumes 1449
- diet  
advice, cystic fibrosis 861  
asthma and 899–900, 904  
*see also* nutrition
- dietary intake, in cystic fibrosis 861
- dietetic support, cystic fibrosis 861
- diethanolamine fusidate 225
- diethylcarbamazepine 610, 1025
- Diff Quik stain *see* Wright–Giemsa stain
- diffuse alveolar damage (DAD) 771, 775  
*see also* adult respiratory distress syndrome (ARDS)
- diffuse lung disease *see* interstitial lung disease
- diffusing capacity 34, 34–5  
carbon monoxide ( $D_{\text{LCO}}$ ) *see* carbon monoxide  
high altitude effect 57  
low values 34  
measurement methods 35  
oxygen 34, 35
- diffusion, gaseous 26, 33–5  
factors affecting 33–4
- ‘digital index’ 111
- digital necrosis 396
- digital subtraction angiography, pulmonary embolism 734
- digital subtraction superior cavagram 113
- dihydrocodeine, pain relief in terminal care  
1525
- dihydroemetine, amoebiasis 606
- dihydrofolate reductase, inhibitors 207
- dihydropteroate synthetase 209
- diltiazem, primary pulmonary hypertension 756
- 1,3-dimethylxanthine *see* theophylline
- dipalmitoyl lecithin 18
- dipalmitoyl phosphatidylethanolamine 18
- 2,3-diphosphoglycerate (2,3-DPG) 36, 56
- diphtheria 339, 347
- diphtheria, pertussis and tetanus (DPT)  
vaccine 352
- Diplococcus pneumoniae* *see* *Streptococcus pneumoniae*
- direct immunofluorescent antibody

- test (DFAT)
  - Pneumocystis carinii* 1368
  - sputum 361
- directly observed therapy, short course (DOTS) 553, 556, 559
- dirithromycin 207
- Dirofilaria* 608
- Dirofilaria immitis* 610
- dirofilariasis 610
- disability, definition 1540
- disease
  - causation 68, 80
  - pathogenetic mechanisms 63
  - 'disease genes' *see* gene(s)
- disinfection, fiberoptic bronchoscopes 170–1
- Diskhaler 989–90
- distal intestinal obstruction syndrome 859–60
- disulfiram reaction 200
- diuretics, in acute exacerbation of COPD 675–6
- divers, commercial 1488, 1490–2
- Divers Alert Network (DAN) 1491, 1492
- diving 1481–94
  - assessing fitness for 1490–2
    - lung function 1491
    - medical history 1490
    - underwater exercise tests 1491
  - asthma and 1492
  - breath-hold 1482, 1483, 1490
  - breathing apparatus 1482
    - failure 1483
  - cold gas effects 1489
  - contraindications 1490
  - decompression illness *see* decompression illness
  - gas densities 1482, 1483
  - hypoxia 1489
  - long-term effects on lung 1489–90
  - loss of buoyancy control 1485
  - near-drowning and 1487
  - oxygen toxicity 1486–7
  - physics 1481–2
  - physiology 1481–3
  - pneumomediastinum 1205
  - pneumothorax 1188, 1202
  - rebreathing apparatus 1489
  - regulations 1490
  - returning after accident 1491–2
  - saturation 1487, 1490
  - training 1485
  - trauma 1488–9, 1489
  - uncontrolled ascent 1483, 1484
- diving reflex 1482
- DNA
  - amplification 1349
    - Pneumocystis carinii* 1362
  - see also* polymerase chain reaction (PCR)
  - analysis, cystic fibrosis 850
  - diagnostics 99
  - fingerprinting, *Mycobacterium tuberculosis* 495
  - probes, pneumonia 364
  - vaccines 99
- DNase, recombinant human 865
  - bronchiectasis 819–20
  - costs 865
  - cystic fibrosis 865
  - mechanism of action 865
- docetaxel 294
- doctors
  - bronchitis, smoking and mortality 621, 621
  - expert witnesses 1539–41
- Doppler effect 724
- Doppler ultrasound, pulmonary thromboembolism 124
- dornase alfa *see* DNase, recombinant human
- doubling time, tumours 1117
- doxapram 280, 702
- doxorubicin 289–90
- doxycycline
  - brucellosis 420–1
  - Legionnaire's disease 391
  - Mycoplasma pneumonia* 395
- drainage
  - autogenic, in cystic fibrosis 864
  - closed 455–7, 473
  - empyema *see* empyema
  - intercostal *see* intercostal tube drainage
  - lung abscess 473
  - open 457, 473
  - underwater seal 456, 473
- drinks, asthma aetiology 945–6
- drowning
  - 'dry' 788–9
  - near-drowning 788–9, 1487, 1488
  - sea-water 789
  - 'secondary' 788–9
- drug abuse/abusers
  - contraindication to lung transplantation 1519
  - lung abscess 465
  - pneumomediastinum 1205
  - pneumonia 357
  - pneumothorax 1188
  - pulmonary oedema 789
  - sleep disorders and 1256
  - traumatic pneumothorax 1187
  - tuberculosis 495–6
- drug-delivery devices, COPD 666
- drug history 102, 889
- drug-induced lung disease 1458–75
  - alveolitis *see* alveolitis
  - bronchiolitis obliterans 1460
  - bronchoconstriction *see* bronchoconstriction
  - cough 1460
  - diagnosis and management 1466–7
  - mediastinal fibrosis 1466
  - miscellaneous 1466
  - pleural fibrosis 1466
  - pulmonary eosinophilia 1024, 1024
  - pulmonary oedema 1465
  - pulmonary vascular disease 1465–6
  - reaction types 1458–66
  - respiratory failure 709, 1229
  - SLE 1462, 1462
  - see also* hypersensitivity
- drug interactions
  - aminoglycosides 214
  - antifungal drugs 231, 232, 233–4
  - ciprofloxacin 226
  - corticosteroids 273
  - cyclosporin 231, 232, 287
  - erythromycin 205
  - metronidazole 217
  - phenytoin and isoniazid 549
  - rifampicin (rifampin) 224, 548
  - tetracyclines 211–12
  - theophylline 226
- drugs 193–310
  - adverse effects/reactions 1458, 1459
  - see also* drug-induced lung disease; hypersensitivity
- antimicrobial 193–228
- asthma aetiology 945–6, 963
- avoidance in asthma prevention 975
- idiosyncratic reactions 98
- modified loading dose 255
- overdose, acute respiratory failure 1229
- pleural effusions associated 1161–2
- volume of drug distribution 255
- see also* individual drugs/drug groups
- dry powder devices 279, 989–91
  - advantages/disadvantages 990
- dry rot fungi 1014
- Duchenne's muscular dystrophy 1511
- ductus arteriosus
  - closure 4
  - patent 713, 762
  - persistent right-sided 1320
  - remnant 19
- dumb-bell tumours 1273, 1274, 1275
  - description and treatment 1278
- duodenum, tuberculosis 537
- dusts 1406, 1407
  - bronchitis 1441
  - coal *see* coal dust
  - cough associated 104
  - cryptogenic fibrosing alveolitis aetiology 878
  - grain, occupational asthma 950
  - house, asthma aetiology 942–3
  - mesothelioma due to 1174
  - mineral *see* mineral dusts
  - occupational asthma 950
  - occupational exposure *see* occupational lung diseases
  - organic 1002, 1003, 1441–4
- dust sampler 1408
- 'Dutch hypothesis,' atopy and COPD 625, 626, 894
- dyes
  - dilution curves 1325
  - occupational asthma 951
- 'dynamic hyperinflation,' COPD 645
- dynein arms, cilia 11, 12, 84
- in ciliary dyskinesia 795
- defects 85, 94
- dysgerminoma *see* seminoma
- dyskeratosis congenita, bronchiectasis
  - association 803
- dyskinetic cilia syndrome 795
- dyspepsia, steroids associated 270
- dysphagia 1504
  - lung cancer 1087
  - management in terminal care 1532
  - mediastinal tumours/cysts 1271
- dysphonia 341
- inhaled corticosteroids and 276, 981–2
- dyspnoea (breathlessness)
  - acute episodic 889
  - adult respiratory distress syndrome 783
  - allergic alveolitis 108
  - asbestosis 1428
  - assessment 58
  - asthma 940, 952
  - atrial septal defect 760
  - behavioural *see* behavioural breathlessness
  - bronchiectasis 807
  - cardiac 107
  - causes 107, 107–8
  - non-cardiorespiratory 107
  - respiratory 108

- dyspnoea (breathlessness) (*Continued*)  
 coal workers' pneumoconiosis 1412  
 COPD 650–1  
 cryptogenic fibrosing alveolitis 877, 882  
 diaphragmatic paralysis 1238  
 diffuse interstitial lung disease 889  
 empyema 449  
 exertional  
   assessment 58  
   emphysematous bullae 661  
   scoliosis 1218  
 grading 109, 109, 952  
 hypersensitivity pneumonitis 1002  
 lung cancer 1086  
 management 109  
   in terminal care 109, 1529–30  
 mechanisms 108  
 mediastinal tumours/cysts 1270, 1271  
 mitral valve disease 759  
 pneumothorax 1189  
 posterior pharyngeal carcinoma 5  
 psychogenic 110  
 pulmonary alveolar proteinosis 1335  
 pulmonary embolism 108, 727, 728  
 respiratory failure 696  
 retrosternal goitre 1297  
 severity 108–9  
 sighing 1267  
 smoking and 314
- ear-drum, trauma 6
- ears, Wegener's granulomatosis 1067–8
- Eastern Cooperative Oncology Group 1116, 1117
- Eaton agent 392
- Eaton–Lambert myasthenic syndrome 1113, 1230
- echinococcosis, chest wall 1228
- Echinococcus*, empyema 449
- Echinococcus granulosus* 612–14
- Echinococcus multilocularis* 612
- echocardiography  
   M-mode, in COPD 649  
   pulmonary embolism 728, 734  
   transoesophageal 127
- echo Doppler, in COPD 649
- echovirus, upper respiratory tract infection 336
- ecological study 67
- ecthyma gangrenosum 408
- ED<sub>50</sub> 246
- edrophonium fluoride, myasthenia gravis 710
- education  
   continuous positive airway pressure (CPAP) 1259, 1260  
   cystic fibrosis 866–7  
   pulmonary rehabilitation in COPD 673  
   sleep apnoea/hypopnoea treatment 1261  
   smoking cessation 314  
   tuberculosis treatment 560
- efavirenz 239
- eformoterol (formoterol) 244  
   asthma treatment 977, 978  
   structure 244
- Ehlers–Danlos syndrome 1382
- eicosanoids 258–9  
   synthesis 261  
   *see also* leukotriene(s); prostaglandin(s)
- Eisenmenger syndrome 761
- elafin 86–7, 639
- elastase  
   airflow obstruction and 637  
   emphysema pathogenesis 634  
   levels in BAL fluid 638  
   *see also* neutrophil elastase
- elastic compression stockings 741
- elasticity  
   bronchial mucus 14  
   high altitude effect 57
- elastic laminae 1413
- elastic properties, lung and thorax *see* compliance
- elastic recoil of lung  
   asthma 955  
   emphysema 634, 642  
   loss 47  
   pressure 43, 45
- elastin  
   decreased synthesis  
     emphysema pathogenesis 640  
     by smoking 636  
   degradation products 640
- elderly  
   fiberoptic bronchoscopy 152  
   glucocorticosteroid adverse effects 268  
   influenza vaccination 350  
   mortality, from pneumonia 356  
   oropharyngeal flora 359  
   pneumococcal pneumonia 378  
   tuberculosis 481, 496, 508
- electrocardiography (ECG)  
   cor pulmonale 750, 750  
   high-pressure pulmonary oedema 769  
   pectus excavatum 1214  
   P pulmonale 753, 753  
   primary pulmonary hypertension 753, 753  
   pulmonary embolism 728, 728  
   right ventricular hypertrophy in COPD 649
- electrolyte(s)  
   abnormalities  
     asthma 986  
     cystic fibrosis 844, 845  
     pentamidine causing 222  
   asthma and 900  
   replacement, pneumonia 373
- electromyogram (EMG)  
   diaphragmatic fatigue 1235  
   diaphragmatic tic 1239
- electrostatic precipitation, particles 1406
- Eloesser flap 457
- embolism  
   air *see* air embolism  
   amniotic fluid 722  
   fat 721  
   pulmonary *see* pulmonary embolism  
   septic, lung abscess formation 461  
   tumour 722, 757
- embolization  
   arteriovenous malformations 1326  
   bronchial artery *see* bronchial artery embolization  
   carcinomatous 1146–7  
   venous, schistosomiasis 611
- embryology  
   diaphragm 1234  
   foregut duplication development 1293  
   lungs 1–4  
   mediastinal neural tumours 1272  
   peripheral nerve cells 1272  
   pulmonary vasculature 1319  
   thymus gland 1278–9  
   thyroid gland 1296–7
- tracheobronchial tree 1309, 1312
- embryonal carcinoma 1284, 1287
- emphysema 616  
   airway resistance 42  
   animal models 634  
    $\alpha_1$ -antitrypsin deficiency 95  
   breath sounds 115  
   bullae *see* emphysematous bullae  
   centriacinar (centrilobular) 629, 630, 630, 633  
     relationship to panacinar form 630  
   chest radiology 658, 658  
   coal dust association 1413, 1414–15  
   compensatory 678  
   dead space increase 698–9  
   definition 616, 629  
   differential diagnosis 1139  
     pneumothorax 1193  
   elastic recoil of lung 634, 642  
   fibrosis absence 631–2  
   forced expiratory volume in 1 s (FEV<sub>1</sub>) 633  
   forms 677–9  
   infantile lobar 677  
   lobar with bronchial atresia 677  
   lung transplantation 1517, 1518–19  
   lung volume reduction surgery 679  
   mechanical ventilation indication 1510–11  
   mediastinal *see* pneumomediastinum  
   metabolic alkalosis 38  
   microscopic 631  
   obstructive, primary pulmonary tuberculosis 509  
   panacinar (panlobular) 629, 630, 630, 633  
   pathogenesis 634  
      $\alpha_1$ -antitrypsin deficiency 623, 636, 638  
   decreased antiprotease function 638–40  
   decreased elastin synthesis 640  
   protease–antiprotease theory 634, 635, 638  
   protease burden increase 637–8  
   without  $\alpha_1$ -antitrypsin deficiency 636–40  
   *see also* antiproteases  
   pathology 629–32  
   periacinar (paraseptal; distal) 629, 630  
   scar (irregular) 630  
   secondary spontaneous pneumothorax 1185  
   severity measurement 631  
   silicosis 1420  
   smoking and 312, 313  
   structure–function relationships 633–4  
   subcutaneous 186  
   subtypes 629–32  
   'surgical' 1190  
   unilateral due to localized bronchiolitis/bronchitis 677–9  
   *see also* chronic obstructive pulmonary disease (COPD)
- emphysematous blebs, in alveolar microlithiasis 1339
- emphysematous bullae 630  
   chest radiography 658, 658, 661–2  
   pneumothorax *vs* 1193, 1194  
   treatment 661–2
- empyema 133–4, 134, 135, 445–59  
   acute and chronic 445  
   calcified chronic 457  
   clinical manifestations 449  
   definition 445

- diagnosis 449–53  
   biochemistry 452–3  
   microbiology 451–2  
   radiography 449–51  
 drainage 455–7  
   closed 455–7  
   failure 456  
   fibrinolytic/irrigation therapy 456  
   open 457  
   suction 456  
   video-assisted thoracoscopic surgery 457  
 exudative stage 445  
 fibrinopurulent stage 445  
 fungal 448, 454  
 localized, lung abscess *vs* 468–9  
 management 453–8, 455  
   aerobes 454  
   anaerobes 453–4  
   antimicrobial therapy 453–5  
   decortication 457–8  
   mycobacteria and rare organisms 454–5  
   thoracoplasty 458  
 microbiology 446–9  
   age effect 448  
   antibiotic influence 447  
   bacteria 448–9  
   predisposing factors 447–8  
   uncommon causes 448–9  
 organizational stage 445  
 pathogenesis 446–9, 447  
 pathology 445–6  
 pneumococcal 454  
 pneumococcal pneumonia complication 385, 447  
 protozoal 449, 454  
   *Staphylococcus aureus* pneumonia 406  
   tuberculous 448, 522  
   treatment 454  
 empyema fluid 451–2  
 empyema necessitatis/necessitans 449, 450, 457  
 encephalitis  
   CNS tuberculosis 529  
   influenza complication 349  
 encephalopathy, penicillins causing 194  
 endobronchial biopsy 158  
 endobronchial bleeding, tamponade 151  
 endobronchial metastases 156, 1146  
 endobronchial tumours  
   biopsy 158  
   fiberoptic bronchoscopy 156  
 endocarditis, Q fever complication 402  
 endocrine cells *see* APUD cells  
 endocrine syndromes, mediastinal  
   tumours associated 1271  
 endocrine system, sarcoidosis 1051–2  
 endodermal sinus tumour 1284, 1287  
 endometriosis 1186  
   catamenial pneumothorax 1202  
   pleural involvement 1178  
   thoracic 1186  
 endoperoxides 41  
 endothelial cells  
   anatomy 20, 21  
   neutrophil interactions *see* neutrophil(s)  
   pulmonary capillaries 16, 20, 21  
   regulation 750  
   vasodilators/vasoconstrictors released 750  
   vulnerability to injury 21  
 endothelin 1 750  
   cryptogenic fibrosing alveolitis 880  
   excess, primary pulmonary  
     hypertension 754  
     mechanism of action 750  
     release in hypoxia 750  
 endothelins 12  
   in systemic sclerosis 1393  
 endothelium 750  
 endothelium-derived hyperpolarizing factor 750  
 endothelium-derived relaxing factor *see* nitric oxide  
 endotoxic shock, *Staphylococcus aureus*  
   causing 406  
 endotoxin *see* lipopolysaccharide (endotoxin)  
 endotracheal aspirates, culture 363  
 endotracheal intubation, in epiglottitis 340  
 endotracheal tubes 704  
   composition/dimensions 1502  
   cuffed or uncuffed 1502–3  
   features/types 1502–3  
   insertion 151  
 endotracheal tube ventilation 1502–4  
   complications 1503–4  
 energy  
   cost of breathing 48, 48  
   requirements, breathing 48  
*Entamoeba histolytica* 604–6, 605  
   ‘anchovy sauce’ pleural fluid 452  
   empyema 449  
   trophozoite and amoebic forms 604  
*Enterobacter*, pneumonia 410  
 Enterobacteriaceae, antibiotics used for 212  
 enteroviruses, common cold 336  
 environmental causes, cryptogenic  
   fibrosing alveolitis 878  
 enzyme immunoassays  
   blastomycosis diagnosis 578  
   *Mycoplasma pneumoniae* 395  
 enzyme immunoassay (ELISA)  
   CNS tuberculosis diagnosis 530  
   *Mycoplasma pneumoniae* 395  
   pneumonia 363  
   pulmonary embolism 729–30  
   tuberculosis 520  
 enzymes  
   inhibitors, secretion by macrophage 89  
   secretion by macrophage 89  
 eosinophil(s) 910–11, 1020–2  
   accumulation, asthma 911  
   adhesion and emigration 917, 917  
   asthma pathogenesis 910–11, 928  
   asthma pathology and 1021  
   bronchoalveolar lavage 928  
   chemotactic factors 917, 935, 1020  
   cryptogenic fibrosing alveolitis 882  
   extravasated 911  
   function 1020–2  
   granules and structure 910–11, 911, 1020, 1021  
   normal blood count 1020  
   in pleural fluid 1164  
   products secreted 882, 910, 911, 917, 1020  
   reduced blood counts 1020  
   removal and apoptosis 782  
   sputum 928, 1022, 1023, 1025  
   synthesis 1020  
   Wegener’s granulomatosis 1065  
 eosinophil cationic protein (ECP) 910, 1020, 1025  
 eosinophilia  
   in hypereosinophilic syndrome 1030  
   in lung cancer 1112  
   pulmonary *see* pulmonary eosinophilia  
   sputum 961  
   strongyloidiasis causing 609  
   trichiniasis 1240  
 eosinophilic pneumonia  
   acute 1031, 1031  
   chronic 1025–8, 1026, 1027  
   rheumatoid disease 1389  
 eosinophil protein X 1028  
 ephedrine 249  
 epidemic myalgia (Bornholm disease) 106, 1153  
 epidemic pleurodynia (Bornholm disease) 106, 1153  
 epidemiologists 63  
 epidemiology 63–82  
   analogy with clinical practice 63, 64  
   causes of diseases 63  
   costs of studies 64  
   defining population for studies 65  
   definition 63  
   descriptions of health/disease profiles 66–7  
   determination of cause of disease 80  
   historical aspects 63  
   principles for studies 64–6  
   questions to use 64  
   screening for diseases 79–80  
   standardization of methods 65–6, 75–9  
     chest radiography 77–9  
     lung function testing 76–7  
     physical examination 76  
     questionnaires 75–6  
   study design 65, 67–75  
   errors 66  
   experimental studies 75  
   mixed studies 74–5  
   problems and bias 66  
   *see also specific types of studies*  
   validation of studies 75, 75  
 epiglottitis 340  
 epileptic seizures, management 1532–3  
 epinephrine (adrenaline) 245, 249  
   angioneurotic oedema 709  
   asthma mortality and 901  
   as bronchodilator 244  
   immunotherapy for asthma and 991  
   indications 249  
   onset of action 247  
   structure 245  
 epithelial cells  
   ciliated *see* ciliated epithelial cells  
   cystic fibrosis 844, 844–5  
   damage in asthma 907  
   hydration of surface 844, 844  
   injured, mediators secreted 918–19  
   injury and shedding, asthma 918–19  
   pericellular dehydration in cystic fibrosis 844, 851  
   pseudostriated columnar 84  
   shedding in common cold 336  
 epithelioid cell(s) 1041  
   sarcoidosis 1040, 1041, 1042  
 epithelioid cell granuloma  
   sarcoidosis 1040, 1054  
   *see also* sarcoidosis  
   tuberculosis 480  
 epithelium  
   airway, ion transport 844–5  
   alveolar *see* alveolar epithelium  
   ciliated *see* ciliated epithelial cells

- epithelium (*Continued*)  
 columnar 5, 11  
 denudation in asthma 919  
 respiratory bronchioles 15  
 stratified squamous 11  
 tumours 1133–7
- epituberculosis 508
- epoxy resins, occupational asthma 951
- Epstein-Barr virus (EBV)  
 cryptogenic fibrosing alveolitis aetiology 878  
 nasal T-cell lymphoma (midline granuloma) 1071  
 non-Hodgkin's lymphoma 1128, 1358  
 pneumonia 418
- 'equal pressure point' concept 640
- equine 'heaves' 912
- ergotamine, adverse effects 1466
- erionite 1174, 1434–5
- erythema, cutaneous, radiotherapy side-effect 1102
- erythema multiforme 210, 396
- erythema nodosum 510–11, 1050  
 sarcoidosis 1036, 1044–5
- erythrocyte sedimentation rate (ESR)  
 Churg–Strauss syndrome 1029  
 interstitial lung disease 889
- erythromycin 204–5  
 administration and excretion 205  
 adverse effects 205  
 dosage 205  
 Legionnaire's disease 390, 391  
 low-dose, diffuse panbronchiolitis 832  
 pertussis 352  
 pneumonia 365, 368  
*Mycoplasma* 395  
 pneumococcal 381  
 resistance 204  
 spectrum of activity 204–5  
 uses 205
- erythropoietin, secondary polycythaemia 698
- Escherichia coli*  
 diarrhoea, cystic fibrosis advantage in 840  
 pneumonia 409
- ethambutol 549–50  
 adverse effects 547, 549–50  
 avoidance in children 557  
 dosage 547  
*Mycobacterium avium-intracellulare*  
 complex disease 569  
 tuberculosis chemoprophylaxis 498  
 tuberculosis treatment 558
- ethamivan 280
- ethionamide 550, 551, 569
- ethmoid sinuses 341  
 structure 5
- ethmoid sinusitis 343
- ethnic factors  
 asthma 895–6  
 sarcoidosis 1038
- etoposide 291–2, 1108
- European Coal and Steel Community 75, 76
- European Community, air quality standards 333
- European Organization for Research on the Treatment of Cancer 1116
- European Respiratory Society (ERS), COPD definition 617
- eustachian tube, structure 5–6
- evidence-based medicine 75
- Ewing's tumour 1226, 1227
- exercise  
 asthma and 930–1, 948  
 bronchoconstriction 5  
 capacity, test 55  
 cystic fibrosis 864  
 ozone pollution effect 331  
 pulmonary function during 54–5
- exercise tests  
 asthma 958  
 COPD 656–7  
 hyperventilation 1267  
*Pneumocystis carinii* pneumonia 1368  
 progressive symptom-limited 657  
 psychogenic hyperventilation 1266  
 self-paced 657  
 steady-state exercise 657  
 underwater 1491
- exercise training, COPD 672  
 rehabilitation 673
- exostosis 1224
- expert medical reports 1539–40
- expert witnesses 1539–41
- expiration 26  
*see also* ventilation, mechanical
- expiratory flow–volume curve, maximum 43–4
- expiratory reserve volume (ERV) 29
- exposure, cumulative/current and estimates 67
- extracorporeal membrane oxygenation 784
- extrinsic allergic alveolitis (EAA) *see* allergic alveolitis, extrinsic
- exudates 452–3  
*see also* pleural exudates
- eyes  
 sarcoidosis 1049–50  
 Wegener's granulomatosis 1067
- face masks, ventilation *see* ventilation, mechanical
- facial nerve palsy 1236
- facial structure, abnormal in sleep apnoea 1251
- faciomaxillary surgery, sleep apnoea treatment 1260–1
- factor V, Leiden mutation 97, 719
- factor X inhibitor 741
- faecal fat, in cystic fibrosis 849
- faecal impaction 1531
- Faenia rectivirgula* 1011
- failure to thrive, cystic fibrosis 847
- fallopian tubes, tuberculosis 538
- Fallot's tetralogy 1320
- famciclovir 235–6
- familial Mediterranean fever (periodic disease) 1153–4, 1163
- family, terminal care and 1524, 1533–4
- farmers, respiratory diseases 1012
- farmers' lung 588, 1002  
 causes 1011–12  
 chest radiography 1003, 1004, 1005  
 management 1010–11, 1012  
*see also* allergic alveolitis
- fat embolism 721
- fatty acids, asthma and 946
- feather allergy 943  
 allergic alveolitis 1008, 1009
- feathers, bloom, bird fancier's lung due to 1015
- female fertility, cystic fibrosis 862–3
- fenestration, empyema 457
- fenoterol 247  
 asthma deaths due to 248–9, 901–2, 925  
 asthma treatment 977  
 doses and half-life 247
- fentanyl, transdermal 1527
- ferruginous bodies 1430
- fertility, cystic fibrosis 862–3
- a-fetoprotein, mediastinal germ-cell tumour 1288, 1289
- fetus  
 abnormalities, corticosteroid effects 271–2  
 airways 712  
 congenital tuberculosis 507  
 effect of asthma therapy on 991  
 lung maturity determination 40–1  
 Th2 cell production 934
- fever  
 fibreoptic bronchoscopy 169  
 miliary tuberculosis 512, 513, 514  
 pneumococcal pneumonia 377–8, 378
- Feyrter cells *see* APUD cells
- fibreoptic bronchoscopy *see* bronchoscopy, fibreoptic
- fibrillin 1381
- fibrin, deposition in hypersensitivity pneumonitis 1005
- fibrinogen, radioactive test for deep vein thrombosis 726
- fibrinogen degradation products 640, 726
- fibrinolysis 721
- fibrinolytic therapy *see* thrombolytic therapy
- fibroblast growth factor, asthma pathogenesis 915
- fibroblasts, glucocorticosteroid actions 263
- fibrocartilaginous layer 13–14
- fibrohistiocytoma 1132
- fibroma 1143  
 pleural 1143, 1172, 1173
- fibronectin 1413  
 in cryptogenic fibrosing alveolitis 878, 882
- fibrosarcoma 1143, 1226  
 chest wall 1223  
 diaphragm 1240
- fibrosing alveolitis  
 chest radiography 141–2  
 CT 142, 143
- fibrosing colonopathy 859
- fibrosis, emphysema and 631–2  
*see also* pulmonary fibrosis
- fibrothorax 446, 1202, 1203
- fibrous dysplasia 1225
- Fick method 31
- Fick principle 749
- filarial worms 609
- filariasis 609  
 treatment 610  
 tropical pulmonary eosinophilia 1024
- fine-needle biopsy *see* percutaneous fine-needle biopsy
- finger clubbing *see* clubbing
- finning 1482
- fire-fighters 1448, 1449
- fishmeal, allergic alveolitis 1016
- fish oils 900, 946
- fitness training 109
- flapping tremor 113, 652
- flax 1441
- Flenley acid–base diagram 38, 39
- flour, occupational asthma 950
- flow, controlled ventilation 1497, 1498

- flow–volume curves/loops 47  
   asthma 955, 956  
   COPD 641, 641, 654  
   maximal 58  
   rheumatoid disease 1389  
   tracheobronchial amyloidosis 1338, 1338  
 flucloxacillin 198–9  
   administration and dosage 199, 199  
   cystic fibrosis 864  
   *Staphylococcus aureus* pneumonia 404  
 fluconazole 230, 231–3  
   adverse effects and interactions 232  
   blastomycosis 578  
   structure 232  
   uses/indication 232  
 flucytosine 230, 234  
 fluid  
   accumulation in alveolar interstitial space 766  
   balance, management, ARDS 784  
   replacement, pneumonia 373  
   requirements 5  
   retention, high-altitude pulmonary oedema 788  
 flukes, lung 611–12  
 flumazenil 152–3  
 flunisolide 278  
 fluorescent (auramine–phenol) stain, mycobacteria 476, 477  
 fluoroquinolones 225–7  
   pneumonia 366, 381  
 fluoroscopy 127  
   COPD 658  
   diaphragm function 1235, 1238  
   fiberoptic bronchoscopy with, lung cancer detection 164  
   percutaneous fine-needle biopsy 173  
   transbronchial lung biopsy 158, 159  
 flu syndrome, rifampicin effect 548  
 fluticasone propionate 277–8  
   asthma 980  
   COPD 667  
   metabolism 982  
   structure 278  
 flutter valves 1199  
 folic acid 222  
 food sensitivity, asthma and 899, 945–6, 963  
 foramen ovale, closure 4  
 forced expiratory volume in 1 s (FEV<sub>1</sub>) 43, 44, 58  
   asthma 924, 956  
   bronchiole obstruction 829  
   coal miners 73, 73  
   coal-workers' pneumoconiosis 1412, 1415  
   COPD *see* chronic obstructive pulmonary disease (COPD)  
   cryptogenic fibrosing alveolitis 886  
   lung cancer 1093  
   smokers 620  
   smokers *vs* non-smokers 620–1, 621  
   smoking cessation effect 621, 621  
   type II respiratory failure 697  
 forced vital capacity (FVC) 43, 44  
   cryptogenic fibrosing alveolitis 886  
   cystic fibrosis 861  
   lung cancer 1093  
 foregut cysts 1293–5, 1294  
   infected, lung abscess *vs* 469  
   pathogenesis 1293  
   perforation 1294  
 foregut duplication 1293–5  
   pathogenesis 1293  
 foreign bodies  
   anterograde passage 341  
   inhaled 9  
   bronchial obstruction 801  
   lung abscess 461  
   respiratory failure 712  
   removal, bronchoscopy 151, 171  
 formaldehyde  
   air pollution due to 332  
   occupational asthma 951  
 formylmethionine leucyl-phenylalanine (fMLP) 780  
 foscarnet 241  
 foundry workers 1416  
 Fowler's method, anatomical dead space measurement 27, 27  
 fractures  
   chest wall 1214–16  
   cough 955, 1216  
   fatigue 1216  
   pathological 1216, 1528  
   rib *see* ribs, fractures  
   vertebral 269  
*Francisella tularensis* 421  
 free radicals 1467  
   obliterative bronchiolitis aetiology 832–3  
   release, particulate air pollutants 330  
   *see also* reactive oxygen intermediates  
 freons 279  
 Friar's balsam 344  
 Friedländer's bacillus 463  
   *see also Klebsiella pneumoniae*  
 Friedländer's pneumonia 406–7  
 frontal sinuses 5, 341  
 frontal sinusitis 343  
 fuel combustion, air pollution 327, 328  
 Fuller's earth 1433  
 functional residual capacity (FRC) 29, 29  
   COPD 641  
 'functional upper airway obstruction' 155  
 fungal allergy 945  
 fungal balls 593  
 fungal infections 573, 577–98  
   bronchiectasis association 803  
   chest wall 1228  
   fiberoptic bronchoscopy 166  
   lung abscess 463  
   differential diagnosis 470  
   pleural effusions 1160  
   pneumonia 228  
   treatment 230  
   rare opportunistic 598  
   sinusitis 342, 344  
   sputum culture 105  
   susceptibility, corticosteroid-induced 271  
   transplantation complication 1347  
   *see also specific infections/fungi*  
 fungi 573–5  
   classification 573, 574  
   growth and reproduction 573–4  
   importance 574  
   indoor air pollution 332  
   pathogenic effects 574–5  
   saprophytic colonization of lungs 575, 577  
   sources 575  
   spores 574, 575, 577, 582  
   asthma aetiology 944–5  
   hypersensitivity pneumonitis due to 1002  
   mushroom worker's lung 1012–13  
   seasonal release 945  
   sputum culture 362  
   unicellular *see* yeasts  
 fungi imperfecti 573, 586  
 furosemide, high-pressure pulmonary oedema 769  
 furrier's lung 1016  
 fusidic acid (sodium fusidate) 225  
*Fusobacterium*  
   lung abscess 462  
   pneumonia 412  
 gallbladder disease, in cystic fibrosis 861  
 gallium-67 lung scanning  
   cryptogenic fibrosing alveolitis 885  
   lung cancer 1094  
   sarcoidosis 1056  
   tuberculosis 521  
 gallstones, in cystic fibrosis 861  
 ganciclovir 240–1  
   administration, excretion and dose 240  
   adverse effects 240–1  
   intraocular 240  
   intravenous 240  
   oral 240, 241  
   structure 240  
   uses/indications 240, 241  
 ganglia, paraganglioma site 1277  
 ganglioneuroblastoma 1272, 1276  
 ganglioneuroma 1143, 1276  
 gangrene, massive pulmonary 470  
 gas cookers  
   pollutants from 327, 330  
 gas cookers, air pollution due to 327, 330, 332  
 gas cylinders 671  
 gas embolism *see* air embolism  
 gases  
   in alveoli 28  
   barotrauma damage and 1483  
   bubbles  
     decompression sickness 1486  
     diving and 1490  
   cold, in diving 1489  
   combustion, air pollution 325, 326  
   density and diving 1482, 1483  
   diffusing capacity (D<sub>L</sub>) 34–5  
   diffusion *see* diffusion, gaseous  
   irritant *see* irritant gases  
   partial pressures 26, 28, 28–9  
   respiratory  
     *see also* arterial blood gases; carbon dioxide; oxygen  
   toxic *see* toxic gases  
   transfer 33–4  
   *see also* arterial blood gases; carbon dioxide; oxygen  
 gas exchange 1501  
   asthma 956–7  
   components 26  
   COPD 643–4  
   extrapulmonary 784  
   during mechanical ventilation 1501–2  
   respiratory failure 696  
   *see also* diffusion; perfusion; ventilation  
 gas laws 1187, 1481  
 gas–liquid chromatography 414, 467  
 gastrectomy, reactivation of tuberculosis 515  
 gastric aspirate, tuberculosis diagnosis 520  
 gastric carcinoma 1166, 1412  
 gastric tuberculosis 537

- gastrin-releasing peptide, lung cancer 1084  
gastroenteric cysts 1293  
Gastrografin 860  
gastrointestinal bleeding, in respiratory failure 708  
gastrointestinal tract  
  cystic fibrosis complications 858–60  
  ion transport 845  
  sarcoidosis 1050–1  
  tuberculosis 536–8  
  Wegener's granulomatosis 1069  
gastro-oesophageal reflux 1300  
  asthma aetiology 948  
  bronchiectasis and 820  
  cystic fibrosis complication 859  
Gaucher's disease 96  
gemcitabine 293–4  
gene(s)  
  candidate 93  
  disease aetiology 91–3  
  'disease genes' 91–3  
  'housekeeping' 841  
  positional cloning 92–3  
  structural 92  
gene delivery  
  cationic liposome-mediated 866  
  non-viral vectors 866  
  viral vectors 866  
  *see also* gene therapy  
gene probes  
  *Legionella* 390  
  *Mycoplasma pneumoniae* 395  
general practice, smoking cessation 314–16  
gene therapy  
  cystic fibrosis 94, 865–6, 866–7  
  vectors 866  
  *see also* gene delivery  
genetic counselling 91  
  cystic fibrosis 94  
genetic heterogeneity 91, 92  
genetic linkage 92, 93  
genetics 91–101  
  lung diseases 93–8  
  microbial 98–9  
  molecular 91  
  monogenetic diseases 91  
  multifactorial diseases 91  
  tumour 98  
genetic syndromes, parenchymal involvement 96  
genetic tests, cystic fibrosis 850  
genistein, new cystic fibrosis treatment and 865  
genitourinary tract  
  sarcoidosis 1052  
  tuberculosis 538–9, 556–7, 560  
  Wegener's granulomatosis 1067  
gentamicin 212, 214–16  
  divided/extended dosage regimens 214–15  
  once-daily dosage regimens 215, 216  
  blood levels 215–16  
  pneumonic plague 425  
  *Pseudomonas aeruginosa* pneumonia 408  
  tularemia 421  
germ-cell tumours  
  mediastinal *see* mediastinal germ-cell tumours  
  tumours  
  subtypes 1284–5  
  terminology 1283  
  thymic 1283  
germinoma *see* seminoma  
ghee, aspiration 428  
Ghon focus 479, 507  
giant cells, sarcoidosis 1040, 1041, 1041  
Gibbs–Donnan equilibrium 37  
gibbus deformity, tuberculosis 533, 535  
Gibson and Cooke test 848  
gingivitis, lung abscess pathogenesis 460  
glanders 407, 424–5  
glass wool, synthetic 1435  
glaucoma, acute angle closure 251  
glomerular basement membrane, antibodies 1330–3  
glomerulonephritis  
  idiopathic rapidly progressive 1332  
  necrotizing, Wegener's granulomatosis 1065  
glucocorticoid-response elements 260  
glucocorticosteroids 259–79  
  administration, metabolism and excretion 263  
  adverse effects 268, 268–73  
  asthma 913  
  dosages 266–8, 267  
  adverse effect reduction 273  
  conversion factors 267  
  inhaled  
    administration method 274–5  
    adverse effects 275–7  
    dosages 275  
    inactivation by hepatic metabolism 275  
    pharmacology and mode of action 274  
    preparations 273–7  
    specific drugs 277–9  
  in lung development 2  
  mode of action 260–3  
     $\beta_2$ -adrenergic receptors 262–3  
    arachidonic acid cascade inhibition 260–1  
    cellular and vascular effects 262  
    gene-modulating effects 260  
    histamine release inhibition 262  
    platelet-activating factor inhibition 261–2  
  oral preparations 263–5  
  parenteral preparations 265–6  
  receptors 260, 273  
  structures 260, 260  
  timing of doses 267–8  
  topical 273–7  
  *see also* corticosteroids  
glucoprotein, in alveolar space 1334  
glucose  
  intolerance, corticosteroid-induced 271  
  pleural effusions 453  
glucose 6-phosphate dehydrogenase deficiency 1372  
glutaraldehyde  
  fiberoptic bronchoscope disinfection 171  
  occupational asthma 951  
gluten enteropathy 1333, 1334  
glycopeptides 219–21, 405  
  tolerance by *Staphylococcus aureus* 405  
glycoproteins  
  of mucus 14  
  surfactant-associated 12, 1334  
glycylcyclines 210  
goblet cells 12  
  chronic bronchitis 628  
  development 2  
  hyperplasia, asthma 907  
  increase in smokers 628  
goitre  
  cervical 1296  
  intrathoracic 1297  
  retrosternal 1271, 1296–8, 1297  
gold, alveolitis due to 1464  
Goodpasture's syndrome 35, 1330, 1331, 1331  
  chest radiography 1331, 1332  
  differential diagnosis 1332  
grain  
  dusts, occupational asthma 950  
  mouldy, hypersensitivity pneumonitis 1002  
  phosphine fumigation 1446  
grain fever 1444  
grain handlers 1404  
grain mites, occupational asthma 950  
Gram-negative aerobes  
  empyema treatment 454  
  lung abscess 463  
  opportunistic, pneumonia 409–10  
Gram-negative bacteria  
  anaerobic, lung abscess 462  
  ciprofloxacin susceptibility 226  
  cystic fibrosis 854  
  empyema pathogenesis 448  
  hospital-acquired pneumonia 371  
Gramoxone 1469  
Gram-positive bacteria  
  empyema 448  
  lung abscess 463  
granular cell myoblastoma 1273  
granulation tissue, lung abscess 464  
granulocyte colony-stimulating factor (G-CSF), CNS tuberculosis 531  
granulocyte macrophage colony-stimulating factor (GM-CSF)  
  asthma pathogenesis 915  
  effect on eosinophil longevity 911  
granulocytes  
  adhesion and emigration 917, 917  
  asthma 908, 909  
  'suicide programme' 782  
  *see also* basophils; eosinophil(s); neutrophil(s)  
granuloma  
  caseous, tuberculosis 479, 480, 536  
  of CNS 529  
  coccidioidomycosis 579  
  formation  
    sarcoidosis 1042–3, 1043  
    Wegener's granulomatosis 1063–4, 1065  
  mast cell 1131–2  
  midline (nasal T-cell lymphoma) 1070–1  
  non-caseating  
    allergic alveolitis 1005, 1008  
    berylliosis 1437, 1438, 1438  
    sarcoidosis *see* sarcoidosis  
  pulmonary hyalinizing 1340–2, 1341  
  schistosomiasis 611  
  tongue worms causing 614  
granulomatosis 1063–76  
  allergic *see* Churg–Strauss syndrome  
  bronchocentric 588, 954, 1072–4, 1074  
  lymphocytic angiitis and 1063–76  
    benign 1071  
  lymphomatoid 1071  
  necrotizing sarcoid 1072, 1072, 1073  
  Wegener's *see* Wegener's granulomatosis  
grepafloxacin 225, 227  
Grocott–Gomori methenamine silver method 361, 1363, 1364  
growth  
  COPD risk and 624–5



- high altitude effect 57
- retardation
  - corticosteroid-induced 271, 276, 955
  - inhaled corticosteroid side-effect 983
- growth factors
  - ARDS pathogenesis 778
  - asthma pathogenesis 915
  - lung cancer 1084–5
- guanosine, analogue *see* ganciclovir
- Guillain–Barré syndrome 349
  - after influenza vaccination 350
  - respiratory failure 711
- gums
  - occupational asthma 950
  - ‘strawberry’ 1067
- gynaecomastia 111, 1287
  - in lung cancer 1112
- H<sub>1</sub>-receptor antagonists, asthma treatment 979
- H<sub>2</sub>-antagonists, in cystic fibrosis 859
- haemagglutination inhibition tests 337
- haemagglutinin 347
- haemangioma
  - capillary, mediastinal 1291
  - chest wall 1222
  - mediastinal 1291
  - pulmonary *see* arteriovenous malformations
  - sclerosing 1137
- haemangiopericytoma 1137
- haematite 1435
- haematocrit, high altitude 56
- haematology
  - hypersensitivity pneumonitis 1008–9
  - pneumococcal pneumonia 378
  - tuberculosis 521
- haematoma
  - pulmonary, lung abscess *vs* 469
  - rib fractures 135
- haematopoietic growth factors, high-dose chemotherapy with 1106
- haemoglobin
  - affinity for oxygen 36
  - carbon dioxide binding 37
  - carbon monoxide affinity 35, 36, 1444–5
  - oxygen transport 35
  - tuberculosis 521
- haemoglobin dissociation curve
  - carbon dioxide 37
  - oxygen *see* oxyhaemoglobin dissociation curve
- haemoglobin S 1382
- haemophilia, protease inhibitor warning 239
- Haemophilus influenzae* 98
  - acute sinusitis 342
  - antibiotic resistance 366
  - antibiotic susceptibility 196, 206, 207, 411
  - ciliary activity inhibition 809
  - in COPD 674–5
  - empyema 448, 454
  - encapsulated and unencapsulated forms 410
  - hospital-acquired pneumonia 371
  - pneumonia 410–11
  - serotypes 410
  - sinus infection and diffuse
    - panbronchiolitis 831
  - in sputum, bronchiectasis 809
  - vaccines 411
- Haemophilus influenzae* type b,
  - epiglottitis 340
- haemopneumothorax 1202–3
- haemopoietic system, sarcoidosis 1051
- haemoptysis 8, 105–6, 1333
  - acute bronchitis 346
  - alveolar haemorrhage causing 1330, 1331
  - bronchiectasis complication 807, 822–3
  - causes 105–6
  - COPD 652
  - cystic fibrosis 856
  - emergency treatment, rigid
    - bronchoscopy 172
  - fibreoptic bronchoscopy 158
  - in immunosuppressed 1348
  - interstitial lung disease 889
  - investigations 106
  - lung abscess 465, 473
  - lung cancer 1086
  - management 106
    - in terminal care 1531
  - massive 106, 516, 1531
  - percutaneous fine-needle biopsy
    - complication 174
  - tuberculosis 516
- haemorrhage
  - alveolar *see* alveolar haemorrhage
  - arteriovenous malformations 1324
  - aspergilloma 591–2
  - cutting-needle biopsy complication 176
  - fibreoptic bronchoscopy complication 167–8
  - massive haemoptysis 106
  - percutaneous fine-needle biopsy
    - complication 174
  - pneumothorax complication 1204
  - pulmonary *see* pulmonary haemorrhage
  - spontaneous pneumothorax with
    - 1202–3
    - subarachnoid 312
  - tracheostomy/endotracheal tube
    - complication 1503
  - transbronchial biopsy complication 167–8
    - see also individual haemorrhages/sites*
- haemorrhagic fever and renal syndrome 419
- haemorrhagic tendency, cephalosporin association 200
- haemosiderin 1333, 1334
- haemosiderosis 1382
  - chest radiography 141
  - idiopathic pulmonary 164–5, 1333–4
- haemothorax 1190
  - pleural biopsy complication 183
- Hageman factor, activated 936–7
- Haldane effect 37
- hallucinations, hypnagogic 1255
- haloperidol 1531, 1533
- halzoun 614
- hamartoma 1143–4, 1144
  - fibroleiomyomatous 1144
  - imaging 138
  - mediastinal 1291
- Hamman–Rich syndrome 877, 882
- Hamman’s sign 1190
- handicap, definition 1540
- Hand–Schüller–Christian disease 1130
- hantavirus pulmonary syndrome 418–19, 1158
- headache
  - β<sub>2</sub>-agonists causing 248
  - miliary tuberculosis 512
  - morning, hypercapnia 700–1
  - sinusitis 343
- head injury, pulmonary oedema link 770
- Head’s paradoxical reflex 52
- Heaf test 492, 493, 493
- health care workers
  - BCG vaccination 498
  - tuberculosis 478
    - screening 497
- health resources, use by COPD 619, 619
- healthy worker effect 66, 68
- heart
  - chest radiography 120
  - in COPD 633
  - development 1
  - rate 55
    - high altitude effect 56
  - size 120
  - sounds, COPD 648, 653
- heart disease
  - asthma management in 992
  - thrombosis predisposition 720
  - Wegener’s granulomatosis 1069
  - see also cardiovascular complications*
- heart failure
  - congestive 1156
  - COPD 649
  - left ventricular failure 128
  - see also right heart failure*
- heart–lung transplantation
  - bronchiectasis and 803, 821
  - COPD 676
  - ‘domino’ operation 1518
  - history 1516
  - infective complications 1347
  - obliterative bronchiolitis aetiology 833
  - results 1521
  - technique 1518
- Heimlich’s manoeuvre 712
- helium, hypothermia during diving and 1489
- helium breathing 45–6, 47
- hemidiaphragm
  - chest radiography 120
  - left and right, position 1234
  - paralysis 710, 1236–7, 1237
  - radiology 1234
  - unequal excursion/movements 1235
  - see also diaphragm*
- hemithorax, opacification 133
- Henderson–Hasselbalch equation 38
- Henry’s law 1481–2
- heparan sulphate 718
- heparin
  - intravenous unfractionated 736
  - low-dose 741–2
    - dosage and indications 741
    - venous thrombosis prevention 741–2
  - low molecular weight
    - deep venous thrombosis 740
    - pulmonary embolism 737, 742
  - pulmonary embolism treatment 736
  - subcutaneous 741–2
  - unfractionated, use in pregnancy 743
- heparinization, pulmonary embolism 736–7
- hepatic cirrhosis, primary pulmonary hypertension with 753
- hepatic disease, tuberculosis treatment in 558
- hepatic encephalopathy 113
- hepatic necrosis, acute, rifampicin effect 548

- hepatitis  
  isoniazid-induced 500, 548  
  ketonazole causing 233  
  pyrazinamide causing 549  
hepatization, red and grey 375  
hepatobiliary complications, cystic fibrosis 860–1  
hepatocellular enzymes, in cystic fibrosis 860  
hepatomegaly 537, 1532  
hepatotoxicity  
  azathioprine 286  
  cyclosporin 288  
  rifampicin (rifampin) 548, 558  
  tetracyclines 211  
hereditary haemorrhagic telangiectasia 97–8, 1140, 1322–6  
Hering–Breuer reflex 52  
Hermansky–Pudlak syndrome 1382  
hernia  
  Bochdalek 1242–3  
  diaphragmatic *see* diaphragmatic hernias  
  hiatus *see* hiatus hernia  
  Morgagni 1243, 1245, 1300  
heroin *see* diamorphine (heroin)  
herpangina syndrome 339  
herpes simplex virus (HSV)  
  aciclovir use 234–6  
  cidofovir treatment 241  
  in HIV infection 1358  
herpesvirus infections, HIV infection 1356–8  
herpes zoster 107, 416, 418, 1236  
hiatus hernia 1242, 1244, 1300  
  lung abscess *vs* 469–70, 471  
hiccups 1238, 1238–9  
  terminal care 1532  
high altitude, comparisons of  
  animals/humans living at 752  
high-altitude diseases 57–8  
  hypoxic pulmonary hypertension 751–2  
high-altitude physiology 55–8  
  circulatory adaptations 56–7  
  haematological adaptations 56  
  miscellaneous adaptive changes 57  
  ventilatory adaptations 55–6  
high-altitude pulmonary oedema 788  
highly active antiretroviral therapy (HAART) 1361  
high-pressure oedema 768, 768–880, 769, 769  
high-pressure pulmonary oedema *see* pulmonary oedema  
hila  
  chest radiography 121  
  enlargement 121, 139  
  imaging 139  
hilar arteries 139  
hilar fibrosis, idiopathic pulmonary 1340, 1341  
hilar lymphadenopathy 139  
  bilateral  
    differential diagnosis 1045  
    sarcoidosis 1036, 1044–5, 1045  
  chest radiography 1046, 1047, 1048  
  coccidioidomycosis 579  
  histoplasmosis 583  
  Hodgkin's lymphoma 1124–5  
  lung cancer 1088  
hilar lymph nodes 21  
  calcification 139, 1047  
  eggshell calcification 1418, 1419  
  metastases, bilateral 1147  
  sarcoidosis 1047  
  tuberculosis 508, 510, 517  
Hippocratic succussion of chest 1182  
hip surgery 742  
hirsutism 268  
histaminase 1021  
histamine 250, 935  
  asthma pathogenesis 913, 916, 931, 935  
  biosynthetic pathway 935  
  cells storing 935  
  functions 913  
  mast cells secreting 910, 913, 935  
  PC<sub>20</sub> 50  
  receptor blockade 935  
  receptor types 935  
  release inhibition, glucocorticosteroids 262  
histamine challenge test 50, 932  
histiocytoma 1131–2  
  fibrous 1132  
histiocytosis 1130–2  
  classification and terminology 1130  
  Langerhans' cell *see* Langerhans' cell histiocytosis  
  histiocytosis X *see* Langerhans' cell histiocytosis  
*Histoplasma*  
  skin sensitivity to 583  
  spores 575  
*Histoplasma capsulatum* 582–8  
  characteristics and growth 582–3  
  mediastinal fibrosis 1302–3  
  mediastinitis 1302  
*Histoplasma capsulatum* var. *duboisii* 584  
histoplasmosis 582–8  
  aetiology 582–3  
  chest radiography 583, 584  
  chronic pulmonary 584  
  clinical features 583–4  
  diagnosis 584–6  
    lung biopsy 584  
  disseminated 230, 513, 584  
  primary pulmonary, treatment 231  
  treatment 230, 234, 586  
history, clinical 102  
HIV  
  accidental exposure of staff 236  
  carriers, fibreoptic bronchoscopy and 170  
  HIV-1 and HIV-2 types 236  
  replication 236  
  transmission to staff, prevention 170  
HIV infection 235, 1351–61  
  bronchiectasis aetiology 800  
  chest radiography 1353  
  classification 1354  
  empyema pathogenesis 448  
  febrile pharyngitis 339  
  herpesvirus infections 1356–8  
  immune response/defects 1351–2  
  interstitial lung disease complications 889  
  *Legionella* pneumonia 387  
  lung defences and 1351–2  
  lymphocytic interstitial pneumonitis 1360  
  'mononucleosis syndrome' 339, 1352  
  morbidity and mortality 1351, 1361  
  mycobacterial infections 565  
  *Mycobacterium avium-intracellulare* infection 565, 1356, 1357  
  non-Hodgkin's lymphoma 1358, 1360  
  opportunistic infections 1348, 1353–5  
  prophylaxis 1361  
  treatment 1350  
  pneumococcal pneumonia 377  
  pneumococcal vaccine use 382–3  
*Pneumocystis carinii* pneumonia *see* *Pneumocystis carinii* pneumonia  
  primary 1352  
  primary lung tumours 1361  
  progressive immunosuppression 1353–6  
  pulmonary disease 1356–61  
    clinical evaluation 1353  
    differential diagnosis 1352, 1352  
    infections 1353–4, 1356–8  
    non-infective 1358–61  
    prevention 1361  
  pulmonary hypertension 758, 759, 1360–1  
  *Rhodococcus equi* infection 1356  
  secondary spontaneous pneumothorax 1186  
  seroconversion illness 1352  
  *Staphylococcus* pneumonia 403  
  treatment 235–40  
    three-drug approach 236  
    *see also* antiretroviral agents  
  tuberculosis *see* tuberculosis (TB)  
  tumours 1354–5  
  *see also* AIDS  
HLA associations  
  allergic reactions 95  
  sarcoidosis 1038–9  
HLA-B8 1038, 1039  
HLA-B27 1218, 1395  
HLA-DR2 1063, 1331  
HLA-DR3 1038, 1395  
hoarseness 340–1, 522  
  left recurrent laryngeal nerve paralysis 7  
  lung cancer 1086  
Hodgkin's lymphoma 1124–6  
  chest radiography 1124–5, 1126, 1127  
  clinical features and diagnosis 1124–5, 1290  
  mediastinal involvement 1290  
  nodular sclerosing 1124, 1126  
  pathology 1126  
  staging 1125, 1125–6  
  thymic cysts with 1283  
  treatment and prognosis 1125–6, 1290  
holistic care, in cystic fibrosis 867–8  
home  
  terminal care 1534  
  ventilation at 1513–14  
homeless, tuberculosis 495–6  
  reactivation 514  
Hong Kong flu 347  
Hong Kong operation 535  
hookworms 608  
Hoover's sign 645, 652, 1235  
horizontal fissure, chest radiograph 121  
hormonal disturbance, COPD 650, 651  
hormonal theory, on clubbing and HPOA 112  
hormone replacement therapy (HRT) 720  
Horner's syndrome 1114, 1204  
hospices 1533  
hospital-acquired infections  
  in ARDS 784  
  aspiration pneumonia 413, 414  
  lung abscess 470–1  
  pneumonia 356, 359  
    *Pseudomonas aeruginosa* 407, 408, 409  
    in respiratory failure 708  
    severity assessment 372

- Staphylococcus aureus* 402  
 supportive treatment 373  
 treatment 367, 368, 371–3  
 treatment  
   ‘core organisms’ 371  
   non-severe infections 372  
   pneumonia 367, 368, 371–3  
   severe infections 372–3  
 hourglass tumours 1278  
 house dust, asthma aetiology 942–3  
 house-dust mites 332  
   allergens 943  
   asthma aetiology 897, 942–3  
 ‘huffing,’ bronchiectasis treatment 819  
 human chorionic gonadotrophin (hCG)  
   1112  
   malignant mediastinal germ-cell tumour  
     1287, 1288  
 Human Genome Project 92  
 human herpes virus 8 (HHV-8) 1358  
 human T-cell leukaemia virus (HLTV-1)  
   1128  
 humidification of air 5, 53  
   with oxygen therapy 672  
 humidifier fever 1443–4  
   related syndromes 1444  
 humidifier lung 1013  
 humidifying systems 1013, 1443  
 humoral immunity, asthma *see* asthma  
 hyaline membrane  
   in ARDS 775  
   formation 712  
   radiation pneumonitis 427  
 hyaline membrane disease *see* respiratory  
   distress syndrome  
 hyalinizing granuloma 1340–2, 1341  
 hyaluronic acid, mesothelioma diagnosis  
   and 1175  
 hydatid cysts 612–13, 613  
   lung abscess *vs* 470  
 hydatid disease 612–13  
   empyema 449, 454  
   pleural effusions 1160  
 hydrocephalus, tuberculosis 529, 557  
 hydrocortisone 259, 264  
   bronchoconstriction due to 1460  
   parenteral 265, 984  
   acute severe asthma 984, 988  
   structure 260, 260, 264  
 hydrogen peroxide 1467, 1470  
 hydrogen sulphide, exposure 1445–6  
 hydromorphone 1527  
 hydropneumothorax 1157  
   chest radiography 1193  
 hydrostatic pressure  
   immersion in water 1482  
   increased, causes 1155  
   pleural 1152, 1155  
 17-hydroxycorticoids 260  
 hydroxyl radicals 1467  
 hydroxyproline 1184  
 5-hydroxytryptamine (5-HT; serotonin)  
   APUD cells 13  
   carcinoid syndrome and 1135  
   receptors, cough reflex 84  
 hyoscine hydrobromide 1530  
 hypercalcaemia, in lung cancer 1110–11  
 hypercapnia  
   clinical evidence 698–9  
   COPD 647, 650  
   daytime 710  
   effects on CNS 698  
   respiratory failure 698–9  
   symptoms 700–1  
 hypereosinophilia 1021  
 hypereosinophilic syndrome 759, 1029–31  
 hypergammaglobulinaemia D 1153–4  
 hyperglobulinaemia, sarcoidosis 1044  
 hyperinfection syndrome, strongyloidiasis  
   609  
 hyperkalaemia, drugs causing 287, 1371  
 hypernatraemia, respiratory distress  
   syndrome 713  
 hypersensitivity  
   to *Aspergillus fumigatus* 954, 1023  
   delayed, tuberculin reaction 493–4  
   drug reactions  
     ampicillin and amoxicillin 197  
     antituberculosis drugs 552–3, 553  
     azathioprine 287  
     penicillins 193  
     rifampicin 548  
     taxanes causing 294  
     thiacetazone 550  
   type I 1023  
   early asthmatic response 908  
   type II, antglomerular basement  
     membrane disease 1331  
   type III  
     allergic alveolitis 1006  
     allergic bronchopulmonary  
       aspergillosis 1023  
     polyarteritis nodosa 1028  
 hypersensitivity pneumonitis 1002–19  
   clinical features 1002–3  
   diagnosis and investigations 1008–10  
   history-taking 1008  
   lung function tests 1009  
   management 1010–11  
   pathogenesis 1005–8  
   pathology 1005, 1006  
   pulmonary function 1003–5  
   *see also* allergic alveolitis  
 hypersensitivity vasculitis, bronchiectasis  
   complication 823  
 hypersomnolence 1256  
 hypertension  
   asthma management and 992  
   catecholamine-producing  
     parangliomas 1277–8  
   sleep apnoea/hypopnoea syndrome  
     causing 1253, 1254–5  
 hyperthyroidism, tremor 113  
 hypertrophic pulmonary osteoarthropathy  
   (HPOA) 111–12, 1111–12, 1112, 1241  
   causes 112, 1111–12  
   management 113, 1112  
   pain relief 1528  
   theories 112  
 hyperventilation 1264–8  
   in arteriovenous fistulae 1266  
   asthma 930–1, 956, 985  
   behavioural *see* behavioural  
     breathlessness  
   breathlessness and 107, 1265–7  
   causes 1264, 1265, 1266  
   definition 1264  
   differential diagnosis 1266  
   explanation to patients 1266–7  
   high altitude 56  
   Kussmaul breathing 110, 1266  
   pneumothorax 1189  
   psychogenic 1264, 1265  
   clinical features 1265  
   management 1266–7  
   tests and diagnosis 1265–6  
   pulmonary embolism 1266  
   respiratory alkalosis 38  
   symptoms 1264–5  
   type I respiratory failure and 697  
 hyperventilation syndrome 1265  
 hyphae 573–4  
 hypnosis, in asthma 948  
 hypocapnia, symptoms 1265  
 hypochondrium, bulging 1241  
 hypogammaglobulinaemia, opportunistic  
   infections 1348  
 hypoglycaemia, pentamidine causing 222  
 hypokalaemia  
   asthma 986  
    $\beta_2$ -agonists causing 248  
 hyponatraemia  
   lung cancer 1111  
   pneumonia 365  
 hypophosphataemia, pneumonia 365  
 hypopnoea, sleep *see* sleep  
   apnoea/hypopnoea syndromes  
   (SAHS)  
 hypoproteinaemia 767, 1157  
 hyposensitization, drug-induced lung  
   disease 1467  
 hypothalamic–pituitary–adrenal (HPA)  
   axis 272  
   inhaled corticosteroid side-effects 982,  
     983  
   suppression 272, 275  
 hypothalamus, sarcoidosis 1051  
 hypothyroidism 1051, 1229  
 hypoventilation 33  
   chronic, respiratory failure 1229–30  
   ‘controlled,’ in asthma 957  
   hypoxaemia due to 696  
   respiratory acidosis 38  
   scoliosis 1218  
   sedatives causing in fiberoptic  
     bronchoscopy 168  
   in sleep *see* sleep apnoea/hypopnoea  
     syndromes (SAHS)  
 hypoxaemia  
   acute severe asthma 986  
   adult respiratory distress syndrome 770,  
     771  
   causes 33  
   clinical evidence 698  
   COPD 647, 700  
   cryptogenic fibrosing alveolitis 886  
   estimation 37–8  
   fiberoptic bronchoscopy 169  
   high-pressure pulmonary oedema 769  
   infections in immunosuppressed 1350–1  
   management 700  
   pneumonia detection 364  
   pneumothorax 1189  
   pulmonary telangiectasia 1140, 1325  
   respiratory failure 696, 698  
   without hypercapnia *see* respiratory  
     failure, type I  
 hypoxia  
   carotid response 50–1  
   COPD 647, 650  
   diving 1489  
   endothelin 1 release 750  
   high-altitude 55, 788  
   nitric oxide release inhibition by 750  
   relief in respiratory failure 701–2  
   secondary polycythaemia due to 698  
   transtracheal aspiration complication  
     186  
   ventilatory response 51

- hypoxic drive 51  
     *see also* respiratory drive  
 hysteresis 40
- ICAM-1, expression, late asthmatic response 917
- idiopathic pulmonary haemosiderosis 164–5, 1333–4
- ifosfamide 285
- imaging 119–47  
     diffuse lung disease 140–7  
     lung scintigraphy 123–4  
     pleural effusions 130–4  
     solitary chest lesions 134–9  
     spiral CT pulmonary angiography 124–5, 125, 126  
     ultrasound 123, 450  
     *see also specific techniques*
- imipenem, empyema 453
- imipenem–cilastatin 204
- immersion in water 1482, 1489
- immigrants, tuberculosis 496
- immobilization, thrombosis predisposition 719
- immotile cilia syndrome *see* ciliary dyskinesia, primary; Kartagener's syndrome
- immune complexes  
     bronchiectasis pathogenesis 802  
     Wegener's granulomatosis 1063–4, 1065
- immune complex nephritis, miliary tuberculosis 514
- immune complex vasculitis, polyarteritis nodosa 1028
- immune response, initiation/control, by alveolar macrophage 89
- immune system  
     in asthma *see* asthma  
     changes, bronchiectasis pathogenesis 801–2  
     cryptogenic fibrosing alveolitis pathogenesis 880  
     disorders, pleural effusions 1160–1  
     IgE and 933–4  
     inherited disorders 96–7  
     Th1 and Th2 cells 934
- immunocompromised patients  
     cytomegalovirus pneumonia 418  
     *see also* immunosuppressed patients
- immunodeficiency 1384  
     antibody deficiency 97, 798, 1384  
     bronchiectasis 798, 820  
     common varied (CVID) 798  
     opportunistic infections 1348  
     severe combined (SCID) 97
- immunoglobulin  
     deficiency 97, 1384  
     functional deficiencies 798  
     lung defence 86
- immunoglobulin A (IgA)  
     in bronchial mucus 14–15  
     deficiency 86  
     dimeric 86  
     functions 15  
     in lung secretions 86  
     secretory 15, 53, 86
- immunoglobulin E (IgE)  
     allergic bronchopulmonary aspergillosis 1023  
     asthma pathogenesis 916, 933  
     atopy locus and 923, 939  
     biological advantage of producing 933–4
- Fc receptors 933
- IgM switch to 93
- in smokers 625
- structure 933
- immunoglobulin G (IgG)  
     in BAL fluid, cryptogenic fibrosing alveolitis 881  
     increased, cryptogenic fibrosing alveolitis 881  
     subclass deficiencies 798
- immunoglobulin M (IgM)  
     *Chlamydia pneumoniae* 399  
     switch to IgE 93
- immunoglobulin superfamily 910
- immunopathogenesis, mechanisms in asthma 933–4
- immunoreactive trypsin (IRT) 850
- immunosuppressed patients  
     coexisting pulmonary infections 597  
     invasive aspergillosis 593–4  
     lung abscess 464  
     non-infectious complications 1347  
     *Pneumocystis carinii* pneumonia *see* *Pneumocystis carinii* pneumonia  
     pulmonary complication patterns 1346–8, 1347  
     reactivation of tuberculosis 515  
     respiratory tract infections 1346–79, 1347  
         clinical features 1348  
         diagnosis 1349  
         prevention 1351  
         radiology and lung sampling 1348–9  
         treatment 1349–51, 1350  
         *see also* opportunistic infections  
     *see also* HIV infection
- immunosuppressive agents 283
- antiglomerular basement membrane disease 1332
- cryptogenic fibrosing alveolitis 887
- lung transplantation 858, 1520
- Pneumocystis carinii* pneumonia after 1363
- immunotherapy  
     asthma 990–1  
     'blunderbuss-type vaccines' prohibited 990  
     infections in cystic fibrosis 854  
     principles 990–1
- impairment, definition 1540
- impedance plethysmography  
     deep venous thrombosis 724  
     in pregnancy 743
- impenem  
     aspiration pneumonia 414  
     lung abscess 472
- incidence of disease, longitudinal (cohort) study 73–4
- incidence rate 65, 66  
     cumulative 66  
     standard (SIR) 67
- inclusion bodies, sarcoidosis 1040, 1041–2
- indinavir 239
- indirect immunofluorescence test, Legionnaires' disease 389–90
- indometacin (indomethacin) 109, 1528
- industrial injuries 1537, 1537–8
- insurance 1416
- Industrial Injuries Advisory Council (UK) 1422, 1537
- inert gas technique 31, 32
- infantile lobar emphysema 677
- infants  
     feeding, asthma and 899  
     infection reduction and asthma increase 940  
     infective bronchiolitis 829, 830  
     lung development 3–4  
     mediastinal tumours/cysts 1271  
     mortality, pneumonia 357  
     nasal breathing 53  
     *Pneumocystis carinii* pneumonia 596  
     pneumonia 357, 358
- infections  
     asthma and 898–9, 946–7  
     bronchiectasis complication 822  
     chemotherapy in lung cancer and 1107  
     early life, asthma risk reduction 899, 934  
     empyema pathogenesis 446  
     infantile, asthma increase and 940  
     inhaled corticosteroid side-effect 982  
     pleural exudates due to 1158–60  
     *see also* respiratory tract infections;  
         *individual infections*
- infectious mononucleosis 339
- infective endocarditis 171
- infective polyneuropathy *see* Guillain-Barré syndrome
- inferior pharyngeal constrictor 5
- inflammation/inflammatory response  
     ARDS pathogenesis 776–81  
     asthma 917–19, 981  
     bronchiectasis pathogenesis 801–4  
     control, by alveolar macrophage 87  
     cryptogenic fibrosing alveolitis pathogenesis 880  
     cystic fibrosis 853–4, 854  
     deep venous thrombosis 723  
     downregulation, loss of ability in  
         cryptogenic fibrosing alveolitis 880  
     inhibition in ARDS therapy 785, 786  
     initiation and control 89  
     resolution in lung 781–2
- inflammatory bowel disease  
     bronchiectasis association 802, 1398  
     obliterative bronchiolitis aetiology 833  
     *see also* Crohn's disease; ulcerative colitis
- inflammatory cells  
     adult respiratory distress syndrome 776–81  
     asthma 907, 908–12, 927
- inflammatory mediators 774
- ARDS pathogenesis 777
- asthma challenge 932–3
- asthma pathogenesis 912–16, 931, 933, 935–6
- redundancy 912
- release, inhibition by  
     glucocorticosteroids 260–1, 261
- inflation reflex 52
- influenza 347–51  
     clinical manifestations 348  
     complications 348–9  
     diagnosis 349  
     incubation period 348  
     mortality 347, 350  
     outbreaks and epidemics 347  
     pneumonia 414–15  
         outbreaks after 357, 376, 385  
     prophylaxis 349, 350–1  
         amantadine 243, 349  
     seasonal variations 347, 348  
     treatment 242–3, 349–50  
     vaccination 350–1  
         COPD 674  
         formalin-inactivated vaccines 350

- live attenuated 350–1
- influenza A virus
  - treatment 242
  - vaccines 350
- influenza B virus 348
  - infections, treatment 243
- influenza C virus 348
- influenza viruses 336, 347
  - animal reservoirs 347–8
  - antigenic shift and drift 347–8
  - subtypes and strains 347
- information for patients 103
- informed consent, fiberoptic bronchoscopy 151
- inhalational injury
  - bronchiectasis aetiology 797
  - obliterative bronchiolitis due to 832
  - see also* smoke inhalation
- inhalation challenge tests 49–50
- inhalation delivery systems 988–90
- inhaled therapy
  - $\beta_2$ -agonists 245, 246–7, 249
  - corticosteroids *see* corticosteroids
  - delivery devices 279
  - ipratropium bromide and oxitropium 250–1
  - nicotine 318
  - nitric oxide *see* nitric oxide (NO)
  - sodium cromoglycate 257
- inhalers
  - CFC-free 279, 989
  - dry powder 279, 989–91
  - shapes for visually impaired 992
  - see also* metered-dose inhalers (MDIs)
- inheritance of disease *see* entries *beginning genetic*
- inotropic agents, pneumonia 373
- inspiration 26, 39
  - noisy 109
  - see also* ventilation, mechanical
- inspiratory pressure support (IPS) 704–5, 708
- inspiratory reserve volume (IRV) 29
  - barotrauma and 1484
- inspiratory squeak sign 1003
- institutions, tuberculosis 495–6, 496
- insulin, diabetes treatment in cystic fibrosis 862
- integrins 910
  - neutrophil–endothelial interactions 779
- interalveolar wall attachment distance (IAAD) 634
  - emphysema 632, 632
- interbronchiolar communication 15
- interception 1406
- intercostal arteries 23
- intercostal neuroma 135, 135
- intercostal tube drainage
  - lung re-expansion failure after 1202
  - pneumothorax 1197–9, 1198
  - sutures for drains 1198
- 'interference,' virus culture 338
- interferon- $\gamma$ 
  - ascitic fluid, in tuberculosis 537
  - CNS tuberculosis 531
  - mesothelioma management 1177
- interferons 243–4
- interleukin(s)
  - bronchiectasis pathogenesis 801
  - secretion by airways 12
- interleukin-1 (IL-1) 914
  - in asthma 908, 909, 914
  - receptor 915
- antagonist 786
- silicosis pathogenesis 1423
- interleukin-2 (IL-2), receptors 1031
- interleukin-3 (IL-3) 915
- interleukin-4 (IL-4) 915
  - asthma pathogenesis 915
  - IgM to IgE switch 93
  - receptor, atopy and 95
- interleukin-5 (IL-5) 881, 915
  - asthma pathogenesis 915
  - effect on eosinophil longevity 911
- interleukin-8 (IL-8) 916
  - ARDS pathogenesis 774, 778
  - neutrophil chemotaxis 917
- interleukin-12 (IL-12) 915
- interlobular effusion 133–4
- intermediate cells 13
- intermittent mandatory ventilation (IMV) 704–5, 1499
  - synchronized 705, 1499
- intermittent positive pressure ventilation (IPPV) 704
  - COPD 646
  - nasal 646, 1218, 1369, 1504
  - bronchiectasis 820
- International Consensus Report on Diagnosis and Management of Asthma 976, 984–5
- International Labour Office (ILO) 68, 1409
- chest radiograph classification 77–8, 78
  - uses 78–9
- international normalized ratio (INR), warfarin 737–8
- interstitial fibrosis *see* pulmonary fibrosis
- interstitial lung disease, diffuse 888
  - causes 888
  - clinical features and history 888–9
  - differential diagnosis 888, 888–90
  - fiberoptic bronchoscopy 164–5
  - high-resolution CT 123
  - imaging 140–7
  - investigations 889–90
  - lung biopsy 180–1, 183
  - see also* cryptogenic fibrosing alveolitis
- interstitial pneumonitis
  - chlorambucil association 289
  - in HIV infection 1360
- interstitial pressure 767
- interstitial space
  - fluid accumulation 766–7
  - fluid clearance 767
- intestinal obstruction, cystic fibrosis
  - complication 859–60
- intima, in COPD 633
- intimal fibrosis, cor pulmonale 750
- intimal proliferation, primary pulmonary hypertension 754, 755
- intraabdominal tumour 105
- intracerebral disease, neurogenic pulmonary oedema 787
- intracranial metastases
  - diagnosis and symptoms 1115, 1532
  - lung cancer 1086, 1095, 1101–2, 1115
  - prophylactic irradiation 1108–9
  - management 1115, 1532
- intracranial pressure, raised 113, 1115
- neurogenic pulmonary oedema 787
- intrapleural pressure 45, 47, 1152, 1182
- intrapulmonary shunting, in pulmonary embolism 722
- intrathoracic pressure 39, 40, 41
- intrauterine nutrition 1477–8
- 'intrinsic positive end-expiratory pressure' 645
- iodine isotope scan 1297
- ionizing radiation *see* radiation
- ion transport, cystic fibrosis 844–5
- IPPB trial,  $\beta_2$ -agonists 664
- ipratropium bromide 250–2
  - administration/dosage 250–1
  - adverse effects 251
  - asthma treatment 979, 987
  - COPD 675
  - effect on exercise in COPD 665
  - nebulized 251, 252
  - structure 250
- iron deficiency anaemia 1331, 1333
- iron oxides 1435
- irrigation therapy, empyema 456
- irritant gases 330, 1445, 1446–8
  - inhalation 426
  - reactive airways dysfunction syndrome 998–1000
  - toxic bronchiolitis 830
  - types 1000
  - see also* toxic gases
- irritant receptors, pulmonary 52
- ischaemic heart disease 312, 314
- Islets of Langerhans 1285
- isocyanates 1449
  - allergic alveolitis due to 1003
  - occupational asthma 951
  - reactive airways dysfunction syndrome 1000
- isolation of patients, tuberculosis 478, 479
- isolation rooms 479
- isoniazid 548–9
  - activity/effectiveness 545–6
  - adverse effects 500, 547, 548–9
  - dosage 547, 548
  - Mycobacterium avium-intracellulare* complex disease 569
  - phenytoin interaction 549
  - tuberculosis prophylaxis 498, 499
  - tuberculosis treatment 544, 557
  - regimens 553, 554
- isoprenaline (isoproterenol) 244, 245
- inhalers, asthma mortality and 901
- onset of action 247
- structure 245
- itraconazole 230–1
  - structure 230
- ivermectin 610
- jacket ventilation 1508–9
- Japanese summer pneumonitis 1014
- jaundice, prolonged neonatal 847
- J chain 86
- jet nebulizers 279
- joints
  - tuberculosis 533–6, 556
  - Wegener's granulomatosis 1068–9
- J receptors 22, 52, 84
- jugular pulse 113–14
  - pulsation absence 113
- jugular venous engorgement, pulmonary embolism 728
- jugular venous pressure
  - COPD 648, 652, 653
  - elevated 114
  - pericardial tuberculosis 532
- kallikreins 936–7
- kanamycin 214, 550, 551
- kaolin 1433–4
- kaolinite 1433

- Kaposi's sarcoma 1137–8, 1138  
 endobronchial involvement 156  
 in HIV infection 1358, 1359, 1360  
 lung involvement 138
- Karnofsky Performance Index 1116, 1117, 1525
- Kartagener's syndrome 94, 795, 796  
 chest radiography 810, 812
- Katayama fever 611
- keratin pearl formation 1082
- Kerley A lines 21, 145, 146, 768, 769
- Kerley B lines 21, 145, 146, 760, 768, 769, 1147, 1303  
 coal workers' pneumoconiosis 1410
- Kerley lines 758, 1091
- 'ketchup bottle method,' bronchiectasis treatment 819
- ketoconazole 233–4  
 adverse effects and interactions 233–4  
 blastomycosis 578  
 coccidioidomycosis 580  
 structure 233  
 terminal care 1532  
 uses/indications 234
- ketotifen, asthma treatment 979
- keyhole surgery, lung cancer 1099
- khellin 256
- Killian's dehiscence 5
- kinins, asthma pathogenesis 913, 936–7
- Klebsiella* 406  
 antibiotic sensitivities 407  
 pneumonia 406–7  
 in sputum, bronchiectasis 809
- Klebsiella oxytoca* 406
- Klebsiella ozaenae*, in sputum 361
- Klebsiella pneumoniae* 406  
 lung abscess 463, 522
- Kleine-Levin syndrome 1256
- Klinefelter's syndrome 1287  
 bronchiectasis association 803
- Klippel-Feil syndrome 1309
- knemometry 276, 983
- Koch's phenomenon 479
- Kohn, pores 15
- Koplik's spots 415
- K-ras oncogene 98, 1085
- Kulchitsky cells *see* APUD cells
- Kussmaul breathing 110, 1266
- Kussmaul's sign 114
- Kveim test 1042, 1050, 1053–5  
 false-positive and value of test 1053  
 method 1054  
 reaction 1054–5  
 test substance 1053–4
- kyphoscoliosis 3, 108, 1214
- kyphosis, absence in straight back syndrome 1214
- laboratory investigations, pneumonia 360–4
- laboratory mammals, allergic alveolitis due to 1016
- laboratory workers, tuberculosis 496
- $\beta$ -lactam antibiotics 193–204  
*see also* penicillin(s)
- $\beta$ -lactamase 195, 404
- $\beta$ -lactam ring 193, 194
- lactate dehydrogenase  
 empyema 453  
 peritoneal fluid, tuberculosis 537  
 pleural fluid 1164  
 serum, *Pneumocystis carinii* pneumonia 1367
- lactation, corticosteroid effects 271–2
- lactic acid 55
- lactoferrin 86
- lamellar bodies 18, 19, 1335  
 osmiophilic 16
- lamina reticularis 926
- lamivudine (3TC) 238
- Langerhans' cell histiocytosis 1130–1, 1131, 1132  
 chest radiography 1132  
 CT 146, 147
- Langerhans' cells 1130, 1130
- Langhans' giant cell 1437
- tuberculosis 479, 480
- larva migrans, visceral 609, 610
- laryngeal carcinoma 7  
 asbestos workers 1426  
 asthma *vs* 961  
 smoking and 311  
 tuberculosis *vs* 540
- laryngeal oedema, respiratory failure 709
- laryngeal swabs, tuberculosis diagnosis 520
- laryngectomy 54
- laryngitis  
 acute 340–1  
 tuberculous 341, 522
- laryngospasm, fiberoptic bronchoscopy 169
- laryngotracheal groove 1
- laryngotracheobronchitis  
 acute 347–8  
 influenza complication 348
- larynx  
 anaesthesia 7  
 benign tumours 8  
 defence role 83  
 fiberoptic bronchoscopy 154  
 muscles 6, 7  
 structure 6–8  
 tuberculosis 7, 540
- laser treatment  
 endobronchial 1102–3  
 tracheobronchial narrowing 151
- latex rubber, allergy 951
- lathrogens 640
- lawyers 1536, 1538
- laxatives 1531
- lead, air pollution 329
- left atrial myxoma 760
- left atrial pressure, increased, causes 759, 760
- left recurrent laryngeal nerve 8  
 anatomy 7, 19  
 paralysis 7
- left ventricular failure 128
- leg  
 growth 276  
 movements, in sleep 1256
- legal issues *see* medicolegal aspects
- Legionella*  
 antigen detection in urine 365, 390  
 characteristics and culture 390  
 gene probes 390  
 identification 390  
 immunity 386  
 lung abscess 461  
 monoclonal antibodies 390  
 pneumonia *see* Legionnaires' disease  
 species 385  
 sputum culture 362
- Legionella bozemanii* 392
- Legionellaceae 385
- Legionella micdadei* 223, 386, 388  
 pneumonia 391–2  
 treatment of infections 391
- Legionella pneumophila* 385–6  
 antibiotic susceptibility 204, 223  
 serotype 1 388
- Legionnaires' disease (*Legionella* pneumonia; legionellosis) 372, 385–92, 1444  
 chest radiography 389, 389  
 clinical manifestations 387–8  
 complications 391  
 discovery/first outbreaks 385  
 epidemiology 386–7  
 extrapulmonary features 391  
 incidence 386  
 incomplete resolution 387, 389  
 investigations 364, 388–9  
 microbiological identification 389–90  
 mortality 391  
 non-*L. pneumophila* pneumonia 391–2  
 pathogenesis 359  
 pathology 387, 388  
 prevention 391  
 treatment 224, 390–1
- leiomyoma, airway 1142
- leiomyosarcoma 1142  
 chest wall 1223  
 mediastinal 1291
- lemmocytes *see* Schwann cells
- length-tension inappropriateness 108
- leprosy 481
- Leptospira icterohaemorrhagiae*, pneumonia 422–3
- leptospirosis 422–3
- leucocyte(s)  
 asthma pathogenesis 910–12  
 chemotactic factors 935  
 inherited abnormalities 97  
*see also* white cell counts; *specific cell types*
- leucocyte adhesion deficiency 97
- leucocytosis, pneumococcal pneumonia 378
- leucopenia, pneumonia 364
- leucovorin 222
- leukaemia 1129  
 chronic lymphatic 1129  
 cyclophosphamide and 285  
 invasive aspergillosis 593  
 myeloid 1129
- leukotriene(s)  
 antagonists, asthma 983  
 ARDS pathogenesis 778  
 asthma pathogenesis 913–14, 935–6  
 pulmonary alveolar proteinosis 1334–5  
 roles 259  
 synthesis 258–9, 937
- leukotriene B<sub>4</sub> 89, 913
- leukotriene modifiers 258–9
- levofloxacin 225, 227
- Libman-Sacks endocarditis 759
- lidocaine  
 absorption 154  
 adverse effects 154  
 cough relief in terminal care 1529  
 fiberoptic bronchoscopy 153, 155, 168–9
- ligamentum arteriosum 19
- lignocaine *see* lidocaine
- lincomycin 218
- Linguatula serrata* 614
- lipid mediators, asthma pathogenesis 913–14, 914
- lipids

- dietary, asthma and 900
  - secretion by macrophage 89
  - Lipiodol 428
  - lipocortin 1260
  - lipoid pneumonia 428–9, 1467, 1531
    - causes 428
    - clinical manifestations 428–9
    - treatment and diagnosis 428
  - lipoma 1143
    - chest wall 1221–2
    - diaphragmatic 1240
    - mediastinal 1291
  - lipopolysaccharide (endotoxin)
    - ARDS pathogenesis 777–8
    - neutrophil priming 780
    - protection from hyperoxia 1468
  - liposarcoma 1143
    - chest wall 1223
    - mediastinal 1291
  - liposomes 229
    - gene delivery in cystic fibrosis therapy 866
  - lipothymoma (thymolipoma) 1283
  - 5-lipoxygenase 89
    - inhibitors 259
  - 5-lipoxygenase-activating protein (FLAP) 259, 914
  - lipoxygenase pathway 935–6
  - lips, pursing 110
  - liquid paraffin 428, 1531
  - Listeria monocytogenes*
    - empyema 449
    - pneumonia 423
  - listeriosis 423
  - litigation, trends 1541
    - see also* medicolegal aspects
  - liver
    - abscess
      - amoebic 605, 1160
      - empyema pathogenesis 446
    - cysts, hydatid 612
    - disease, in cystic fibrosis 860
    - enlargement, lung cancer 1087
    - enzymes, induction by rifampicin 548
    - function tests, tuberculosis 521
    - metastases
      - carcinoid tumour 1135
      - lung cancer 1095
    - transplantation 1347
  - Loa loa* 609
  - Loeffler's syndrome (simple pulmonary eosinophilia) 1022–3
  - lomefloxacin 225, 227
  - lomustine 291
  - longitudinal (cohort) study 65, 71–4
    - examples 71–4, 72
    - incidence of disease 73–4
    - lung function decline 73
    - mortality studies 72–3, 72
    - problems 71
  - lorazepam, fibreoptic bronchoscopy 152
  - loviride 239
  - low birthweight infants
    - asthma prediction 897
    - chronic lung disease 1477, 1478
  - lower respiratory tract
    - colonization with pyogenic organisms, lung abscess formation 461
    - defences 53–4, 83
    - infections 365
      - see also* pneumonia
    - structure 8–19
    - Wegener's granulomatosis 1067
  - see also* airway(s); bronchi; trachea
  - L-selectin 774, 775
  - lung
    - accessory bud 1318
    - agenesis 1313–15
    - apices, pneumonic infiltration 144
    - azygos lobe 1315, 1316
    - benign lesions, doubling time 181
    - blood flow distribution 31, 32
    - blood vessels 19–21
    - as bubble filter 1486, 1491
    - bud, development 1
    - burst, in barotrauma 1483, 1485
    - calcification 138, 138
      - tuberculosis 508, 509, 517
    - calcified lesions, varicella pneumonia 416, 417
    - cavitation *see* cavitation (lung)
    - cellular development 2–3
    - chest radiograph 121
    - collapse/consolidation
      - cystic fibrosis 856
      - imaging 127–30, 1090
      - primary tuberculosis 509
    - compliance *see* compliance
    - compression in barotrauma 1483
    - congenital adenomatoid malformation 1313
    - congestion, lobar pneumonia 374
    - cysts, Langerhans' cell histiocytosis 1131
    - defences 1346
      - HIV infection 1351–2
    - density, CT measurement in COPD 660, 660
    - development 1–4
      - postnatal 3–4
    - developmental disorders 797, 1309–29, 1478
      - parenchymal 1313–19
      - pulmonary vasculature 1319–26
      - tracheobronchial 1309–13
      - see also* individual disorders
    - elastic properties 39–41
      - see also* compliance
    - elastic recoil *see* elastic recoil of lung
    - embryology 1–4
    - embryonic 1
    - functions 1, 26–62
    - gaseous diffusion 33–5
      - see also* diffusion, gaseous
    - grey hepatization 375
    - Hodgkin's lymphoma involving 1125
    - honeycomb 883, 884, 885
    - hydatid cysts 612–13, 613
    - hypoplasia 678, 1313–15, 1315, 1320
      - scimitar syndrome 1321
    - infarction *see* pulmonary infarction
    - injury *see* lung injury
    - innervation 22–3
    - intrauterine growth 1478
    - lavage, unilateral 1335–7
    - 'leaky' 722
    - lobar collapse
      - breath sounds 115
      - chest radiography 130, 131, 132
    - lobar consolidation 127–8, 128, 379
      - imaging 127–30, 129
    - lobes 10, 10–11
    - lobulation, congenital anomalies 1315–16, 1316
    - lobules 15
    - lymphatics 21–2, 766
    - lymph drainage pattern 21, 22, 766
  - mechanics 39–50
    - COPD 640–3
    - mechanical ventilation aims 1501
  - necrosis 464
  - nodules *see* pulmonary nodules
  - opacification/opacities 133, 141
  - ILO classification 78, 78–9
    - sarcoidosis 1045, 1047, 1049
  - overinflation
    - consequences 658
    - COPD 644, 652
    - emphysematous bullae 661
    - reduction by lung volume reduction surgery 679
    - see also* chest, overinflation
  - physiology in diving 1481–3
  - popcorn calcification 138, 138
  - protection from free radical damage 1467
  - protective proteins 85–7, 86
  - proteinase–antiproteinase imbalance 639–40
  - radiation damage 1470
    - see also* radiation fibrosis; radiation pneumonitis
  - red hepatization 375
  - re-expansion after pneumothorax 1199
    - failure 1202
    - pulmonary oedema 1203–4
  - re-expansion oedema 789
  - rupture, barotrauma and 1483, 1485
  - segmental anatomy 10, 10–11
  - sequestered segment 10–11
    - bronchiectasis aetiology 797
  - sequestration 1316–19, 1317, 1320–1
    - aetiology and pathology 1317–18
    - clinical features and treatment 1318–19, 1319
    - comparison of types 1317
    - extralobar 1316, 1317, 1317, 1318
    - intralobar 1316, 1317, 1317, 1318
  - solitary masses, imaging 134, 136–7, 137–9
  - sounds *see* breath sounds
  - squeeze 1483
  - in systemic diseases 1380–403
  - tumours *see* lung cancer; lung tumours
  - ventilation–perfusion scans *see* ventilation–perfusion ( $V_A/Q$ ) scans
  - volumes *see* lung volumes
  - zones 31, 121
  - see also* entries beginning pulmonary, respiratory; respiratory tract, defences
- lung abscess 460–75
  - actinomycosis 463, 470, 575
  - amoebic 605, 606
  - aspiration pneumonia 413
  - clinical manifestations 464–6
  - definition 460
  - diagnosis, radiography 462, 466, 467
  - differential diagnosis 468–70
  - fibreoptic bronchoscopy hazard 169
  - fungal 463
  - healed, appearance 466
  - investigations 466–8
    - microbiological 467–8
    - radiography/imaging 466, 466–7, 467
  - Legionella* pneumonia 387, 388
  - lung cancer with 461, 468
  - mechanisms of infection 460–1
  - meliodiosis 423
  - microabscesses 464



- lung abscess (*Continued*)  
 microbiology 462–4  
 aerobes 462–3  
 anaerobes 460, 462  
 unusual causes 463–4  
 multiple, treatment 472  
 pathology 464  
 pneumococcal pneumonia complication 385  
 posture effect 465  
 rare causes 464  
 risk factors 460–1  
 secondary spontaneous pneumothorax 1185  
 single 463  
 sites 464  
 treatment 470–3  
   antibiotics 470–2  
   bronchoscopy 473  
   drainage 473  
   physiotherapy 473  
   surgery 473  
 tuberculosis *vs* 522  
lung biopsy 172–83  
 allergic alveolitis 1009  
 aspiration 172, 173, 174  
 bronchoscopic *see* transbronchial lung biopsy  
 choice of procedure 181–2  
   diffuse disease 182–3  
   localized disease 183  
 closed 172–9  
 contraindication, bleeding diathesis 172, 175  
 co-ordination of staff 174, 179  
 cryptogenic fibrosing alveolitis 878, 886  
 cutting-needle biopsy 175–7, 182  
   complications 176–7  
   contraindications 177  
   diagnostic accuracy 177  
   mortality 177  
   needles 175, 175  
   technique 175–6  
 decision tree 182  
 indications 172, 180–3  
   diffuse disease 180–1  
   localized disease 181  
 open 179, 182  
   advantages 183  
   disadvantages 182–3  
   in immunosuppressed patients 1349  
   transbronchial lung biopsy *vs* 165  
 opportunistic mycobacterial disease 568  
 percutaneous fine-needle *see* percutaneous fine-needle biopsy  
 pneumothorax after 1187  
 pre-biopsy checks 172  
 respiratory secretion collection 363  
 transbronchial *see* transbronchial lung biopsy  
 trephine (drill) 177–9, 182  
   complications and mortality 178–9  
   diagnostic accuracy 178  
   technique 177–8  
 video-assisted thoracoscopic 179, 183, 184  
lung cancer 1077–123  
 abscesses in actinomycosis mimicking 575  
 acinar and papillary adenocarcinoma types 1082, 1082–3  
 adenocarcinoma 1082, 1082–3, 1086, 1219  
 aetiological factors 1077–80  
 air pollution 1079  
 asbestos 1079, 1080  
 occupational factors 1079, 1079, 1449  
 passive smoking 314, 1077  
 pulmonary scarring 1079–80  
 radon exposure 1079  
 smoking *see below*  
 asbestos and 1079, 1080, 1424, 1425, 1426, 1432  
 autocrine growth stimulation 1084, 1085  
 biology 1084–5  
 bronchiectasis complication 823  
 carcinoid tumours 138  
 cavitating 137  
   chest radiography 469, 1088  
   lung abscess *vs* 468  
 clinical features 111, 148, 1085–7  
 central tumours 1085–6  
 cough 103–4, 148, 1086  
 peripheral tumours 1086  
 clinical presentation 1085–6  
 cryptogenic fibrosing alveolitis and 1080  
 diagnosis, bronchoscopy 148–9  
 doubling time 1117  
 endobronchial, fibreoptic bronchoscopy 163  
 epidemiology 1077–80  
   smoking trends and 1078  
 genetic abnormalities 1085  
 growth factors role 1084–5  
 histological classification 1080–1, 1081  
 hypercalcaemia 1110–11  
 hypertrophic pulmonary osteoarthropathy (HPOA) in 1111–12, 1112  
 intramural, fibreoptic bronchoscopy 163–4  
 investigations 1087–97  
   bronchoscopy 163–4, 1090, 1093  
   chest radiography 122, 136, 136–7, 469, 1088, 1088–9, 1089, 1090, 1091, 1092  
   computed tomography 1094, 1094, 1096–7  
   imaging 136, 136–7  
   MRI 126, 126, 1094  
   outline 1087  
   sputum cytology 1082–3, 1089–90  
 laboratory studies 1080–5  
 large-cell carcinoma 1084, 1084  
 lung abscess with 461, 468  
 lung transplantation 1518  
 mechanical effects 1089  
 metastases 142, 1086, 1095, 1095  
   intracranial *see* intracranial metastases  
   small-cell carcinoma 1083–4  
 mortality 311, 1077, 1077, 1118  
   age-standardized rates 1078  
   smokers 72  
 natural history 1117–18  
 non-small-cell  
   chemotherapy 283, 285, 1103, 1103, 1103–4  
   combined modality 1103–4  
   growth factors 1084  
   palliative treatment 1101, 1101–2  
   prognosis 1118  
   radiotherapy 1100–2, 1103, 1104  
   staging 1097–8  
   superior vena cava obstruction 1113, 1114  
   surgery 1099–100, 1103–4  
   treatment 1099–104  
 oncogenes and 1085  
 operability determination 1093–5  
 paraneoplastic syndromes 1110–13  
 pathogenesis, histological types 1080, 1080  
 peripheral tumours 164, 1086  
 pleural effusions 1086, 1087, 1115  
 preoperative management 1096–7  
 prognosis 1117–18  
 quality of life 1116–17  
 sarcoidosis and 1080  
 ‘scar cancers’ 523, 1079–80  
 screening 79, 80  
 shale industry and 70, 70, 71  
 SIADH 1111  
 small-cell (oat-cell) *see* small-cell lung cancer  
 smoking and 80, 311–12, 621, 1077–8, 1085  
   case-control studies 71  
   death rates 72  
   effect, case-control studies 71  
 spread 1086  
   assessment 1093–5  
   distal, assessment 1095  
   distant 1086  
   local, assessment 1093–5  
   lymphatic 1086  
   tracheal 1115–16, 1116  
 squamous cell carcinoma 1081–2, 1082, 1085  
   tomogram 136  
 staging 1097–8, 1098  
 imaging methods 137  
   per-bronchoscopic needle aspiration 163  
 superior sulcus tumours 1114–15  
   *see also* Pancoast’s syndrome  
 superior vena cava obstruction 113, 1113–14  
 survival 1098  
 treatment 1098–110  
   *see also* lung cancer, non-small-cell; small-cell lung cancer  
 tuberculosis complication 523  
 tuberculosis *vs* 522  
 tumour markers 1085  
 vocal cord paralysis 154, 1086  
lung disease  
 chronic *see* chronic lung disease  
 diffuse interstitial *see* interstitial lung disease  
 drug-induced *see* drug-induced lung disease  
 genetics 91–101, 93–8  
 in HIV infection *see* HIV infection  
 hypersensitivity *see* hypersensitivity pneumonitis  
 obstructive 44  
 occupational *see* occupational lung diseases  
 paediatric influences 1476–80  
 restrictive 43, 43, 44, 58  
 sarcoidosis 1045–9  
 suppurative *see* suppurative lung disease  
lung fibrosis *see* pulmonary fibrosis  
lung flukes 611–12  
lung function 54–8  
 asbestosis 1429  
 asthma 900–1, 955–8, 957–8  
 coal-workers’ pneumoconiosis 1412–13  
 disorders, obstructive/restrictive

- patterns 43
  - during exercise 54–5
  - fitness for diving 1491
  - hypersensitivity pneumonitis 1003–5
  - impairment
    - bronchiectasis 808–9
    - lung cancer 1093
    - pneumothorax 1189
  - neuromuscular diseases 1230
  - pectus excavatum 1213
  - prevention of weaning from ventilation 1511
  - scoliosis 1217
  - silicosis 1421–2
  - variability in asthma 76, 951, 955
- lung function tests 43–5, 808–9
  - allergic alveolitis 1009
  - asthma 957–8
  - clinical applications 58
  - cryptogenic fibrosing alveolitis 877
  - cystic fibrosis 808
  - epidemiological studies 76–7, 77
  - fitness for diving 1491
  - hypersensitivity pneumonitis 1009
  - obliterative bronchiolitis 834
  - reactive airways dysfunction syndrome 999
  - sarcoidosis 1053
  - systemic sclerosis 1393
- Lung Health Study
  - COPD prognosis 627
  - drug compliance in COPD 666
  - FEV<sub>1</sub> in smokers 621, 621
- lung infarction *see* pulmonary infarction
- lung injury
  - acute
    - early events 776, 776–7
    - outcome 781–2
  - acute inflammatory 770–1, 772, 773
    - see also* adult respiratory distress syndrome (ARDS)
  - inhalational *see* inhalational injury score (Murray's) 772, 772
- lung metastases 156, 1145–7
  - diffuse nodular infiltration 1146, 1146
  - endobronchial 1146
  - fibreoptic bronchoscopy 164
  - multiple cannonball 1145, 1145
  - solitary 1145
    - imaging 137–8
- lung parenchyma
  - amyloidosis 1337
  - anomalies 1313–19
- lung parenchyma diseases
  - breathlessness 108
  - genetics 95–6
- lung resection
  - bilateral, bronchiectasis 821
  - lung abscess 473
  - segmental, lung cancer 1099
  - sleeve resection of tumour 1099
- lung scintigraphy 123–4
- lung secretions
  - protective proteins in 85–7, 86
  - see also* bronchial secretions; respiratory secretions
- lung transplantation 1516–23
  - alveolar microlithiasis 1340
  - bilateral sequential single 676
  - bronchiectasis and 803, 821
  - children 1518
  - cloning of organs 1522
  - complications 676–7
  - CMV infection 858
    - late 1521
    - management 1520–1
    - obliterative bronchiolitis 676–7, 858, 1521
  - contraindications (relative/absolute) 676, 1519
  - COPD 676–7, 1517
  - cryptogenic fibrosing alveolitis 887, 1517, 1518
  - cystic fibrosis *see* cystic fibrosis
  - donor lung preservation 1519–20
  - donor selection 1519–20
  - donor surgery 1520
  - double 676, 1519
    - results 1521
  - effectiveness and costs 1521–2
  - emphysema 1517, 1518–19
  - future prospects 1522
  - history 1516–17
  - indications 676, 1517–18
  - living-related donation 1519
  - lung cancer 1518
  - lung volume reduction surgery *vs* 679
  - organ donation 1516, 1519
  - paraquat poisoning 1469
  - perioperative care 1520
  - philosophy and limitations 1516
  - primary pulmonary hypertension 756, 1517, 1518
  - pulmonary fibrosis 1517, 1518
  - rejection 1520
  - results 1521
  - sarcoidosis recurrence 1040
  - selection criteria (recipient) 1516, 1519
  - single lung 676, 1516, 1518–19
    - results 1521
  - survival 1521–2
  - techniques 1518–19
- lung tumours 1124–51
  - adenocarcinoma *see* lung cancer
  - carcinoid tumours *see* carcinoid tumours
  - classification 1125
  - epithelial tumours 1133–7
  - histiocytoses 1130–2
  - HIV infection 1361
  - Hodgkin's lymphoma *see* Hodgkin's lymphoma
  - in leukaemia 1129
  - lymphoproliferative 1132–3
  - metastatic tumours *see* lung metastases
  - of mixed-cell origin 1143–5
  - muscle and connective tissue 1142–3
  - neural tissue 1143
  - non-Hodgkin's lymphoma 1127–9, 1128
  - plasmacytoma 1129–30
  - sarcoma, imaging 138
  - 'vanishing' 1154
  - vascular tissue tumours 1137–42
    - see also* lung cancer; pulmonary neoplasms
- lung volume reduction surgery *see* pneumonectomy (lung volume reduction surgery)
- lung volumes 29
  - airway resistance relationship 42, 43
  - bronchiectasis 808
  - changes on immersion in water 1482
  - closing 46–7
  - COPD 654–5
  - cryptogenic fibrosing alveolitis 886
  - dynamic 43
  - increase in divers 1489–90
  - low, airflow rates 829
  - measurement 29, 29
  - reduced, high-pressure pulmonary oedema 769
  - in scoliosis 1217
  - static 58
- lupoid reactions, BCG vaccination 498
- lupus anticoagulant 719, 1392
- lupus pernio 1050
- lupus pneumonitis, SLE 1390–1
- lupus vulgaris 539
- lymph, pulmonary drainage pattern 21, 22
- lymphadenitis, superficial tuberculous 531, 531, 532, 556
- lymphadenopathy
  - hilar enlargement *see* hilar lymphadenopathy
  - primary pulmonary tuberculosis 507
- lymphangiectasia, pulmonary 1141
- lymphangioliomyoma 1138–40, 1139
- lymphangioliomyomatosis 1292
- lymphangioma
  - cavernous (cystic hygroma) 1222, 1223
    - mediastinal 1291–2, 1292
  - cystic 1291, 1292
  - mediastinal 1291–2
- lymphangiomatosis 1291
- pulmonary 1141–2
- lymphangiomyoma, mediastinal 1292
- lymphangitis carcinomatosa 1089, 1146, 1147
- lymphangitis reticularis tuberculosa 513
- lymphatic drainage
  - anatomy 21–2, 1165–6
  - blockage, pulmonary oedema 767
  - chest radiography 145, 145, 146
  - lung 21–2, 766
  - pleura 23, 1152
- lymphatic ducts, anatomy 1165–6
- lymphatic lines *see* Kerley lines
- lymphatic spread, lung cancer 1086
- lymphatic system, sarcoidosis 1049
- lymphatic vessels 21–2
  - dilatation 22
  - valves 21
- lymph nodes
  - cervical 21
  - hilar *see* hilar lymph nodes
  - involvement in tuberculosis 507, 531, 531, 532
  - mediastinal *see* mediastinal nodes
  - mesenteric 536
  - para-aortic 21
  - pulmonary 21, 22
  - rupture in tuberculosis 479
  - sampling, per-bronchoscopic needle aspiration 163
- lymphocytes
  - asthma pathogenesis 912
  - in BAL fluid, COPD 628
  - proliferation in lung 1132
  - sarcoidosis 1042
  - see also* B cells; T cells
- lymphocytic angitis *see* pulmonary lymphocytic angitis
- lymphocytic interstitial pneumonitis, HIV infection 1360
- lymphocytosis, pneumonia 364
- lymphoedema 1162
- 'lymphogranuloma benigna' 1035
- lymphoid interstitial pneumonia 1132, 1133
- lymphokines, in sarcoidosis 1042

- lymphoma  
 chylothorax in 1166–7  
 endobronchial, fibreoptic bronchoscopy 156  
 Hodgkin's *see* Hodgkin's lymphoma  
 mediastinal 1270, 1290  
 superior vena cava obstruction 113, 114  
 thymic 1283  
*see also* non-Hodgkin's lymphoma  
 lymphomatoid granulomatosis 1071  
 lymphopenia, sarcoidosis 1043  
 lymphoproliferative conditions 1132–3  
 lymphosarcoma 1127  
 lysozyme 86  
 lysyloxidase 640
- Macleod's syndrome 832, 1320  
 Macmillan nurses 1534  
 macroglobulinaemia, Waldenström's 1398  
 macroglossia, amyloid 1337  
 macrolides 204–7  
   empyema 454  
   lung abscess 472  
   *Mycoplasma pneumoniae* 395  
   pneumococcal pneumonia 381  
   pneumonia 368  
 macrophage  
   alveolar *see* alveolar macrophage  
   asbestos and 1431  
   *Aspergillus* defence mechanism 587  
   asthma pathogenesis 908–9  
   emphysema pathogenesis 638  
   haemosiderin-laden 1333, 1334  
   *Histoplasma* resistance to killing by 582, 585  
   products secreted 933  
   sarcoidosis 1042–3  
   tuberculosis 479, 481  
 macrophage colony-stimulating factor 16  
 magnesium, as bronchodilator 900  
 magnetic resonance imaging (MRI) 125–7, 126  
   advantages 126–7  
   lung cancer staging 137  
   neurofibroma 1274, 1274, 1275  
   Pancoast tumour 1094  
   sleep apnoea/hyponoxea syndrome 1252  
   tuberculoma 530  
 major basic protein (MBP) 85, 1020  
   low levels 1021–2  
 malaria 607–8  
 Malecot catheters 1198  
 male fertility, cystic fibrosis 862  
 malignant disease *see* cancer  
 Mallory–Weiss tear 1300  
 malnutrition, reactivation of tuberculosis 514  
 MALT tumours 1133  
 maltworkers' lung 1013  
*Mammomonogamus* 608  
*Mammomonogamus laryngeus* 604, 610  
 Manchester comparative reagent (MCR) 737  
 mandatory minute ventilation 705  
 manganese exposure 1449  
 Mantoux technique 491, 492, 492  
 maple bark disease 1002  
 maple bark stripper's lung 1013  
 Marfan's syndrome 96, 1213, 1298  
   pulmonary manifestations 1381–2  
 masks, surgical, tuberculosis transmission prevention 479  
 mass media, smoking cessation and 318  
 mass spectrometry, laser microprobe 1438  
 mast cell granuloma 1131–2  
 mast cells 14  
   airway narrowing 42  
   allergic alveolitis pathogenesis 1007  
   asthma 908, 909–10, 928  
     pathogenesis 916, 917, 933  
   degranulation 909–10  
     allergic alveolitis 1008  
     asthma 926  
   glucocorticosteroid effects 262  
   granules 14  
   histamine release 910, 913  
   mediators 42, 910  
     release 938, 939  
   membrane, stabilization 256, 257  
   nasal, seasonal increases 262  
   sputum 928  
   triggers 916  
   tryptase 916  
   ultrastructure 909, 911  
 maternal mortality 720  
 maxillary sinuses 341  
   in colds 344  
   structure 5  
 maxillary sinusitis 343  
 maximum expiratory flow–volume (MEFV) curve 44  
 maximum voluntary ventilation (MVV), diving and 1483  
 Maxwell box 1188, 1189  
 McLeod's syndrome 677–9  
   chest radiography 677, 678, 678  
 measles  
   atopy reduction 899, 940  
   atypical 415  
   bronchiectasis aetiology 799  
   pneumonia 415  
   vaccine 415  
 measles virus 415  
 meat, allergy 946  
 mechanical ventilation *see* ventilation, mechanical  
 meconium, inspissated fetal 846  
 meconium ileus 846–7  
 media, pulmonary artery 20  
 medial hypertrophy, pulmonary hypertension 758, 759  
 mediastinal abscess 1300, 1301, 1302  
 'mediastinal crunch' 1190  
 mediastinal cysts 1269–72, 1271  
   classification 1271  
   clinical features 1270–1  
   congenital 1293–6  
   developmental 1293–6  
   incidence 1269–70  
 mediastinal displacement 133, 1292  
 mediastinal emphysema *see* pneumomediastinum  
 mediastinal fibrosis 578  
   cryptogenic 1302–4  
     associated disorders 1303  
     causes 1302–3  
     pathology and clinical features 1303  
   radiography 1303  
   drug-induced 1466  
 mediastinal germ-cell tumours 1283–90, 1285  
   benign 1285–7  
     *see also* teratoma  
   histogenesis 1285  
   malignant 1287–90  
     metastases 1288, 1289  
   non-seminomatous 1287–8  
   seminoma 1288–90, 1289  
     treatment and prognosis 1288, 1290  
 mediastinal lymphadenitis, tuberculous 532  
 mediastinal neural tumours 1272, 1272–8  
   autonomic nervous system 1276–8  
   peripheral nerve sheath tumours 1273–6  
   synonyms 1272  
 mediastinal nodes, lung cancer 1089, 1090  
   staging 137  
 mediastinal pain, causes 106  
 mediastinal structures 1269, 1270  
   compression 1271  
 mediastinal tissue, air *see* pneumomediastinum  
 mediastinal tumour-like lesions 1291–3  
 mediastinal tumours 1227, 1269–72, 1271, 1290–3  
   amyloidosis 1291  
   carcinoid 1278  
   classification 1271  
   clinical features 1270–1  
   endocrine/systemic syndromes associated 1271  
   incidence 1269–70  
   leiomyosarcoma 1291  
   lipomas and liposarcoma 1291  
   lymphangioma 1291–2  
   lymphoma 1270, 1290  
   melanoma 1278  
   mesenchymal 1291–3  
   sympathetic 1276  
   types 1269, 1270  
 mediastinitis 1300–4  
   acute 1300–2  
   chronic 578, 1302  
   fibrosing (sclerosing) *see* mediastinal fibrosis  
   necrotizing 1302  
   tuberculous 1300, 1302  
 mediastinoscopy  
   lung cancer 1094–5  
   tuberculosis diagnosis 520  
 mediastinum 1269–304  
   anatomy 1269  
   assessment in lung cancer 1094  
   compartments and contents 1269, 1270  
   'danger space' infection 1300  
   deviation 114  
   hydrocele (pleuropericardial cysts) 1295–6, 1296  
   idiopathic fibrosis *see* mediastinal fibrosis  
   infections 1300  
   lesions 1269, 1270  
   masses 1269, 1279  
     chest radiography 135  
     *see also* thymus gland  
   opacities 1273  
   parathyroid adenoma 1298  
   'medical-alert' 272  
 medical reports, expert 1539–40  
 Medical Research Council (MRC)  
   domiciliary oxygen therapy trial, COPD 668–9, 669  
   questionnaire 75  
   tuberculosis vaccine trial 483, 483, 484  
 medicolegal aspects 1536–41  
   civil litigation 1536, 1538–9  
   compensation 1536–9  
   court appearances 1540–1  
   doctors as experts 1539–41

- lawyers and fee systems 1536, 1538  
 litigation trends 1541  
 no-fault benefits 1536–8  
 occupational asthma 949  
 Mediterranean spotted fever 421  
 medroxyprogesterone acetate 280–1  
 obstructive sleep apnoea 281  
 oral administration 281  
 medulla oblongata  
   breathing control 50  
   cough reflex 84  
   dorsal and ventral respiratory cell groups 50  
 megaloblastic anaemia, co-trimoxazole causing 210  
 Meigs' syndrome 1157, 1161  
 melanocytes 1278  
 melanoma, malignant  
   bronchial 1136  
   mediastinal 1278  
 melioidosis 423–4  
 melphalan 1338  
 membrane phospholipid derivatives 778  
 Menghini technique 176  
 meningitis  
   cryptococcal 230, 231, 529  
   pneumococcal pneumonia and 381  
   tuberculous 483, 512, 528–9  
     differential diagnosis 529  
     mortality 557  
     pathology 528–9  
     treatment 530, 557, 560  
 meningocoele, intrathoracic 1273–4  
 meningococcal pneumonia 419–20  
 menstruation, recurrent pneumothorax and 1186  
 mercury fumes 1448  
 meropenem 204, 453  
 mesenchymal tumours, mediastinal 1291–3  
 mesenchyme 1, 1318  
 mesenteric lymph nodes, tuberculosis 536  
 mesna 284  
 mesothelial cells 23  
 mesothelial cysts 1240  
 mesothelioma  
   benign (pleural fibroma) 1143, 1172, 1173  
   malignant 1173–8, 1424  
     aetiology 1173–8  
     asbestos association 80, 1173–4  
     clinical features and diagnosis 1175  
     endemic areas 1174  
     hydropneumothorax 1157  
     management 1176–8  
     metastases 1175, 1240  
     mortality 1174, 1175, 1178  
     mortality by occupation 1425, 1426  
     pathogenesis 1432  
     pathology 1176, 1177  
     pleural exudates 1157–8  
     radiography 1176  
   risk with pleural plaques 1169  
 metabolic acidosis 38  
   COPD 657  
   hyperventilation 1266  
   respiratory distress syndrome 713  
 metabolic alkalosis 38, 699  
   respiratory compensation 38  
 metachronism 12  
 metal fume fever 1448  
 metal fumes 1448–9  
 metals, occupational asthma 951  
 metaproterenol *see* orciprenaline  
 metastases  
   chest radiography 121  
   diaphragmatic 1240  
   endobronchial 156, 1146  
   *see also* intracranial metastases; liver; lung metastases  
 metered-dose inhalers (MDIs) 279  
    $\beta_2$ -agonists 245, 246–7  
   dosages 249  
   breath-actuated 989  
   corticosteroids 273, 274–5  
   ipratropium bromide and oxitropium 250–1  
   method of use 988–9  
   pressurized 988–9  
   sodium cromoglycate 257  
 methacholine 250  
 methacholine challenge test 50, 932–3, 999  
 methadone linctus 1529  
 methaemoglobinaemia 110  
 methane, as asphyxiant 1444  
 methicillin 198–9  
   administration and dosage 198, 199  
   metabolism 198  
 methicillin-resistant *Staphylococcus aureus* (MRSA) 198  
   antibiotics for 203, 212, 226  
   rifampicin 224  
   vancomycin 219  
   in cystic fibrosis 854  
 methotrexate 293, 1465  
 methyl alcohol, poisoning 1266  
 methylprednisolone 264  
   acute eosinophilic pneumonia 1031  
   acute severe asthma 988  
   structure 264  
 methylxanthines 252  
   COPD 665, 675  
   *see also* theophylline  
 methyprednisolone  
   high-dose 266  
   parenteral 265–6  
   pulse treatment 266  
 methysergide 1161  
   mediastinal fibrosis association 1303  
   pleural fibrosis due to 1171, 1466  
 metronidazole  
   amoebiasis 606  
   anaerobic infections 217–18  
   aspiration pneumonia 414  
   empyema 453  
   lung abscess 471–2  
 mezlocillin 199  
 mica 1434  
 microaspiration, pneumonia pathogenesis 359  
 microbial genetics 98–9  
 microfilaria 1024  
 microimmunofluorescence (MIF) 398, 399  
*Micropolyspora faeni* (*Faenia rectivirgula*) 1011  
 microtubules 11  
   in ciliary dyskinesia 795  
 microvascular injury, acute 771, 773  
 microvilli 11, 12, 13  
 midazolam 152, 706  
 middle lobe syndrome 799, 801  
 midline granuloma (nasal T-cell lymphoma) 1070–1  
 military personnel  
   adenovirus pneumonia 416  
   chickenpox pneumonia 416  
   measles virus pneumonia 415  
 meningococcal pneumonia 419, 420  
 pneumonia 392  
*Pseudomonas pseudomallei* pneumonia 423  
 milk, unpasteurized, brucellosis 420  
 mill fever 1444  
 milrinone, new cystic fibrosis treatment and 865  
 mineral dusts 831, 1408  
   bronchiolitis 831, 832  
 mineral oil  
   aspiration 1465, 1467  
   lipoid pneumonia 428  
 mineral pneumoconioses *see* pneumoconioses  
 minerals 1433  
 minimally invasive diagnostic procedures 148–92  
   *see also* biopsy; bronchoscopy  
 mining  
   asbestos 1424, 1426  
   coal 1408–9  
   haematite 1435, 1449  
   lung cancer and 1079  
   miscellaneous minerals 1433–5  
   silica 1416  
   tin 1440  
 minocycline, adverse effects 211, 212  
 minute ventilation 26, 54  
   ventilators 705  
 'Mississippi mud' 219, 220  
 mithramycin 1111  
 mitomycin 290  
   alveolitis due to 1464  
 mitral regurgitation 759  
 mitral stenosis 47, 759  
 mitral valve disease 759  
   chest radiography 759, 760  
 mixed connective tissue disease 288, 1396  
 Monge's disease 751  
 monobactams 203–4  
 monoclonal antibodies  
   CMV detection 1349  
   myeloma 1130  
 monocytes 16  
   asthma pathogenesis 908–9  
   chemotactic factors 917  
   cryptogenic fibrosing alveolitis 878, 879  
 mononeuritis multiplex 1029  
 montelukast 259  
 Montreal Protocol 279  
 mood abnormalities, corticosteroid-induced 271  
 'moon face' 268  
*Moraxella catarrhalis*  
   antibiotic resistance 196, 412  
   antibiotic susceptibility 204, 206, 207, 212  
   bronchiectasis and 809  
   COPD 674–5  
   laryngitis 341  
   pneumonia 411–12  
 Morgagni, foramen 1243  
 Morgagni hernia 1243, 1245, 1300  
 morphine  
   administration route 1527  
   cough relief in terminal care 1529  
   dose equivalence of other opioids 1528  
   dose titration 1526–7, 1527  
   fiberoptic bronchoscopy 152  
   for intractable pain 1528  
   modified-release 1526  
   nebulized 1530

- morphine (*Continued*)  
 oral 1526  
 pain relief in terminal care 1526  
 morphine sulphate 1526  
 mortality  
 maternal 720  
 pneumonia 356  
 postoperative, pulmonary embolism causing 719  
 standardization of studies 65–6  
 mortality rates 66–7  
 crude 66  
 proportionate 66–7  
 standardized 67  
 Mortimer's malady 1035  
 motoneurons 49  
 motor/sensory loss, bone and joint tuberculosis 533  
 Mounier-Kuhn syndrome (tracheobronchomegaly) 797, 1310–11  
 mouth pressures, inspiratory/expiratory  
 COPD 644–5  
 measurement 646  
 mucins 14  
 in cystic fibrosis 853  
 secretion by goblet cells 12  
 mucociliary clearance 14  
 assessment 84–5  
 factors reducing 85  
 impairment  
 bronchiectasis aetiology 794–8  
 clinical features and diagnosis 796  
 Sjögren's syndrome 1395  
 mechanism *see* mucociliary escalator  
 particles 1407–8  
 mucociliary escalator 53–4, 83, 84, 84–5, 341, 1407  
 mucoepidermoid tumours 1136  
 mucolytics, bronchiectasis 819–20  
*Mucor* 598  
 mucormycosis 598  
 mucosa, airways 11–13  
 mucosal inflammation, asthma 926  
 mucosal oedema, asthma 918, 928  
 mucous glands 2, 13  
 hypertrophy in chronic bronchitis 628  
 mucous membrane, paranasal sinuses 341  
 mucoviscidosis 839  
*see also* cystic fibrosis  
 mucus 14, 53, 84, 85  
 asthma 907, 925–6, 929  
 control and mediators in 85  
 cystic fibrosis 85, 845, 853  
 functions 14, 85  
 glycoproteins 14  
 hypersecretion 617, 907  
 COPD 619–20, 628  
 secretion, histamine role 913  
 sol and gel layers 14  
 tracheal velocity 53  
 viscosity and elasticity 14  
 mullite 1435  
 multidisciplinary team, terminal care 1534  
 multidrug resistance, tuberculosis 497, 556, 559, 559  
 'multifocal fibrosclerosis' 1303  
 multiple inert gas technique, ventilation-perfusion ( $V_A/Q$ ) 643  
 multiple myeloma *see* myeloma  
 multiple organ failure, ARDS and 773, 774, 775  
 Munchausen's syndrome 461  
 muscarinic antagonists *see* anticholinergic bronchodilators  
 muscarinic receptors 250  
 muscle  
 disease  
 bilateral diaphragmatic paralysis 1237  
 respiratory failure 1229, 1230  
 fibres, diaphragm 1235  
 tumours 1142–3  
 weakness, respiratory muscles 48–9  
 'muscular cirrhosis of lung' 880  
 muscular dystrophies 98, 1230  
 musculoskeletal disorders, corticosteroid-induced 269–70  
 musculoskeletal system, sarcoidosis 1052  
 mushroom worker's lung 1012–13  
 mutagens 98  
 mutations 98  
 cystic fibrosis gene *see* cystic fibrosis  
 myasthenia gravis 1280–2  
 respiratory failure 710–11  
 streptomycin contraindication 549  
 thymic disease and 1280–2  
 vital capacity (VC) 49  
 myasthenia syndrome, D-penicillamine causing 1229  
 myasthenic crisis 710  
 mycelium 574  
 mycetoma 591–2, 592  
 imaging 138–9  
 intracavitary 145  
 management 592, 592  
*see also* aspergilloma  
 myc genes, lung cancer 1085  
 mycobacteria 476–7, 565  
 atypical 565  
 antibiotic susceptibility testing 567  
 disease *see* mycobacterial disease  
 fast and slow growers 566, 567  
 fiberoptic bronchoscopy 165–6  
 isolation/culture 567  
 non-specific tuberculin reaction 492  
 pleural effusions 1160  
 Runyan classification 566, 567  
 staining 165, 567  
*see also* individual mycobacteria  
 mycobacterial disease,  
 atypical/opportunistic 565–72  
 antibiotic treatment 223–5  
 bacteriology 566–7  
 species causing 565, 566  
 clinical manifestations 568  
 cystic fibrosis 855  
 diagnostic criteria 567–8  
 distribution and extent 565–6  
 epidemiology 565–6  
 management 568–71  
 radiology 568  
 sources of infection 566  
 tuberculosis *vs* 522  
 mycobacterial infections  
 bronchiectasis aetiology 799  
 fiberoptic bronchoscopy 150, 165–6  
*Mycobacterium africanum* 476  
*Mycobacterium avium* 565  
*Mycobacterium avium-intracellulare* complex (MAC) 565, 566  
 antibiotic susceptibility 206, 207, 224–5  
 bronchiectasis aetiology 799  
 cystic fibrosis 855  
 disseminated disease 570  
 drug resistance 567, 568  
 duodenal infection 537  
 fiberoptic bronchoscopy 165–6  
 in HIV infection 1356, 1357  
 non-specific tuberculin reaction 492  
 prophylaxis 1361  
 pulmonary disease 568–70  
 treatment 569–70  
 in silicosis 1422  
*Mycobacterium bovis* 476, 494  
*Mycobacterium chelonae* 568  
*Mycobacterium chelonae*  
 bronchiectasis aetiology 799  
 cystic fibrosis 855  
*Mycobacterium fortuitum*  
 bronchiectasis aetiology 799  
 cystic fibrosis 855  
 treatment of infection 571  
*Mycobacterium haemophilum* 567  
*Mycobacterium intracellulare* 565  
*Mycobacterium kansasii* 565, 566, 567, 568, 1422  
 drug resistance 570  
 treatment of infection 570  
*Mycobacterium mageritense* 566, 567  
 treatment of infection 570  
*Mycobacterium scrofulaceum* 565  
*Mycobacterium tuberculosis* 98, 476–7, 544  
 antibiotic resistance 99  
 culture 476, 519  
 in cystic fibrosis 855  
 DNA fingerprinting 495  
 drug resistant mutants 544, 559  
*see also* tuberculosis (TB), drug resistance  
 identification tests 476  
 populations 546  
 rapidly growing 546  
 sarcoidosis aetiology and 1039–40  
 size importance to transmission 477  
 slowly growing 544, 546  
*see also* tuberculosis  
*Mycobacterium xenopi* 566, 567, 570  
*Mycoplasma* 392  
 cryptogenic fibrosing alveolitis aetiology 878  
 culturing and identification 394–5  
 subgroups 392  
*Mycoplasma hominis* 392  
*Mycoplasma pneumonia* 392–6  
 chest radiography 393, 394  
 clinical manifestations 393  
 cold agglutinins 364, 394, 396  
 complications 395–6  
 epidemiology 392–3  
 gene probes 395  
 incidence 392  
 incubation period 393  
 investigations 364, 393–5  
 pathology 393  
 serological tests 394  
 spread and epidemics 392–3  
 treatment 395  
*Mycoplasma pneumoniae* 392  
 mycotoxicosis 1002, 1003, 1012  
 neutrophil leucocytosis 1008  
 pathology 1005  
 myelin 19  
 myeloma 1129, 1129–30  
 ribs 121, 1226  
 myelosuppression *see* bone marrow suppression  
 myocardial infarction  
 fiberoptic bronchoscopy  
 contraindication 169

- low-dose heparin effect 741  
 risk in sleep apnoea/hypopnoea syndrome 1255  
 smoking and 312, 313  
 myocardium, high altitude effect 57  
 myoepithelial cells 13  
 myofibroblasts 633, 927  
 myopathy, steroid 270  
 myosin, actin interaction 938  
 myosine ATPase 938, 939  
 myosin light chain kinase 938–9  
 myringitis, bullous 393  
 myxoedema 712, 1157  
 myxoma, left atrial 760
- NADPH oxidase 97  
*Naegleria gruberi* 1013  
 nafcillin 198–9  
 naloxone hydrochloride 152  
 narcolepsy 1255–6  
 nasal biopsy, asthma 926  
 nasal decongestants 338, 344  
 nasal masks *see* ventilation, mechanical  
 nasal mucous membranes, tuberculosis 540  
 nasal obstruction, common cold 337  
 nasal polyps 343, 848, 855  
 nasal potential difference, cystic fibrosis diagnosis 849  
 nasal septal perforation 1050  
 nasal sinuses *see* paranasal sinuses  
 nasal T-cell lymphoma (midline granuloma) 1070–1  
 nasal ulcers, nasal mask complication 1505  
 nasopharyngeal flora 376, 377  
 nasopharyngitis *see* common cold  
 National Tuberculosis Association 478  
 natural killer (NK) cells, HIV infection 1352  
 nausea and vomiting  
   cytotoxic drugs causing 284, 288, 291, 292  
   management in terminal care 1531–2  
   side-effect of narcotic analgesics 1529  
 NBT-PABA, urinary test for cystic fibrosis 849  
 Nd:YAG laser, lung volume reduction surgery 679  
 near-drowning 788–9, 1487, 1488  
 nebulizers 279, 990  
   home therapy, COPD 666, 675  
   jet 987, 990  
   ultrasonic 990  
*Necator americanus* 608  
 necrotizing sarcoid granulomatosis 1072, 1072, 1073  
 nedocromil sodium 257, 257–8  
   asthma treatment 979  
   modes of use 258  
   sodium cromoglicate comparison 258  
 needlestick injury 170, 236  
*Neisseria meningitidis*, pneumonia 419–20  
 nelfinavir 239  
 nematodes 605, 608–10  
 neomycin 212  
 neonates  
   BCG vaccination 498  
   Bochdalek hernia 1243  
   bronchopulmonary dysplasia 1477  
   chronic lung disease 1477  
   cystic fibrosis screening 848, 1476  
   prolonged jaundice 847  
   pulmonary hypertension 1319
- respiratory distress syndrome 712–14  
   *see also* respiratory distress syndrome  
 nephritis, tuberculous interstitial 538  
 nephrotoxicity  
   aminoglycosides 213–14, 214  
   amphotericin 229  
   cephalosporins 200  
   cidofovir 242  
   cisplatin 292  
   cyclosporin 287, 288  
   foscarnet 241  
   pentamidine 221–2  
   vancomycin 220  
 nerve blocks 1529  
 nerve supply  
   lung 22–3  
   pleura 23, 1152  
 nervous system 22–3  
   sarcoidosis 1051–2  
   Wegener's granulomatosis 1069  
   *see also* autonomic nervous system  
 Netherlands, tuberculosis trends 489  
 netilmicin 213, 216  
 Neufeld's capsular precipitin (Quellung reaction) 361, 380  
 neural crest cells 1272  
 neuralgic amyotrophy 1236  
 neural mechanisms, asthma 937–8  
 neural tumours 1143  
   mediastinal *see* mediastinal neural tumours  
 neuraminidase 347  
 neurenteric cysts 1293  
 neurilemmoma 1143  
 neuroblastoma 1276–7  
 neurocytes 1272  
 neuroectodermal tumours 1223  
 neuroepithelial bodies 13  
 neurofibroma 1143  
   chest wall 1222, 1224  
   magnetic resonance imaging 1274, 1274, 1275  
   mediastinal 1273–4, 1274, 1275  
   clinical features 1273–4  
   pathology 1273  
 neurofibromatosis  
   genes 1381  
   pulmonary manifestations 1380–1  
   type 1 *see* von Recklinghausen's syndrome  
   type 2 1381  
 neurofibrosarcoma 1274  
 neurogenic pulmonary oedema 709–10, 787–8  
 neurogenic sarcoma 1274  
 neurogenic theory, on clubbing and HPOA 112  
 neurokinin A, bronchoconstriction 938  
 neurological disorders  
   hyperventilation 1266  
   respiratory failure 709, 1229  
 neurological syndromes/signs  
   bone and joint tuberculosis 533  
   CNS tuberculosis 529  
   oxygen toxicity 1486  
   paraneoplastic 1112–13  
 neuroma, intercostal 135, 135  
 neuromuscular control, upper airway 1251–2  
 neuromuscular disease  
   affecting respiration 1228–30  
   lung involvement 1399  
   type II respiratory failure 699
- neuromuscular disorders, inherited 98  
 neuromuscular junction, in paraneoplastic syndrome 1113  
 neuromuscular syndromes, non-metastatic, in lung cancer 1112–13  
 neuropeptides, mucus secretion control 85  
 neuroradiological scanning, CNS tuberculosis 530  
 neurosarcoma 1143, 1274  
 neurotoxicity  
   amphotericin 229  
   cisplatin 292  
   vinca alkaloids causing 291  
 neurotransmitters 23  
 neutropenia  
   ARDS in 776  
   ganciclovir causing 241  
   infections in 1346, 1347  
   taxanes causing 294  
   zidovudine causing 237  
 neutrophil(s) 776  
   activation 882  
   adhesion 774, 917, 917  
   inhibition in ARDS therapy 786  
   adult respiratory distress syndrome 776–81  
   in airspaces of smokers 637  
   allergic alveolitis pathogenesis 1008  
   apoptosis 782, 786  
   in ARDS 774  
   asthma pathogenesis 912, 931  
   process 916–17  
   in BAL fluid, COPD 628  
   bronchiectasis pathogenesis 801  
   in capillary 777  
   chemotactic factors 637, 912, 917, 931, 935  
   cryptogenic fibrosing alveolitis pathogenesis 882  
   emigration 637, 917, 917  
   endothelial interactions 777, 778–9  
   abnormal in ARDS pathogenesis 778–80  
   restricted intercellular microenvironment 778–9, 779  
   surface adhesive molecules 779  
   granules 781  
   half-life 90  
   increased by glucocorticosteroids 262  
   priming 780, 780–1  
   products secreted 777, 781, 781, 917  
   in pulmonary capillaries 90  
   pulmonary margined pool 90  
   recruitment 916–17  
   reduced deformability 779–80  
   sequestration in capillaries 629, 785–6  
   'suicide programme' 782  
   triggering and product secretion 780–1  
   tuberculosis 479  
   Wegener's granulomatosis 1064, 1064  
 neutrophil elastase 776  
   antielastase imbalance by smoking 636, 637  
    $\alpha_1$ -antitrypsin affinity/inhibition 635, 636  
   bronchiectasis pathogenesis 801  
   cystic fibrosis 854  
   emphysema pathogenesis 637  
   fibrinogen cleavage 640  
   inhibition by antileucoprotease 639  
   inhibitors 865  
 neutrophil protease, in cryptogenic fibrosing alveolitis 882

- nevirapine 239
- newborn *see* neonates
- nexin links 11, 12
- nicotine
  - addictive nature 662
  - chemotactic action 637
  - effect on weight 319
  - inhaled/nasal spray 318
  - reduction in level in cigarettes 663
  - transdermal 315, 318, 663
- nicotine chewing gum 315, 316, 317–18, 663
- nicotine skin patches 315, 318, 663
- Niemann–Pick cells 96
- Niemann–Pick disease 96, 1384
- nifedipine, primary pulmonary hypertension 756
- night sweats, tuberculosis 516
- NIH score, cystic fibrosis 851
- nikethamide 280
- nitric oxide (NO) 750
  - actions and mechanism of action 89, 750
  - formation 330
  - inhaled
    - ARDS treatment 784
    - primary pulmonary hypertension 756
  - role in COPD 647
  - secretion
    - by ciliated epithelial cells 12
    - by endothelial cells 16
    - inhibition in hypoxia 750
  - smoking effect 313
- nitric oxide synthetase 16
- nitrofurantoin, alveolitis due to 1462
- nitrogen
  - anatomical dead space measurement 27, 27
  - partial pressure, closed pneumothorax and 1195, 1196
- nitrogen dioxide 1447–8
  - air pollution, COPD 622
  - asthma trigger 947
  - health effects and mechanisms 330
  - obliterative bronchiolitis due to 832
  - ozone formation 327
  - as pollutant 327, 1447
  - toxic exposures 1447
- nitrogen oxides 313, 1447–8
  - as air pollutants 327, 898, 1447
  - health effects and mechanisms 330, 1447
- nitroimidazole 217
- Nocardia* 573
  - empyema 448
  - pleural effusions 1160
- Nocardia asteroides* 576
- nocardiosis 576–7
- nocturia 1253
- nocturnal oxygen therapy trial (NOTT) 668–9, 669
- non-adrenergic non-cholinergic (peptidergic) system 23
  - asthma 938
- non-Hodgkin's lymphoma 1127–9, 1128
  - in HIV infection 1358, 1360
  - mediastinal involvement 1290
  - see also* lymphoma
- non-invasive positive pressure ventilation (NIPPV)
  - aims 702–3
  - modes 703
  - resources for 703–4
  - respiratory failure 702–4
  - type II 702–3
- selection criteria 703
- weaning 708
- non-steroidal anti-inflammatory drugs (NSAIDs)
  - adverse effects 270
  - bronchoconstriction due to 1459, 1459
  - cystic fibrosis 866
  - tolerance induction 1467
- non-steroidal prophylactic drugs, asthma 256–9
- Nordenstrom biopsy needle 173, 174
- Northern score, cystic fibrosis 852, 853
- Norway, smoking cessation 314
- nose
  - anatomy 342
  - functions 5, 83
  - mucous membranes 4
  - structure 4–5
  - see also* entries beginning nasal
- nose drops, lipoid pneumonia after 428
- nosocomial infections *see* hospital-acquired infections
- notification rates, tuberculosis (TB) 485–8, 486, 487, 488
- nucleoside analogues *see* reverse transcriptase inhibitors
- nutrition
  - asthma and 899–900, 904
  - chylothorax management 1166–7
  - COPD risk and 624–5
  - cystic fibrosis 858, 861
  - intrauterine 1477–8
  - mechanical ventilation and 707
- nutritional supplementation, COPD 646, 707
  - rehabilitation 673–4
- nystatin, terminal care 1532
- oat-cell carcinoma *see* small-cell lung cancer
- obesity
  - breath sounds 115
  - contraindication to lung transplantation 1519
  - COPD 674
  - sleep apnoea/hypopnoea syndrome 1254
  - upper airway narrowing 1251
- obliterative bronchiolitis 832–6
  - aetiology 832–3
  - chest radiography 833–5, 834
  - chronic, *Mycoplasma* pneumonia 396
  - classification 830, 830
  - clinical course and management 835–6
  - constrictive 835, 835
  - drug-induced 1460
  - idiopathic 832, 835–6
  - lung transplantation complication 676–7, 858, 1521
  - pathology 835, 835
  - presenting features 833–5
  - progressive 836
  - proliferative 830, 835
  - rheumatoid disease 1388–9
  - subtypes 830, 835
- observation, of patient 102, 109
- obstructive lung disease 44
  - see also* airflow obstruction
- obstructive sleep apnoea *see* sleep apnoea/hypopnoea syndromes (SAHS)
- occupation
  - interstitial lung disease 889
- lung cancer causes 1079, 1079
- neoplasms due to 1404, 1449
- reactivation of tuberculosis 514–15
- risk factors, COPD 623–4
- see also* workplace
- occupational allergens 897–8
- occupational asthma 897–8, 949–51, 1404
  - causes 949–51, 998
  - epidemiology 1000
  - incidence, studies 74
  - peak flow rates 962
  - see also* reactive airways dysfunction syndrome
- occupational hazards 1405, 1405
- occupational infections, HIV 236–7
- occupational lung diseases 1404–57
  - allergic alveolitis 1008, 1009, 1011–14
  - allergic bronchopulmonary aspergillosis 588
  - anthrax 425–6
  - bronchitis 1441
  - brucellosis 420
  - Chlamydia psittaci* pneumonia 396–7
  - compensation 1536–9, 1537
  - dust exposure, COPD 623, 652
  - expert medical report compilation 1539–40
  - historical aspects 1404
  - humidifier fever 1443–4
  - malignant mesothelioma 1173–4
  - management 1449–50
  - mineral dusts causing bronchiolitis 831, 832
  - organic dust diseases 1441–4
  - particle deposition/clearance 1406–8, 1407
  - pneumonic plague 425
  - prescribed (UK) 1537
  - Q fever 401
  - regulations and 1432, 1433, 1450
  - systemic sclerosis and 1393
  - toxic gases *see* irritant gases; toxic gases
  - types and frequencies 1404–6
  - see also* pneumoconioses; *specific diseases*
- occupational medicine 1404
- occupational posture, effect on lung abscess 465
- ocular effects, corticosteroids 270–1
- ocular manifestations, tuberculosis 540
- oedema 766
  - ankle 1253
  - cerebral 530, 788, 1532
  - COPD 648–9, 650, 653
  - deep venous thrombosis 723
  - laryngeal 709
  - lung re-expansion 789
  - mucosal, asthma 918, 928
  - pulmonary *see* pulmonary oedema
  - in respiratory distress syndrome 713
  - retinal 540
- oesophageal reflux 104
- oesophagitis, terminal care 1532
- oesophagus
  - carcinoma 312, 1205
  - compression 1271, 1312
  - terminal care 1532
- cysts 1293
- pain 106
- perforation 1300
- rupture 1187
- stricture, pneumomediastinum after dilatation 1205
- tears 1206



- tuberculosis 537
- oestrogen therapy 720
- ofloxacin 225, 227
  - tuberculosis 551, 551
- oil
  - inhalation 1465, 1467
  - iodinated 428
  - lipoid pneumonia due to 428
- oilseed rape, allergen 944
- oil-shale miners 1434
  - see also* shale industry
- Old Tuberculin test *see* Heaf test
- oligohydramnios 3–4
- olive oil 428
- omega-3 fatty acids, asthma and 900
- oncogenes 98, 1085
- oncotic pressure 1152
  - reduced 767, 1155
- Ondine's curse 1230
- onion-skin bodies 1339
- Operation Everest II 56, 57
- opiates/opioids
  - constipation due to 1529, 1531
  - cough reflex inhibition 84
  - dyspnoea management in terminal care 1530
  - for mechanical ventilation 706
  - pain relief in terminal care 1525
  - pulmonary oedema due to 1465
  - respiratory failure due to 709
  - side-effects 1529
  - weak and strong 1526
- opportunistic infections
  - after lung transplantation 1520
  - azathioprine and 286
  - fungal 598
  - HIV infection *see* HIV infection
  - in immunosuppressed 1346, 1347
  - mycobacterial *see* mycobacterial disease
  - pneumonia 409–10
  - pulmonary alveolar proteinosis 1334
  - see also* immunosuppressed patients; *specific infections*
- opsonization 54
- oral contraception 212
  - antibiotic antagonistic effect 863
  - in cystic fibrosis 863
  - pulmonary thromboembolism 1465
  - rifampicin effect 548
  - thrombosis and 720
- orciprenaline 244, 245
  - doses and half-life 247
- organic dust diseases 1002, 1003, 1441–4
- organophosphorus compounds 1012, 1229
  - poisoning 709
- ornithosis 396–8
  - see also* *Chlamydia psittaci* pneumonia
- oropharyngeal candidiasis 981
- oropharyngeal contents, aspiration *see* aspiration
- oropharyngeal flora
  - alterations 361
  - anaerobes 412
  - aspiration 460–1, 461, 465
  - Gram-negative bacilli 461
  - in hospital patients and elderly 359
- orthopnoea, type II respiratory failure 699
- Osler–Weber–Rendu disease 97–8, 1140, 1322–6
- osmium tetroxide 1449
- osmotic pressure
  - colloid 30
  - pleural 1152
- pulmonary oedema 766
- osteoarthritis, hypertrophic pulmonary
  - see* hypertrophic pulmonary osteoarthritis (HPOA)
- osteochondroma 1224
- osteoclastoma 1225
- osteogenic sarcoma 1226
- osteoid osteoma 1225
- osteomeatal complex 341, 345
- osteomyelitis 345
  - chest wall 1226–7
  - mediastinal 1300
- osteonecrosis 269
- osteoporosis
  - contraindication to lung transplantation 1519
  - corticosteroid-induced 269–70, 983
- ostium primum defect 761
- ostium secundum defect 760
- otalgia 540
- otitis media
  - common cold complication 338
  - pertussis complication 352
  - tuberculous 540
- otorhinolaryngological surgery, sleep apnoea treatment 1260
- ototoxicity
  - aminoglycosides 214, 864
  - streptomycin 549
  - teicoplanin 220
  - vancomycin 220
- overinflation of chest *see* chest, overinflation
- oxacillin 198–9, 199
- oxalic acid 593
- oximetry, sleep apnoea/hypopnoea syndrome 1257
- oxitropium bromide 250–2
  - administration/dosage 250–1
  - COPD 665
- oxygen
  - abnormal uptake in sarcoidosis 1053
  - alveolar–arterial  $P_{O_2}$  difference 28
  - arterial partial pressure 28, 35
    - acute severe asthma 986
    - asthma 956, 957
    - lowest for life 698
    - respiratory failure 696, 699
    - type II respiratory failure 701
  - arterial saturation, pneumonia 364
  - bound, transport 35
  - consumption by heart at high altitude 57
  - cost of breathing 48
  - delivery to tissues, factors affecting 707
  - diffusing capacity 34, 35
  - diffusion 34
  - dissolved 35
  - fibreoptic bronchoscopy 152
  - forced inspiratory 707
  - free radicals *see* reactive oxygen intermediates
  - haemoglobin affinity 36
  - haemoglobin saturation 35
  - nocturnal saturation, almitrine bimesylate effects 283
  - partial pressure 26, 28, 28–9
    - altitude effect 56
    - alveolar 28
    - breath-hold diving 1482
    - closed pneumothorax and 1195, 1196
    - control during mechanical ventilation 1500
    - high-altitude 55
- hypersensitivity pneumonitis 1003
- transcutaneous monitoring 38
- reserves in blood 37
- saturation ( $Sa_{O_2}$ ), measurement 38
- singlet 1467
- toxicity 707, 1467
  - in diving 1486–7
  - management 1468
  - mechanisms 1467, 1468, 1487
  - in paraquat poisoning 1469
  - symptoms 1486, 1487
  - ventilator lung 1467–8, 1468
- transport in blood 35–8
- oxygen concentrators 671
- oxygen therapy
  - acute COPD 675, 701–2
  - acute-on-chronic COPD 701–2
  - asthma 986
    - acute severe 986
  - carbon dioxide retention 700
  - costs 672
  - cystic fibrosis 856
  - delivery systems 671–2
    - masks 672, 986
    - nasal prongs 672, 701, 986
  - domiciliary
    - COPD 627, 668–72
    - criteria 670–1
    - scoliosis 1218
  - gas cylinders 671
  - high-altitude pulmonary oedema 788
  - high-flow rates 769–70
    - Pneumocystis carinii* pneumonia 1369
  - high-pressure pulmonary oedema 769–70
  - hypercapnia increased by 700
  - long-term 671
    - COPD 668, 670
    - prescribing criteria 670
  - mechanical ventilation and 706
  - pneumomediastinum 1206
  - pneumonia 373
  - pneumothorax 1195
  - portable 670, 671
  - respiratory distress syndrome 713
  - respiratory failure 699–700
  - short-burst 670
  - in terminal care 1530
  - transtracheal 672
  - travel and 671
  - type I respiratory failure 697, 700
  - Venturi mask 701
- oxyhaemoglobin dissociation curve 35, 35
  - factors affecting 35–7
  - high altitude 56
  - high  $V_A/Q$  ratios and 32
  - left-shift 36
  - respiratory failure definition 696
  - right-shift 35–6, 36, 56
- ozone 1448
  - asthma trigger 947
  - COPD 622
  - distribution 328, 328
  - formation 327–8
  - health effects and mechanisms 331
  - as pollutant 327–8, 622, 1448
  - regeneration 327
- ozone layer 325
- p53 gene, mutations 98
- paclitaxel 294
- pain
  - gate control theory 1529

- pain (*Continued*)  
mediastinal 106  
morphine resistance 1528  
neurogenic 1528  
nociceptive 1528  
paradoxical 1528  
perception 1525  
referred to shoulder 107, 1153  
rib 107  
terminal disease 1525  
thoracic 1529  
*see also* chest pain; pleural pain
- pain relief  
cancer 1525, 1525–9  
pleural pain 1153  
side-effects of narcotics 1529  
terminal care 1525, 1525–9  
bony pain 1528  
intractable pain 1528–9  
*see also* morphine  
three-rung ladder 1525–8
- pains, air pollution due to 332
- palpation, chest 114
- palygorskite 1435
- panbronchiolitis, diffuse 831–2
- Pancoast's syndrome 580, 1114–15
- Pancoast's tumour 1089, 1092, 1114–15  
treatment 1114–15
- pancreas  
function tests 849–50  
ion transport 845  
tuberculosis 537
- pancreatic enzyme supplements 858–9
- pancreatic extracts, allergic alveolitis due to 1016
- pancreatic insufficiency 843, 847  
cystic fibrosis 858–9
- pancreatitis  
acute 1398  
adult respiratory distress syndrome after 773  
cystic fibrosis complication 859  
pleural effusions 1161  
sarcoidosis 1051
- pancreolauryl test, cystic fibrosis 849
- panic attacks 1265
- papilloma, bronchial 1136
- paprika, *Mucor* spores and lung disease 1014
- para-aminosalicylic acid 550, 550
- para-aortic nodes 21
- paracetamol, pain relief in terminal care 1525
- Paracoccidioides brasiliensis* 581–2
- paracoccidioidomycosis 581–2
- paraffin granuloma (paraffinoma) 428, 1467
- paraganglioma 1143, 1277–8  
aorticopulmonary 1277  
aorticosympathetic 1277  
mediastinal 1272, 1277–8  
sites 1277
- paragonimiasis, lung abscess *vs* 470
- Paragonimus westermani* 611, 1022  
empyema 449, 454
- parainfluenza viruses  
common cold 335  
pneumonia 418
- paramyxoviruses, common cold 335
- paranasal sinuses  
adenocarcinoma 5  
anatomy 5–6, 341, 342  
aspiration 344  
calcification 344
- development 341  
functions 5  
inflammation *see* sinusitis  
mucous membrane 341  
radiography 343  
Wegener's granulomatosis 1067
- paraneoplastic syndromes 1110–13
- paraplegia, bone and joint tuberculosis 533, 535
- parapneumonic effusions 452–3
- paraproteinaemia 1132
- paraquat poisoning 1468–9
- parasitic diseases of lung 604–15, 605  
arthropods 614  
nematodes 608–10  
platyhelminths 610–14  
protozoal 604–8
- parasitic infections, eosinophil role 1021
- parasternal heave 648
- parasympathetic nerves 22  
control, asthma 937–8
- parasympathomimetic drugs,  
bronchoconstriction induced 937
- parathyroid adenoma 1298
- parathyroid cysts 1298
- parathyroid hormone, ectopic secretion 1110
- paratracheal nodes 21
- parotid glands, enlarged, sarcoidosis 1051, 1051
- particles, air pollution *see* air pollutants
- passive smoking 313–14, 621–2  
asthma aetiology 898, 948  
COPD risk factor 621–2  
effect on children 1478  
lung cancer risk 1077
- Pasteurella multocida* 419  
empyema 449, 454  
pneumonia 419
- patent ductus arteriosus 713, 762
- Paul-Bunnell test 339
- peak expiratory flow rate (PEFR) 43, 45, 45, 46  
asthma 957–8  
diagnosis 958, 961, 962  
monitoring of management 974  
COPD 640, 654  
morning dip 45, 941  
response to toluene diisocyanate vapour 932
- peanut, allergy 946
- pectus carinatum (pigeon chest) 110–11, 1212–13
- pectus excavatum (funnel chest) 110–11, 1213–14  
radiology 1214, 1215
- pelvic veins, pulmonary emboli 721
- D-penicillamine 1388  
bronchiolitis obliterans due to 1460  
myasthenia syndrome due to 1229  
systemic sclerosis 1394
- penicillin(s) 193–200  
actinomycosis 576  
acute pharyngitis 340  
antipseudomonal, lung abscess 472  
antistaphylococcal 198, 198–9, 199  
cross-sensitivity 194  
decreased susceptibility definitions 384  
distribution and excretion 193  
empyema 453  
extended-spectrum (antipseudomonal) 199–200  
hypersensitivity reactions 193, 369–70
- mode of action 193  
narrow-spectrum  
long-acting 196  
short-acting 195–6  
'natural' 195  
parenteral, pneumococcal pneumonia 381  
pneumonia treatment 369, 370  
prophylactic, after splenectomy 383  
resistance  
reasons for spread 384  
*Streptococcus pneumoniae* 380, 381, 384  
semisynthetic 194  
structure 193, 194  
wider-spectrum 196–8
- penicillinase ( $\beta$ -lactamase) 195
- penicillin-binding proteins 193
- penicillin G *see* benzylpenicillin
- penicillin V 196, 383
- Penicillium* 575, 598
- Penicillium casei* 1014
- Penicillium notatum* 195
- pentamidine 221–2  
adverse effects 221–2, 222, 1371  
aerosolized 221, 222, 1371, 1374–5  
*Pneumocystis carinii* pneumonia 597, 1369, 1371, 1374–5
- pentamidine isethionate 221, 1369
- pentoxifylline, ARDS 785
- peptic ulcers 270, 312
- peptide hormones, small-cell lung cancer 1110, 1110
- peptidergic system *see* non-adrenergic non-cholinergic (peptidergic) system
- Peptostreptococcus*  
lung abscess 462  
pneumonia 412
- peracetic acid 171
- per-bronchoscopic needle aspiration 162–3
- percussion  
chest 114  
transmission of sound assessment 115
- percutaneous fine-needle biopsy 172–5  
complications 174–5, 1187  
contraindications 175  
diagnostic accuracy 175  
indications 172–5, 182  
lung abscess specimen 468  
lung cancer 1093  
mortality 175  
needles 172, 172–3  
respiratory secretion collection 362  
screw-needle 173  
specimen processing 174  
techniques 173–4  
tuberculosis diagnosis 520
- perfusion 26, 30–1
- perfusion scans 123
- peribronchial alveolar attachments, in emphysema 632, 633
- peribronchial fibrosis, bronchiectasis 806
- peribronchiolar fibrosis  
asbestosis 1430  
smokers' bronchiolitis 831
- pericardectomy 533
- pericardial cysts 1295–6, 1296
- pericardial effusions 114
- pericardiocentesis 533
- pericarditis  
constrictive 114  
pleural transudates due to 1157  
tuberculosis 532
- purulent, in pneumococcal

- pneumonia 385
- radiation 1102
- sarcoidosis 1053
- tuberculous 528, 531–3, 560
- pericardium, congenital laxity 1213
- periodic acid–Schiff (PAS) stain,
  - pulmonary alveolar proteinosis 1334, 1335
- periodic disease (recurrent polyserositis) 1153–4, 1163
- periodic limb movement disorder 1256
- peripheral nerve cells, embryology 1272
- peripheral nerve disease, bilateral
  - diaphragmatic paralysis 1237
- peripheral nerve sheath tumours 1273–6
  - benign 1273–4, 1274, 1275
  - malignant 1273, 1274–6
- peripheral neuropathy
  - isoniazid-induced 548
  - paraneoplastic syndrome 1113
  - vinca alkaloids causing 290–1
- peritoneal biopsy, tuberculosis 537
- peritoneal fluid, culture in tuberculosis 537
- peritoneal tuberculosis 536–8
- peritonsillar abscess (quinsy) 340
- peroxidase 1467
- pertussis (whooping cough) 351–2
  - bronchiectasis aetiology 799
  - clinical manifestations 351
  - complications 352
  - cough 103, 351
  - diagnosis and treatment 351–2
  - prophylaxis for contacts 352
  - vaccination 352
    - adverse reactions 351, 352
    - asthma and 899
- petrol combustion 326–7
- pH
  - blood 38
  - pleural effusions 453
- phaeochromocytoma 1272, 1277
- phagocytic cells
  - recruitment 89
  - tuberculosis 481
  - see also* alveolar macrophage; neutrophil(s)
- phagocytosis
  - by alveolar macrophage 87, 88–9
  - inhibition by *Aspergillus* 587
  - microbial killing 97
- phagolysosome 88
- phagosomes 16
- phakomatoses 96
- pharmaceutical products, occupational
  - asthma 950
- pharmacogenetics 98
- pharyngeal pouch 5, 6
- pharyngitis
  - acute 338–40
  - anaerobic 339
  - febrile 339
- pharyngoconjunctival fever 337
- pharyngotonsillitis, acute 338–40
- pharynx
  - carcinoma 5
  - muscles 5
  - obstruction 5
  - patency 1251
  - structure 5
  - tuberculosis 540, 541
- phase-spanning cells 50
- phenobarbital (phenobarbitone) 1533
- phenoxymethylpenicillin (penicillin V) 196, 383
- phenylbutyrate, new cystic fibrosis
  - treatment and 865
- phenytoin, isoniazid interaction 549
- phlegm *see* sputum
- phlyctenular conjunctivitis 511, 540
- phosgene 1448
- phosphine, exposure 1446
- phosphodiesterase
  - inhibition 252, 978
  - isoenzymes 253
  - PDE-4 253
- phospholipase A<sub>2</sub> 260, 261
- phospholipase D 1021
- photodynamic therapy 1102–3
- phrenic nerve 1236
  - in bronchogenic carcinoma 1236
  - paralysis 1230, 1236
    - lung cancer 1089
  - stimulation 1235, 1236
- phthisis 477
  - see also* tuberculosis (TB)
- physiological dead space 27–8, 1501
- physiological shunts 32
  - measurement 33
- physiotherapy
  - acute exacerbation of COPD 676
  - asthma 986
  - bronchiectasis 818–19
  - cystic fibrosis 864
  - lung abscess 473
  - mechanical ventilation and 707
  - pneumonia 373
- pickwickian syndrome 281
- pigeons, bird fancier's lung 1014–16, 1015
- pink puffers 643, 646, 653
- pinocytic vesicles 16
- piperacillin 199
- piperacillin–tazobactam 199–200
- piperazine citrate 1023
- pipe smokers 311, 619, 620
  - lung cancer 1077–8
- pirodavir 338
- Pittsburg pneumonia agent *see* *Legionella micdadei*
- pituitary gland, sarcoidosis 1051
- pituitary snuff 1465
- pituitary snuff-taker's lung 1016
- pK values 38
- plague, bubonic/pneumonic 425
- plasma cell granuloma 1133
- plasma cells
  - allergic alveolitis pathogenesis 1008
  - Castleman's disease 1342
- plasmacytoma 1129–30
- plasma D-dimer, pulmonary embolism 729–30
- plasma expanders, dextran 742
- plasmapheresis 1113, 1332
- plasminogen activator 718
- Plasmodium falciparum* 604, 607
- Plasmodium vivax* 604, 608
- platelet-activating factor (PAF)
  - antagonists, in asthma 913, 914
  - ARDS pathogenesis 778
  - asthma pathogenesis 914, 936
  - eosinophils synthesising 911
  - inhibition 261–2
- platelet counts, minimal, for transbronchial
  - lung biopsy 168
- platelet-derived growth factor (PDGF),
  - asthma pathogenesis 915
- platelet factor 4 916
- platyhelminth 605, 610–14
- plethysmography 29, 43
  - COPD 654
  - inductance 1258
- pleura
  - abrasion 1200–2, 1201
  - adhesions, round atelectasis 142
  - anatomy 23, 1152, 1182
  - calcification 134, 1159
  - 'decortication' 1172
  - endometriosis involving 1178
  - nerve supply 23, 1152
  - parietal 23, 1152
    - fibrous lesions *see* pleural plaques
  - physiology 1152
  - sarcoidosis 1049
  - splenic tissue transplantation 1178
  - thickening 1169
  - visceral 23, 1152
    - lung abscess site 464
    - rupture 1188
- pleural aspiration 1163–4
- pleural biopsy 183–5, 1163–4
  - complications 183, 1187
  - diagnostic yield 185
  - mesothelioma 1175
  - needle biopsy 183–4
  - pneumonia diagnosis 364
  - simple thorascopic 184–5
  - site 1165
- pleural cavity (space) 23, 1152, 1182
  - air in *see* pneumothorax
  - fluid in *see* pleural effusions; pleural fluid
  - intercostal tube drainage 1197–8
  - negative pressure 1152, 1182
  - pus in *see* empyema
  - pyogenic infection 1203
  - rupture 1183, 1184, 1185
- pleural disease 1152–81
  - in rheumatoid disease 1385
  - ultrasound 123
- pleural effusions 23, 1154–65
  - in AIDS 1355
  - ankylosing spondylitis 1219
  - aspiration, terminal care 1530
  - causes 1155–63
  - clinical features 1154
  - 'complicated' parapneumonic 453
  - connective tissue disease 1160–1
  - drug-induced 1161–2
  - exudates *see* pleural exudates
  - glucose 453, 1164
  - imaging 130–4, 1154–5, 1162, 1164
    - radiology 1154–5, 1155, 1162, 1163
    - ultrasound 133, 1163
  - interlobar 1154
  - investigations 1163–5
  - Legionnaires' disease 389, 391
  - lobar collapse with 133
  - loculated 133–4, 134
  - malignant
    - lung cancer 1086, 1087, 1115
    - management 1165
    - mesothelioma 1175
    - thorascopic talc pleurodesis 185
  - management 1165
  - milky 1166
  - Mycoplasma pneumoniae* 393
  - needle biopsy and 183, 184, 1163
  - non-tuberculous mycobacteria 1160
  - parapneumonic 452–3

- pleural effusions (*Continued*)
    - pH 453
    - pleural fibrosis after 1169
    - pneumococcal pneumonia complication 385
    - pneumothorax 1190
    - pseudochylous 1385
    - radiation pneumonitis 427
    - rheumatoid disease 453, 1160, 1385
    - sarcoidosis 1049, 1161
    - in SLE 1389–90, 1390
    - subpulmonary (intrapulmonary) 133
    - terminal care 1530
    - transudates 1155, 1155–7, 1165
    - tuberculous 184, 364, 448, 453, 483, 511, 1158–60, 1355
    - calcification 1159
    - disseminated TB 1159
    - management 1165
    - pericardial TB 532
    - postprimary disease 1158–9
    - in primary TB 1158
    - yellow nails syndrome 767, 1161, 1162
    - see also* pleural fluid
  - pleural exudates 1157–63, 1158, 1165, 1170
    - causes 1157–63, 1158
    - pleural fibrosis after 1170
  - pleural fibroma 1143, 1172, 1173
  - pleural fibrosis 1169–72
    - asbestosis 142–3, 1162, 1428, 1428
    - causes 1170, 1170
    - chest radiography and CT 1170, 1171
    - clinical features 1169–70
    - diffuse 134
    - drug-induced 1466
    - investigation and management 1170–2
    - round atelectasis 142, 143
  - pleural fluid 23, 130, 1152, 1154
    - composition 1164
    - culture 451–2, 1164
    - empyema 445
    - examination 1164–5
    - macroscopic/microscopic appearance 1164
    - milky 1164
    - physiology 1152
    - pneumonia 364, 380
    - specimens 451–2, 1163, 1164
    - see also* pleural effusions
  - pleural leaks, hydrocarbon marker gas 1196, 1197
  - pleural lymphatics 23, 1152
  - pleural membrane 445
  - pleural pain 23, 107, 1152–3
    - causes 106
    - differential diagnosis 1153
    - pneumococcal pneumonia 378
    - treatment, in pneumonia 373
  - pleural plaques 134, 1167–9
    - aetiology and management 1169, 1432
    - asbestos causing 1429, 142, 1167, 1167, 1169, 1427
    - chest radiography 1167, 1168
  - pleural rind (peel) 1202
  - pleural rub 116, 1153
    - pulmonary embolism 727–8
  - pleural space *see* pleural cavity
  - pleural transudates 1155, 1155–7, 1165
  - pleural tuberculosis, biopsy 185
  - pleural tumours 1172–8
    - biopsy 185
    - localized fibrous (pleural fibroma) 1143, 1172, 1173
  - mesothelioma *see* mesothelioma
  - metastatic 1157–8, 1175
  - pleural exudates 1157–8
  - sarcoma 1172–3
  - pleurectomy 1172
    - apical 1200
    - indications 1201, 1201
    - parietal 1200–2, 1201
  - pleurisy 1152–4
    - causes 1153
    - clinical features 1152–3
    - diagnosis and management 1153
    - dry or fibrinous 1152–4
    - in SLE 1389–90, 1390
    - tuberculosis complication 522
  - pleuritic pain *see* pleural pain
  - pleurocutaneous fistula 457
  - pleurodesis 185, 1165
    - chemical
      - pneumothorax management 1199–200
      - tetracyclines for 212, 1200
    - in cystic fibrosis 856
    - malignant mesothelioma 1177
    - talc 185, 1165, 1200
    - tetracycline hydrochloride 1200
  - pleurohilar veins 19
  - pleuropericardial cysts 1295–6, 1296
  - pleuroperitoneal membranes 1234
  - pleuropulmonary fibrosis, drug-induced 1466
  - PM<sub>10</sub>, airborne particles 325, 326
  - pneumatocoeles 403, 424–5
  - pneumocele 630
  - pneumococcal antigen 365
    - detection methods 363, 380
  - pneumococcal bacteraemia 375–6, 377, 384
  - pneumococcal pneumonia 369, 373–85
    - benzylpenicillin use 195–6
    - clinical manifestations 377–8, 378
    - elderly 378
    - epidemics 377
    - epidemiology 375–7
    - groups at risk 382
    - hospital-acquired 371
    - investigations 378–80
    - mortality 381, 384–5
    - conditions increasing 385, 385
    - pathology and pathogenesis 374–5
    - penicillin resistance 384
    - predisposing factors 377
    - prevalence 373–4
    - prevention 381–4
    - antibiotic prophylaxis 383
    - vaccines 381–3
    - treatment 380–1
  - pneumococcal vaccines
    - groups at risk 382
    - in HIV infection 382–3
    - immunity induced and efficacy 382, 383
    - pneumonia prevention 381–3
    - protein–conjugate vaccines 383
    - safety 383
    - types available 382
  - pneumoconioses 1408–41
    - aluminium 1439
    - berylliosis 1436–8, 1437
    - case–control studies 71
    - cavitated lesions, lung abscess *vs* 469
    - coal-workers' *see* coal-workers'
    - pneumoconiosis
    - mixed-dust 1418, 1435–6
    - other minerals causing 1439–41
    - silicosis *see* silicosis
  - terminology 1408
  - Pneumocystis carinii* 98–9, 595–8
    - characteristics 1362, 1363
    - classification 1361–2
    - cyst walls 1363, 1364
    - detection in sputum 361
    - epidemiology 595
    - infection process 1363
    - life cycle 1362
    - PCR diagnosis 99, 1369
    - transmission 595
    - trophozoites 595, 1362, 1363
  - Pneumocystis carinii* pneumonia 595–8, 1346, 1361–75
    - after lung transplantation 1520
    - antimicrobial treatment 222–3, 596–8, 1350, 1369–72, 1370
    - atovaquone 1372
    - clindamycin–primaquine 1372
    - co-trimoxazole 208–10
    - dapsone–trimethoprim 1371–2
    - first-line (co-trimoxazole) 1370–1
    - second-line (pentamidine) 221–2, 1371
    - trimetrexate–folinate 1371
  - bronchiectasis aetiology 800
  - chest radiography 144, 144, 145, 596, 1365, 1365
  - clinical features 595–6, 1348, 1364–5
  - corticosteroid treatment 1372–3
  - diagnosis 596
  - epidemiology 1362
  - fibreoptic bronchoscopy 150, 166
  - histopathology 597
  - in HIV infection and AIDS 595, 597, 1358, 1362–3, 1365
  - fibreoptic bronchoscopy 150
  - prophylaxis 1373
  - immunosuppressed patients 595
  - investigation and diagnosis 1365–9
  - imaging 1365, 1365–7, 1366, 1367
  - microbiological 1368–9
  - non-microbiological 1367–8
  - lung transplantation complication 858, 1363
  - outbreaks 1362
  - pathophysiology 1363–4
  - prophylaxis 1351, 1361, 1373, 1373–5
  - aerosolized pentamidine 1374–5
  - co-trimoxazole 209, 210, 1373–4
  - dapsone 1374
  - pentamidine 221
  - reactivation 1362
  - secondary spontaneous pneumothorax 1186
  - supportive treatment 1369
  - susceptibility 1362–3
- pneumocytes
  - destruction in paraquat poisoning 1469
  - development 2
  - type I 16, 17, 766
  - particle removal 1407
  - type II 16, 17, 18, 766
  - cryptogenic fibrosing alveolitis 878, 879
  - repair after acute inflammation 782
  - surfactant synthesis 19, 85
- pneumocytoma, sclerosing 1137
- pneumomediastinum 1204–7
  - aetiology and classification 1204–5, 1205
  - barotrauma causing 1188, 1188, 1205, 1484, 1485
  - clinical/radiographic features 1205–6, 1206

- diagnosis and management 1206–7  
 pneumothorax with 1206  
 tracheostomy complication 1503  
 pneumonectomy (lung volume reduction surgery) 679  
 bronchiectasis 821  
 COPD 679  
 emphysema 1517  
 lung cancer 1093, 1099  
 thoroscopic laser 679  
 pneumonia 356–444, 424–5  
   acute eosinophilic 1031, 1031  
   adenovirus 415–16  
   anaerobes causing 372, 412–14  
   antibiotic-resistant pathogens 365, 366  
   antimicrobial treatment 365–73  
     empirical antibiotics 365, 366  
     factors influencing 366–7  
     hospital-acquired disease 371–3  
     inpatients with community-acquired pneumonia 366–71  
     outpatients 365–6  
   ARDS differential diagnosis 783  
   aspiration *see* aspiration pneumonia  
   atypical 357  
     antibiotics 210  
     chest radiography 141, 141  
     mycoplasma causing 392  
   *Bacillus anthracis* 425–6  
     *see also* anthrax  
   bacterial 357, 373–414  
     unusual 419–26  
   bronchiectasis aetiology 798–9, 799–800  
   *Brucella* 420–1  
   caseous 509  
   causative agents 357, 358–9, 369  
   chickenpox 235  
   *Chlamydia* 396–400  
     *see also Chlamydia psittaci* pneumonia  
   chronic destructive 463  
   chronic destructive cavitatory 462  
   chronic eosinophilic 1025–8, 1026, 1027  
   classification 358, 358–9  
   community-acquired *see* community-acquired pneumonia  
   costs/burden 356  
   *Coxiella* *see* Q fever  
   cryptogenic organizing 830, 835  
     *see also* bronchiolitis obliterans with organizing pneumonia (BOOP)  
   in cystic fibrosis 856  
   cytomegalovirus 418  
   definition 356  
   diagnosis 1349  
   elderly 356  
   eosinophilic 1020  
     *see also* pulmonary eosinophilia  
   epidemiology 356–8  
   *Escherichia coli* 409  
   *Francisella tularensis* 421  
   Gram-negative aerobic opportunistic bacilli 409–10  
   group A streptococcal 419  
   *Haemophilus influenzae* 410–11  
   hospital-acquired *see* hospital-acquired infections  
   immunocompetent patients, fibreoptic bronchoscopy 166  
   infants 357, 358  
   influenza complication 348–9, 414–15  
   secondary bacterial 348–9, 415  
   investigation 360, 360–5  
     arterial oxygen saturation and blood gases 364  
     chest radiography 129, 364  
     laboratory 360–4  
     pleural fluid 364  
   *Klebsiella* 406–7  
   *Legionella* *see* Legionnaires' disease  
   *Leptospira icterohaemorrhagiae* 422–3  
   lipoid *see* lipoid pneumonia  
   listerial 423  
   lobar 358, 374  
     clinical manifestations 377  
     pathology 375, 376  
     *see also* pneumococcal pneumonia  
   lobular 358  
   lymphoid interstitial 1132, 1133  
   measles virus 415  
   mechanical ventilation indication 1510  
   meningococcal 419–20  
   *Moraxella catarrhalis* 411–12  
   *Mycoplasma* *see* *Mycoplasma* pneumonia  
   necrotizing 406, 460  
     causes 461  
     chest radiography 466  
     lung abscess from 463  
   nosocomial *see* hospital-acquired infections  
   *Pasteurella multocida* 419  
   pathogenesis 359–60  
   pertussis complication 352  
   pleural exudates due to 1158  
   pneumococcal *see* pneumococcal pneumonia  
   predisposition and spread 359–60  
   primary influenza virus 348  
   protozoa causing 604  
   *Pseudomonas* 407–9  
   *Pseudomonas mallei* 407, 424–5  
   *Pseudomonas pseudomallei* 423–4  
   rare 419–26  
   in respiratory failure 708  
   ricketsial 421–2  
   *Salmonella* 422  
   seasonal 357, 376, 386  
   segmental 358  
   severity, markers 360  
   severity assessment 366, 367–8  
   SLE 1392  
   specific types 373–426  
   *Staphylococcal* 402–6  
     *see also Staphylococcal* pneumonia  
   subsegmental 358  
   systemic sclerosis 1394  
   terms in common usage 358–9  
   transplantation complication 1347  
   tuberculosis presenting with 516  
   tuberculosis *vs* 517, 522  
   varicella (chickenpox) 416–18  
   viral 414–19  
   *Yersinia pestis* 425  
   *see also specific types of pneumonia*  
 pneumonitis 356  
   bronchographic contrast media causing 428  
   chemical 426  
   desquamative interstitial 879, 879  
   fatty material aspiration *see* lipoid pneumonia  
   haemorrhagic 1016  
   hypersensitivity *see* hypersensitivity pneumonitis  
   interstitial *see* interstitial pneumonitis  
   Japanese summer 1014  
   lipoid *see* lipoid pneumonia  
   lupus, SLE 1390–1  
   radiation *see* radiation pneumonitis  
   relapsing organizing, systemic sclerosis 1394  
   toxic  
     beryllium exposure 1436  
     oxides of nitrogen causing 1447, 1447  
   types 426–9  
   *see also* pneumonia  
 pneumonostomy, lung abscess drainage 473  
 pneumopericardium 532  
 pneumoperitoneum, artificial in tuberculosis 545  
 pneumoplasty (lung volume reduction surgery) 679  
   *see also* pneumonectomy (lung volume reduction surgery)  
 pneumothorax 1182–211  
   after diving 1485  
   artificial 1188–9, 1202, 1203  
     in tuberculosis 545  
   barotrauma 1187–8, 1202  
   breathlessness 108  
   catamenial 1202  
   causes 1183  
   chronic 1202  
   classification and terminology 1182–9, 1183  
   clinical features 1189–90  
   complications 1202–4  
   contraindication to diving 1490  
   cutting-needle biopsy complication 176  
   cystic fibrosis 856  
   definition 1182  
   differential diagnosis 1192–3, 1193, 1194  
   failure to re-expand after 1202  
   fibreoptic bronchoscopy complication 167  
   haemorrhage after 1204  
   iatrogenic 1186–7  
   lung biopsy complication 1187  
   lung re-expansion oedema 789  
   management 1193–202  
     active 1195–6  
     aspiration 1196–7, 1197  
     chemical pleurodesis 1199–200  
     complications 1202–4  
     conservative 1193–5  
     flutter valves 1199  
     intercostal tube drainage 1185, 1197–9, 1198  
     pleurectomy and pleural abrasion 1200–2  
   in Marfan's syndrome 1381–2  
   open and closed types 1182, 1195  
   percutaneous fine-needle biopsy complication 174  
   physiology 1189  
   pleural aspiration complication 1164  
   pleural biopsy complication 183, 1187  
   pneumomediastinum with 1206  
   radiography 1190–2, 1191, 1192  
   recurrence 1186, 1202  
   in respiratory distress syndrome 714  
   spontaneous (simple, idiopathic) 1182–6, 1189  
     aetiology 1183, 1183–5  
     bilateral 1190  
     familial 1183–4  
     intercostal drainage indications 1185  
     lung function 1189  
     management 1193–202

- pneumothorax (*Continued*)  
 pregnancy 1201  
 primary 1182–5  
 recurrence 1202  
 secondary 1182, 1185–6  
 small 1193–4  
*Staphylococcus aureus* pneumonia 406  
 tension 1182, 1189, 1192  
   barotrauma (diving) causing 1484, 1485  
   radiography 1192, 1192  
 tracheostomy complication 1503  
 traumatic 1186–7  
   causes 1183, 1186  
 volume 1195
- pneumoperitoneum, barotrauma causing 1485
- Poiseuille's equation 41
- poisoning  
   carbamate 1229  
   cyanides 1445  
   methyl alcohol 1266  
   paraquat 1468–9  
   respiratory failure due to 709, 1229
- Poland's syndrome 1214
- poliomyelitis  
   bulbar 711  
   respiratory failure 711  
   scoliosis 1217, 1218  
   spinal 711
- pollens 897, 943–4  
   seasonality 944
- pollution, air *see* air pollution
- polyarteritis nodosa 1028–9, 1396  
   allergic granulomatosis overlap syndrome 1028
- polyarthralgia  
   sarcoidosis 1045  
   Wegener's granulomatosis 1068–9
- polyarthritis, Poncet's disease 524
- polychondritis, relapsing 155, 1221, 1396
- polycyclic aromatic hydrocarbons (PAHs) 328, 329
- polycythaemia  
   COPD 657, 669  
   high altitude 56  
   persistent hypoxia causing 698  
   secondary 698, 1325
- polyene antifungals 228
- polymerase chain reaction (PCR) 99  
   *Chlamydia pneumoniae* 400  
   *Chlamydia psittaci* pneumonia 398  
   CNS tuberculosis diagnosis 530  
   cystic fibrosis test 850  
   *Mycobacterium tuberculosis* in sarcoidosis 1039–40  
   *Mycoplasma pneumoniae* 395  
   *Pneumocystis carinii* pneumonia 99, 1369  
   pneumonia 364  
   tuberculosis 520–1, 530
- polymorphonuclear leucocytes *see* neutrophil(s)
- polymyxin 216–17
- polyneuropathy, respiratory failure 711
- polyserositis, recurrent 1153–4
- polysomnography 1256–7, 1257  
   costs 1258
- polytetrafluoroethylene (Teflon) 1449
- polyvinyl chloride (PVC) 68, 69, 1439–40
- Poncet's disease 524
- pons, breathing control 50, 1264
- Pontiac fever 385, 387  
   *see also* Legionnaires' disease
- population at risk, defining 65
- Porphyromonas*  
   lung abscess 462  
   pneumonia 412
- portal hypertension 860
- positional cloning method 92–3
- positive end-expiratory pressure (PEEP) 705, 1497, 1513  
   ARDS 784  
   auto-PEEP (intrinsic PEEP) 706, 1497, 1513  
   in type I respiratory failure 700
- positive pressure ventilation (NIPPV), non-invasive *see* non-invasive positive pressure ventilation (NIPPV)
- post-cardiac injury syndrome 1161
- posterior fossa, tuberculoma 529, 531
- postmenopausal women  
   lymphangioma 1139  
   osteoporosis 269
- postnasal discharge 337
- postoperative apnoea 709
- post-polio syndrome 711
- post-tricuspid shunts 761–2
- postural drainage  
   bronchiectasis 818–19  
   methods/positions 818–19
- posture  
   effect on lung abscess 465  
   supportive treatment of pneumonia 373  
   terminal care 1530
- potassium, sweat 844, 849, 849
- Pott's disease *see* spinal tuberculosis
- Pott's puffy tumour 345
- poverty, asthma and 896
- practolol 1161  
   mediastinal fibrosis association 1303  
   pleural fibrosis due to 1466
- pranlukast 259
- praziquantel 611, 612
- precipitins 890
- prednisolone 260  
   acute eosinophilic pneumonia 1031  
   adrenal suppression 272  
   asthma 984, 985  
   chronic eosinophilic pneumonia 1027–8  
   COPD 666–7  
   reversibility assessment 656  
   cryptogenic fibrosing alveolitis 887  
   oral preparations 263, 666–7  
   parenteral 265  
   radiation pneumonitis 427  
   sarcoidosis 1057–8  
   structure 263  
   tuberculosis 560  
   CNS 531  
   pericardial 533
- prednisone  
   oral preparations 263  
   parenteral 265  
   structure 263
- pregnancy  
   antibiotics 863  
   asthma management 991  
   corticosteroid effects 271–2  
   cyclophosphamide in 285  
   cystic fibrosis 863  
   deep venous thrombosis prevention 743  
   pulmonary embolism prevention 743  
   smoking cessation 317  
   smoking in 313, 1477  
   spontaneous pneumothorax 1201  
   thrombosis predisposition 720
- tuberculosis treatment 558
- premature infants  
   asthma prediction 897  
   chronic lung disease 1477  
   respiratory management 1477  
   surfactant deficiency 19, 41
- premedication, fiberoptic bronchoscopy 152, 168
- prenatal detection, cystic fibrosis 79
- pressure of secretions theory, bronchial dilatation 805
- pressures  
   changes in controlled ventilation 1497, 1498  
   changes on immersion 1482  
   *see also* specific pressures/gases
- pressure–volume curves 48  
   COPD 641, 642  
   lung 39, 40
- pressurized metered-dose inhalers (MDIs) 988–9
- prevalence rate 65, 66
- Prevotella*  
   lung abscess 462  
   pneumonia 412
- primaquine 223
- prisons  
   pneumococcal pneumonia 377  
   tuberculosis 496
- procaine benzylpenicillin 196
- procarbazine 294–5
- prodigiosin 410
- prodrugs, aminopenicillins 196
- progestogens 280–1
- progressive massive fibrosis  
   chest radiography 141, 142  
   clinical features 1412  
   coal workers 74, 1410, 1411, 1411  
   pathogenesis 1414  
   pathology 1413, 1414  
   silicosis 1419, 1421–2, 1422
- propylidone (Dionosil) 428
- Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) 730–1
- prostacyclin  
   actions and mechanism of action 750  
   pulmonary hypertension treatment 756  
   synthesis 935, 936
- prostaglandin(s)  
   ARDS pathogenesis 778  
   asthma pathogenesis 913, 935  
   coughing and 84  
   inhibitors 742  
   synthesis 935, 936
- prostaglandin PGD<sub>2</sub>, synthesis 935, 936
- prostaglandin PGF<sub>2α</sub>, bronchoconstriction 935–6
- prostatic carcinoma, metastases 1223, 1225
- protease inhibitors 236, 238–9, 1361
- proteases  
   antiprotease imbalance in lungs 639–40  
   increase in emphysema pathogenesis 637–8  
   *see also* antiproteases
- protected specimen brush (PSB) 362  
   lung abscess specimen 468
- proteinase 3 638
- α<sub>1</sub>-proteinase inhibitor *see* α<sub>1</sub>-antitrypsin
- protein C 719
- protein-calorie malnutrition 900

- protein kinase C 939  
proteinosis, pulmonary alveolar *see*  
pulmonary alveolar proteinosis  
protein S 97  
proteins  
  bronchial secretions 15, 85–7, 86  
  removal from alveoli 768  
proteolysis hypothesis 95  
*Proteus*, pneumonia 409–10  
prothionamide, tuberculosis 550, 551  
prothrombin time 737  
proton pump inhibitors, in cystic fibrosis 859  
protozoa 604–8, 605  
  empyema 449  
protriptyline 281  
*Pseudoallescheria boydii* 463, 598  
‘pseudocallus’ 121  
pseudolymphoma 1132, 1133  
pseudomembranous colitis  
  antibiotics associated 197, 226  
  antibiotic treatment 218, 220  
  pathogenesis 218  
*Pseudomonas*, pneumonia 407–9  
*Pseudomonas aeruginosa*  
  antibiotic susceptibility 199, 203, 216, 408, 864  
  carriage rate 407  
  culture 408  
  in cystic fibrosis 854, 864  
  colonization 853, 853  
  immunotherapy 854  
  empyema 448  
  lung abscess 461, 463  
  pneumonia 407–9  
    hospital-acquired 371  
    treatment 369  
  sinus infection and diffuse  
    panbronchiolitis 831–2  
  in sputum, bronchiectasis 809  
  virulence factors 854  
*Pseudomonas mallei*  
  pneumonia 407, 424–5  
  transmission 424  
*Pseudomonas maltophilia* 407  
*Pseudomonas pseudomallei*  
  antibiotic resistance 424  
  bacteraemia 423, 424  
  characteristics and transmission 423  
  culture 424  
  pneumonia 407, 423–4  
  *see also* melioidosis  
*Pseudomonas pyocyaneus see Pseudomonas aeruginosa*  
pseudomycosis, bacterial *see* botryomycosis  
psittacosis 396–9  
psoas muscle, abscess 537  
psychiatric illness, sleep apnoea *vs* 1256  
psychological factors, asthma aetiology 948  
psychological issues  
  cystic fibrosis 867  
  terminal care 1533  
psychological sleepiness 1256  
psychotropic drugs, terminal care 1533  
puerperium  
  deep venous thrombosis prevention 743  
  pulmonary embolism prevention 743  
  thrombosis predisposition 720  
puff-ball spores 1014  
pulmonary adenoma 1133  
pulmonary agenesis, bronchiectasis  
  aetiology 797  
pulmonary alveolar microlithiasis 96, 1339–40  
pulmonary alveolar proteinosis 96, 1334–7  
  aetiology 1334–5  
  chest radiography 1335, 1336  
  fiberoptic bronchoscopy 150, 164  
  pathology and clinical features 1335, 1335  
  treatment and prognosis 1335–7  
pulmonary angiography 127  
arteriovenous malformations 1324–5, 1326  
  emphysematous bullae 662  
  massive pulmonary embolism 736  
  pulmonary embolism 733–4, 734, 736  
  pulmonary thromboembolism diagnosis 124  
  spiral CT 124–5, 125, 126  
pulmonary angioma *see* arteriovenous malformations  
pulmonary arterial pressure 30, 749  
  COPD 648, 650, 669  
  mean pressure 749  
  normal 749  
  pulmonary embolism 722  
  response to cardiac output changes 30, 30  
pulmonary arteriogram 20, 1141  
pulmonary arterioles 19, 20  
  remodelling in COPD 633  
pulmonary arteriovenous malformations  
  *see* arteriovenous malformations  
pulmonary artery (arteries) 15, 1319  
  abnormal venous connections 1140  
  absent unilateral 1320  
  anatomy 19, 20  
  anomalies 1320  
  branches 19  
  congenital absence 678  
  development 1, 2  
  dilatation, cor pulmonale 750  
  elastic tissue 20  
  left, anomalous origin 1320, 1321  
  muscular structure 20  
  postnatal development 4  
  remodelling in COPD 633  
  right, measurement 750  
  ‘sling’ syndrome 1320, 1321  
  smooth muscle 2  
  stenosis (coarctation) 1320  
  thrombosis, breathlessness 108  
pulmonary artery trunk, absent 1319  
pulmonary bleb 1183, 1184  
pulmonary blood flow 30  
  distribution in lung 31, 32  
  at high altitude 57  
  increased, causes 760–2  
  measurement 31  
pulmonary capillaries 15, 19–20  
  alveolar–capillary structures 766, 767  
  anatomy 20  
  diameter 90  
  endothelial cells *see* endothelial cells  
  neutrophils in 90  
  thrombotic occlusion 21  
pulmonary capillary haemangiomatosis 1141  
pulmonary capillary pressure 30  
pulmonary cavernous angioma *see* arteriovenous malformations  
pulmonary circulation 19–21  
  blood flow rate 30  
control 30  
COPD 647  
  development 1  
  diseases, breathlessness 108  
  functions 20–1, 30–1  
  mechanics 749  
  obstruction *see* pulmonary embolism  
  perfusion 30–1  
  variation 30  
pulmonary complications  
  inherited disorders (systemic) 1380–4  
  systemic diseases 1380–403  
  *see also* individual disorders/diseases  
pulmonary congestion 52  
pulmonary cystic disease 1313  
pulmonary embolectomy 733–4, 736  
  procedure and mortality rates 740  
pulmonary embolism 718–47  
  acute  
    management 736–40  
    prognosis 743  
  cardiovascular effects 722  
  chest radiography 728–9, 730, 731  
  chronic 743  
  clinical features 723–36  
    breathlessness 108, 727, 728  
  clinical presentation 727–8  
  COPD 676  
  definition and terminology 718, 722  
  diagnosis 1153  
    confirmation 728–34  
    strategy 734–6, 735  
  genetic disorders associated 97, 720  
  hyperventilation in 1266  
  management 736–40  
    heparinization 736–7  
    oral anticoagulants 737–8  
    thrombolytic therapy 738–9  
    vena caval interruption 739–40  
    *see also* pulmonary embolectomy  
  massive 727, 728  
    diagnosis/management 736  
    prognosis 743  
    pulmonary hypertension 757  
  mechanisms of thrombosis 718–19  
  non-thrombotic 721–2  
  pathogenesis 720–1  
  pathology 729  
  pathophysiological response 722–3  
  physical examination 727–8  
  physiological shunts 32–3, 722  
  pleural effusions 1161  
  pleural transudates due to 1157  
  postoperative deaths 719  
  prevalence 718  
  prognosis 743  
  prophylaxis 740–3  
    methods 741–2  
  pulmonary angiography 733–4, 734  
  pulmonary infarction 722–3  
  resolution/fragmentation 723  
  respiratory effects 722  
  risk assessment 740  
  risk factors 741  
  scintigraphy 123  
  secondary spontaneous pneumothorax 1186  
  septic 721  
  SLE 1392  
  thrombotic 718–21  
    *see also* thrombosis  
  ventilation–perfusion (V/Q) scans 730–1, 732, 733



- pulmonary eosinophilia 608–10, 991, 1020–34
  - asthmatic 1023–4
  - see also* allergic bronchopulmonary aspergillosis
  - classification 1022, 1022–31
  - cryptogenic 1025–8, 1026, 1027
  - definition 1020
  - drug-induced 1024, 1024
  - simple (Loeffler's syndrome) 1022–3
  - tropical 609, 1024–5
- pulmonary eosinophilic pneumonia, imaging 144, 145
- pulmonary epithelial permeability, smoking effect 313
- pulmonary fibrosis 877
  - ankylosing spondylitis 1219, 1220, 1396, 1397
  - around lung abscess 464
  - asbestosis 1424, 1427, 1427
  - azathioprine causing 287
  - bronchial dilatation secondary to 805
  - bronchiectasis 822
  - chemotherapy causing 285, 1518
  - cor pulmonale 750–1
  - deposition 880
  - diffuse, lung cancer and 1079–80
  - drug-induced 1462, 1464, 1465
  - hilar, idiopathic 1340, 1341
  - hypersensitivity pneumonitis 1005
  - idiopathic *see* cryptogenic fibrosing alveolitis
  - interstitial
    - aluminium causing 1439
    - radiation pneumonitis 1471
    - rheumatoid disease 1387
    - Sjögren's syndrome 1395
    - SLE 1391
  - lung transplantation 1517, 1518
  - management 1387–8
  - paraquat poisoning 1469
  - progressive massive *see* progressive massive fibrosis
  - rheumatoid disease 1386–8, 1387, 1388
  - systemic sclerosis 1393, 1394
  - upper lobes 144–5, 1396, 1397
- pulmonary function *see* lung function
- pulmonary haemodynamics
  - assessment, in COPD 648–9
  - COPD 647–8, 648, 648–9, 669
- pulmonary haemorrhage
  - acute diffuse, in SLE 1391
  - fibreoptic bronchoscopy complication 167–8
  - massive 1333
  - see also* alveolar haemorrhage
- pulmonary hyalinizing granuloma 1340–2, 1341
- pulmonary hypertension 748–65
  - ARDS 783
  - asthma 955
  - bronchiectasis 806
  - causes 749, 749–62
    - increased pulmonary blood flow 760–2
    - increased pulmonary vascular resistance 750–9
    - increased pulmonary venous pressure 759–60
  - chest radiography 649, 661, 751, 754, 758, 760, 761, 810
  - connective tissue disease with 756–7
  - COPD 633, 647–50, 653
    - factors contributing 647
    - embolic causes 757
    - genetic resistance to in high-altitude animals 752
    - high altitude effect 56–7
    - HIV infection 758, 759, 1360–1
    - hypoxic 750–2
    - obstructive 752–9
    - oral contraception causing 1465
    - persistent in newborn 1319
    - physiological considerations 748–9
    - plexogenic 754, 756
    - primary 752–6
      - aetiology 753, 754–6
      - chest radiography 754
      - clinical features and associations 752–4
      - familial and genetics 98, 753
      - lung transplantation 1517, 1518
      - management 756, 757
      - pathology 754, 755
      - remissions 753–4
    - progressive, in sarcoidosis 1049
    - rheumatoid disease 1389
    - SLE 1392
    - systemic sclerosis 1393–4
    - veno-occlusive disease causing 757–9
- pulmonary infarction 1383
  - pleural effusions 1161
  - pulmonary embolism 722–3
  - tuberculosis *vs* 522
- pulmonary infiltration with eosinophilia (PIE syndrome) 1020
- pulmonary irritant receptors 52
- pulmonary ligament 23
- pulmonary lymphangiectasia 1141
- pulmonary lymphangiomatosis 1141–2
- pulmonary lymphocytic angiitis 1063–76
  - benign 1071
  - see also* granulomatosis; Wegener's granulomatosis
- pulmonary neoplasms *see* lung tumours
- pulmonary nodules 140–1, 142
  - causes 141
  - chest radiography 140–1
  - malignant *vs* benign 181
  - rheumatoid disease 1385–6, 1386
  - solitary
    - fibreoptic bronchoscopy 165
    - lung biopsy 181
  - Wegener's granulomatosis 1067, 1068
- pulmonary oedema 21, 766–93
  - anatomy and physiology 766–8
  - causes 145, 146
  - chest radiography 1025, 1027
  - chronic 768
  - chronic eosinophilic pneumonia
    - resembling 1025, 1027
  - definition 766
  - differential diagnosis, pneumonia 128
  - drug abusers 789
  - drug-induced 1465
  - head injury link 770
  - high-altitude 788
  - high-pressure (cardiogenic) 766, 768, 768–70, 769
    - causes 768
    - increased permeability oedema *vs* 769
    - management 769–70
    - radiology 768, 769
  - immersion-induced 1489
  - lobar consolidation 128
  - lung re-expansion 789, 1203–4
- malaria 608
  - neurogenic 787–8
  - pathogenesis 21–2, 30–1
  - radiology 768, 769
  - respiratory failure 709–10
- pulmonary overpressurization, in diving 1486
- pulmonary perfusion, systemic, anomalous 1320–1
- pulmonary pressure, postnatal 4
- pulmonary rehabilitation
  - COPD 672–4
  - evaluation 673
- pulmonary sickling 1383
- pulmonary stretch receptors 51–2
- pulmonary telangiectasia 1140–1, 1322–6
  - definition 1322
  - functional abnormalities 1325
  - treatment 1326
  - see also* arteriovenous malformations
- pulmonary thromboembolism
  - diagnosis, imaging 124
  - oral contraception 1465
- pulmonary vascular disease, drug-induced 1465–6
- pulmonary vascular plexus 1319
- pulmonary vascular resistance 749
  - control 30, 750
  - increased
    - causes 30, 750–9
    - hypoxia causing 750–2
    - obstructive pulmonary hypertension 752–9
  - normal and normal control 749, 750
- pulmonary vascular tone, regulation 749–50
- pulmonary vasculature
  - anomalies 1319–26
  - COPD 633
  - embryology 1319
  - reactivity and continuum 755
- pulmonary vasodilators
  - ARDS treatment 784
  - primary pulmonary hypertension 756
  - systemic sclerosis 1395
- pulmonary veins 10, 15, 1319
  - anomalous 2, 4, 1321, 1321–2
  - development 2
  - partial obliteration in veno-occlusive disease 758
  - single common 1322
  - structure 20
- pulmonary veno-occlusive disease 757–9
- pulmonary venous drainage, anomalous 1321, 1321–2
- pulmonary venous plexus 1319, 1321
- pulmonary venous pressure, increased, causes 759–60
- pulmonary ventilation *see* ventilation
- pulse oximetry
  - COPD 656
  - during type II respiratory failure treatment 702
- pulsus paradoxus 952, 957, 1205
- purified protein derivative (PPD) 490–1, 491
  - in HIV infection 1361
  - PPD-S 491, 492
  - standards 491
- purpura, in cystic fibrosis 862
- pyopneumothorax 1159, 1203
- pyrazinamide 549
  - activity/effectiveness 545–6

- adverse effects 547, 549
- dosage 547, 549
- tuberculosis regimens 553, 554
- pyrethrum 1016
- pyrexia of unknown origin 513
- pyrimethamine, toxoplasmosis 607
- Q fever 400–2
  - pathogenesis 359
  - treatment 401–2
  - vaccine 402
- quality of life
  - after lung transplantation 1522
  - long-term ventilation 1512
  - lung cancer 1116–17
  - measurement 1116–17, 1117
  - pulmonary rehabilitation 673
- quartz 1416, 1417, 1418, 1423
  - see also* silicosis
- Quellung reaction 361, 380
- questionnaires, epidemiological studies 75–6
- Quick test 737
- quinine, malaria 608
- quinolones, tuberculosis 551, 551
- quinsy (peritonsillar abscess) 340
- radiation 426
  - damage 1469–70
  - doses, units and fractionation 426
  - ionizing 1100, 1100
- radiation fibrosis 427–8
- radiation pneumonitis 426–7, 1102, 1469–71, 1470
  - clinical features 427, 1470
  - mechanism 1469–70
  - pathology and management 1471
  - recall 426, 427
  - treatment 427
- radioactive fibrinogen test 726
- radioactivity, occupational sources, lung cancer and 1079
- radioallergosorbent test (RAST), penicillin hypersensitivity 194
- radiography
  - bone and joint tuberculosis 534, 535
  - chest *see* chest radiography
  - paranasal sinuses 343
- radiometric culture system 519, 530
- radionuclide scanning 123–4
- empyema 450
- radiotherapy
  - continuous hyperfractionated accelerated (CHART) 1101
  - cranial 1101–2
  - endobronchial 1102–3
  - hyperfractionation 1108
  - lung cancer 1100–2, 1103, 1104
    - chemotherapy with 1104, 1108
    - palliative 1101, 1101–2
    - postoperative 1103
  - radical 1100–1
  - small-cell 1108–9
  - surgery with 1103
- lung damage *see* radiation fibrosis; radiation pneumonitis
- malignant mesothelioma 1177
- prophylactic cranial 1108–9
- side-effects 1102
- superior vena cava obstruction 1113, 1114
- thymoma 1280
- total dose and fractionation 1100–1
- toxicity 1467
- tracheobronchial narrowing 151
- units 1100, 1100
- radon daughters 1435, 1449
- radon exposure, lung cancer and 1079
- RADS *see* reactive airways dysfunction syndrome
- ragweed allergen 944
- râles *see* crepitations
- randomized controlled trials (RCT) 75
- RANTES 916, 917
- rapeseed oil, contaminated 1471
- rapid detection techniques, pneumonia 364
- rapid microagglutination test (RAMT) 389–90
- rashes
  - ampicillin and amoxicillin causing 197
  - antituberculosis drugs 548, 552
  - erythema nodosum in TB 510–11
  - penicillins causing 193, 194
- Raynaud's syndrome 753, 754
- reactive airways dysfunction syndrome 103, 949, 998–1001, 1446
  - causes 1000
  - clinical features 998–9
  - definition and diagnostic criteria 998
  - frequency 999–1000
  - management 1000
  - pathology 1000
  - see also* occupational asthma
- reactive oxygen intermediates 1467, 1487
- ARDS pathogenesis 776
- asthma pathogenesis 918, 933
- neutrophils secreting 781
- secretion by macrophage 89
- see also* free radicals
- recompression, barotrauma in diving
  - management 1485
- recurrent laryngeal nerve 6, 7
  - bilateral paralysis 7
  - in lung cancer 1086
  - palsy 7, 7, 1051
  - unilateral paralysis 7, 1086
  - see also* left recurrent laryngeal nerve
- recurrent polyserositis 1163
- red blood cells, malarial parasites in 607, 607, 608
- 'red man syndrome' 220
- redundancy, mediators 912
- Reed–Sternberg cells 1124, 1126
- refugees, tuberculosis 496
- rehabilitation, occupational lung diseases 1450
- Reid index 628
- relapsing polychondritis 155, 1221, 1396
- relaxation pressure–volume curve 39, 41
- relaxation techniques 1529
- REM (rapid eye movement) sleep 281
- 'renal asthma' 894
- renal calculi 1052
- renal dialysis 1398–9
- renal disease
  - systemic sclerosis 1392
  - tuberculosis treatment 557–8
  - Wegener's granulomatosis 1065, 1067
- renal failure, chronic 789
- renal function, changes in COPD 650
- renal impairment, grading of severity 558
- renal insufficiency, tetracyclines effect 211–12
- renal lesions, Wegener's granulomatosis 1065–6
- renal transplantation 1347, 1398–9
- renin–angiotensin–aldosterone system, in COPD 650, 651
- residual volume (RV) 29, 29, 46
- respiration
  - accessory muscles 26
  - diaphragm function 1235
  - neuromuscular diseases affecting 1228–30
  - periodic *see* Cheyne–Stokes breathing
  - in respiratory distress syndrome 713
  - supplementation by mechanical ventilation 1500
  - timing 50
  - see also* breathing
- respirators, allergic alveolitis 1010–11
- respiratory acidosis 38, 701
- respiratory alkalosis 38
  - high-altitude 55
- respiratory bronchioles 9, 15, 829
- walls 15, 829
- 'respiratory bronchiolitis causing interstitial disease' 831
- respiratory complications, fiberoptic bronchoscopy 169
- respiratory depression, opioids causing 152
- respiratory disease
  - of farmers 1012
  - signs 109–16
  - symptoms 102, 103–9
- respiratory distress syndrome (hyaline membrane disease) 40, 41, 712–14
  - aetiology 712
  - clinical features and radiology 713
  - complications and prognosis 714
  - diagnosis 713
  - functional abnormalities 713
  - pathology 712
  - treatment and prevention 713
- respiratory drive 51, 647, 700
- improvement by long-term ventilation 1512
- mechanical ventilation aims 1500
- prevention of weaning from ventilation 1511
- respiratory effort, increased in sleep apnoea 1252
- respiratory failure 696–717
  - acute 696, 701, 1229
    - neuromuscular causes 1229, 1229
    - ventilation 1509–11
  - acute-on-chronic 701, 701
  - mortality 709
  - cervical cordotomy 712
- in children *see* respiratory distress syndrome
- chronic 696, 1230
  - neuromuscular causes 1229, 1229–30
- clinical features 698–9
- complications 708
- cystic fibrosis 856
- definition 696, 699
- diagnosis 699–700
- drug-induced 709
- gastrointestinal bleeding 708
- hypoxaemia 696, 698
- inhaled foreign body 712
- laryngeal oedema 709
- Legionnaires' disease 391
- management 281, 700–8
- mechanical ventilation 1500
- myxoedema 712

- respiratory failure (*Continued*)  
  neurological disorders 709  
  neuromuscular causes 1228–30, 1229  
  paraquat poisoning 1469  
  in pneumothorax 1203  
  prognosis 708–9  
  pulmonary oedema 709–10  
  respiratory muscle dysfunction 710–12  
  scoliosis 1218  
  in sleep apnoea/hypopnoea syndrome 1255  
  sudden onset 697–8  
  type I 696–7  
    causes 697  
    management 700  
  type II (hypercapnic) 697–8  
    causes 697  
    hypoxia relief 701–2  
    management 700–8  
    mechanical ventilation 704–8  
    mechanisms/pathogenesis 698  
    natural history in COPD 700–1  
    non-invasive ventilation 702–4  
    *see also* ventilation, mechanical  
  types 709–12  
  respiratory mechanics *see* lung, mechanics  
respiratory muscles 48  
  acute paralysis 1229  
  in COPD 644–6  
  dysfunction, respiratory failure 710–12  
  fatigue 48–9, 706, 1512  
    COPD 645, 706  
    detection tests 49  
    myasthenia gravis 710  
    relief by long-term ventilation 1512  
  mechanical ventilation aims 1500–1  
  scoliosis 1218  
  spasms 711  
  strength measurement 710  
  training, COPD 645–6, 673  
  weakness 48–9, 710  
    polyneuropathy 711  
respiratory myoclonus (diaphragmatic tic) 1239  
respiratory pump  
  prevention of weaning from ventilation 1511  
  ventilation aim 1500  
respiratory rate 110  
respiratory secretions 14–15  
  impaired drainage, lung  
    agenesis/hypoplasia 1315  
    invasive methods to obtain 362–3  
  pressure, bronchial dilatation theory 805  
respiratory sensors, sleep  
  apnoea/hypopnoea syndrome  
  detection 1257  
respiratory stimulants 280–3, 702  
respiratory support  
  ARDS 783–4  
  pneumonia 373  
  *see also* ventilation, mechanical  
respiratory syncytial virus (RSV)  
  asthma and 899  
  bronchiolitis 899, 1478  
  children, infection 1478  
  common cold 335  
  pharyngotonsillitis 338  
  pneumonia 357, 418  
respiratory tract  
  colonization, pneumonia pathogenesis 359  
  defences 52–4, 83–90  
  immunological 86, 87–90  
  physical 83–5  
  protective proteins 85–7, 86  
  *see also* alveolar macrophage  
  development 1–4  
  inflammation, bronchiectasis  
  pathogenesis 801–4  
  structure 4–19  
  Wegener's granulomatosis 1067  
respiratory tract infections  
  asthma after 941–2  
  bronchiectasis pathogenesis 798–800, 801–4  
  children 624, 1478  
  as COPD risk factor 624  
  cystic fibrosis 853–4  
  diagnosis, bronchoscopy 150, 165–6  
  in HIV infection 1352, 1352  
  immunosuppressed patients *see*  
    immunosuppressed patients;  
    opportunistic infections  
  postoperative in lung cancer 1099  
  recurrent, cystic fibrosis 847–8  
  recurrent lower tract, bronchiectasis  
    aetiology 796, 798–9  
  rheumatoid disease 1389  
  symptoms 103  
  upper tract *see* upper respiratory tract  
    infections  
  viral *see* viral infections  
  *see also* specific infections/anatomical regions  
restlessness, terminal care 1533  
resuscitation, near-drowning 789  
reticuloendothelial system tumours 1124–33  
reticulum cell sarcoma 1127  
retinal oedema, tuberculosis 540  
retinitis, CMV, treatment 240–2  
retrobulbar neuritis 549  
retrognathia 1254  
retropharyngeal abscess 340  
retrospective study *see* case-control study  
retrosternal airspace, increased, COPD 658  
retrosternal goitre *see* goitre  
Rett's syndrome 1266  
reverse transcriptase 236  
reverse transcriptase inhibitors 236, 241  
  non-nucleoside 236, 239  
  nucleoside 237–9, 1361  
Reye's syndrome 338, 349  
rhabdomyolysis, pneumococcal  
  pneumonia complication 385  
rhabdomyosarcoma 1142  
rhDNase *see* DNase, recombinant human  
rheumatic fever 1160, 1396  
rheumatoid disease 1385–9  
  bronchiectasis association 802, 1389  
  bronchiolitis obliterans 833, 1388–9  
  coal workers 1411  
  pleural disease in 1385  
  pleural effusions 453, 1160, 1385  
  pulmonary fibrosis 1386–8, 1387, 1388  
  pulmonary hypertension 1389  
  pulmonary nodules 1385–6, 1386  
  respiratory tract infections 1389  
rheumatoid factor 802, 878  
rhinitis  
  genetics 94–5  
  haemorrhagic 1016  
  seasonal 943  
rhinorrhoea 343  
  watery, treatment 252  
rhinosinusitis *see* sinusitis  
rhinoviruses  
  common cold 335, 336  
  culture 337–8  
  infection prevention 244  
  pneumonia 418  
*Rhizopus* 598  
*Rhodococcus*, antibiotic sensitivity 223  
*Rhodococcus equi*  
  in HIV infection 1356  
  lung abscess 464  
rhonchi *see* wheeze  
ribavirin (tribavirin) 244, 416  
rib cage  
  diameter and motion, COPD 645  
  movement 1235, 1236  
  *see also* thoracic cage  
ribs  
  bifid 1212  
  bone cysts 1224–5  
  cervical 1212, 1213  
  chest radiography 121  
  congenital abnormalities 1212  
  cough fractures 955  
  defects 1221  
  fractures 121, 135, 1214, 1216  
  dry pleurisy with 1153  
  metastases 121, 122  
  movement 110  
  myeloma 1226  
  notching 1221, 1222  
  osteomyelitis 1226–7  
  pain 107  
  periostitis 575  
  slipping (clicking, rib tip) syndrome 1219  
  superior marginal defects 1221  
  thirteenth pair 1243  
  tumours 107  
*Rickettsia*, pneumonia 421–2  
*Rickettsia burnetii* *see* *Coxiella burnetii*  
rickettsioses 421–2  
rifabutin 223, 224–5, 569  
  tuberculosis 551, 551–2  
rifampicin (rifampin) 223–4, 546–8  
  absorption 546–7  
  activity/effectiveness 545–6  
  adverse effects 224, 547, 548, 1458  
  hepatotoxicity 548, 558  
  detection in urine 547  
  dosage 547  
  formulations/administration routes 547–8  
  interactions 224, 548  
  Legionnaire's disease 390  
  *Mycobacterium avium-intracellulare*  
  complex disease 569  
  Q fever 402  
  resistance 223, 570  
  *Staphylococcus aureus* pneumonia 405  
  tuberculosis regimens 553, 554, 557  
  use restricted to tuberculosis 560  
  uses 224  
Rifater 553  
Rifinah 553  
right heart failure 757  
  COPD 649–50  
  sleep apnoea/hypopnoea syndrome 1255  
right recurrent laryngeal nerve 7  
right ventricle  
  dimension assessment 649  
  enlargement, pulmonary hypertension 753, 754

- right ventricular function  
   assessment 650  
   in COPD 649–50  
 right ventricular hypertrophy  
   COPD 633, 647  
   cor pulmonale 750  
   prevalence 648  
 rigors, pneumococcal pneumonia 377  
 Rimactazid 553  
 rimantadine 242, 242, 349, 350  
 rimiterol 247, 977  
 risk assessment, pulmonary embolism 740  
 ritonavir 239  
 road traffic accidents, sleep apnoea causing 1254  
 rock wool 1435  
 Rocky Mountain spotted fever 421  
 roxithromycin 207, 395  
 rubber, latex, occupational asthma 951  
 Runyan classification 566, 567  
 Russian flu 347
- saccharin screening test, ciliary function 4, 84–5  
 salbutamol  
   asthma 977  
   doses and half-life 247, 248  
   intravenous, acute severe asthma 986–7  
   parenteral 247  
   slow-release formulations 977  
   structure 245  
 saline, bronchoalveolar lavage 162  
 saliva  
   aspiration and lung abscess 460  
   flora 460  
 salmeterol  
   adverse effects in asthma 249  
   asthma treatment 977  
   structure 244  
*Salmonella*, pneumonia 422  
*Salmonella enteritidis*, empyema 449, 454  
 salt  
   balance, COPD 650, 651  
   intake, asthma and 946  
 saquinavir 239  
 ‘sarcoid’ 1035  
 sarcoid follicles 1042  
 sarcoidosis 1035–62  
   aetiology 1039–40  
   alveolar macrophage 1042–3  
   berylliosis *vs* 1437  
   bronchial 1049  
   chronic 1042  
   chronic fibrotic (upper tract) 1050  
   clinical presentation modes 1044–53, 1049  
   as communicable disease 1038, 1039–40  
   CT 1056  
   definition 1035  
   epidemiology 1036–9  
     incidence and prevalence 1036–7, 1037  
   extrathoracic 1049–53  
     treatment 1058  
   granuloma 1039, 1040, 1041, 1041–2, 1051, 1052, 1054  
     formation 1042–3, 1043  
     Kveim biopsy 1054  
   historical background 1035–6, 1036  
   HLA associations 1038–9  
   immunology 1042–4  
   interstitial lung disease due to 889  
   investigations 1053–7
- biopsy 1055, 1055, 1057  
   chest radiography 140, 1045, 1046, 1047, 1048  
   fiberoptic bronchoscopy 164  
   gallium-67 scanning 1056  
   Kveim test *see* Kveim test  
   lung function tests 1053  
   serum angiotensin-converting enzyme 1055–6  
   strategy 1056–7  
   lung cancer and 1080  
   lymphocytes 1042  
   nodules 143–4, 1050  
   pathology 1040–2, 1041, 1042  
   pleural 1049  
   pleural effusions 1161  
   pulmonary 1045–9  
   pulmonary opacities 1045, 1047, 1049  
   recurrence after transplantation 1040  
   thoracic 1044–9  
     stages 1046  
     treatment 1057–8  
   transbronchial lung biopsy 149  
   treatment 1053, 1057–8  
   unitarian concept 1054–5  
 sarcoma  
   chest wall 1223  
   Kaposi’s *see* Kaposi’s sarcoma  
   lung 138  
   neurogenic 1274  
   osteogenic 1226  
   pleural 1172–3  
   reticulum cell 1127  
*Sauropus androgynus* 832  
 scalene node biopsy 113  
 ‘scar cancers’ 523, 1079–80  
 Schaumann bodies 1040–1  
*Schistosoma* 604, 610  
*Schistosoma haematobium* 610, 611  
*Schistosoma japonicum* 610, 611  
*Schistosoma mansoni* 610  
 schistosomiasis 610–11  
 Schwann cells 1272  
 Schwannoma 1272–3, 1273–4  
 scimitar sign 2, 4  
 scimitar syndrome 1321–2  
 scimitar vein 1321  
 scleroderma 1392  
 scleroderma-like syndrome, drug-induced 1393  
 sclerosing pneumocytoma (haemangioma) 1137  
 scoliosis 1216–18  
   aetiological classification 1216, 1216–17  
   clinical features and treatment 1218  
   idiopathic 1216  
   paralytic 1217  
   physiology 1217–18  
   ‘scratch test’ 1190  
 screening 79–80  
   antenatal *see* antenatal screening  
   cystic fibrosis 848, 850  
 scrofuloderma 539  
 scrotal swelling, tuberculosis 538  
 scrub typhus 422  
 scuba diving 1188, 1481  
   *see also* diving  
 seasonal factors, pneumonia 357, 376, 386  
 secretory leukoprotease inhibitor (SLPi) 86, 87  
 sedatives  
   avoidance in asthma 985  
   avoidance in type II respiratory
- failure 702  
   fiberoptic bronchoscopy 152–3  
     complications 168–9  
   for mechanical ventilation 706  
   respiratory failure due to 709  
   terminal care 1533  
 sedimentation, particles 1406  
 seizures 226  
   analeptic drug adverse effect 280  
   theophylline causing 255  
 selectin family 910  
 selenium, asthma prevention 900  
 seminoma 1284  
   mediastinal 1288–90, 1289  
   testicular 1285  
 sepiolite 1435  
 sepsis, adult respiratory distress syndrome after 773  
 septic arthritis, chest wall 1227  
 septic emboli, lung abscess formation 461  
 septum transversum 1234  
 sequoiosis 1013  
 serine proteinases, inhibitors,  $\alpha_1$ -antitrypsin 635  
 serological tests  
   common cold 337  
   *Mycoplasma pneumoniae* 394  
   pneumonia 363–4  
   tuberculosis 520  
 serosal cysts (pleuropericardial cysts) 1295–6, 1296  
 serotonin *see* 5-hydroxytryptamine (5-HT; serotonin)  
 serous cells 12, 13  
 serous tubules 13  
 serpin family 87, 97  
*Serratia marcescens*, pneumonia 409–10  
 serum sickness, penicillins causing 194  
 severe combined immunodeficiency (SCID) 97  
 sewage sludge fever 1444  
 sex differences  
   asthma 895  
   COPD prevalence 617  
   sarcoidosis 1037–8  
 shale industry 1434  
   estimated risks of death 72  
   longitudinal studies involving 72  
   lung cancer studies 70, 70, 71  
   shift work, sleep disorders and 1256  
   ‘shock lung’ 770  
 short neck syndrome 1309  
 shoulder, pain referred to 107, 1153  
 ‘shrinking lung’ 1389  
 shunting, bronchiectasis 806, 808  
 shunts 32  
   absent pulmonary artery trunk 1319  
   arteriovenous malformations 1325  
   bronchiectasis 806, 808  
 shunt theory, clubbing and HPOA 112–13  
 Shwachman–Kulczycki score, cystic fibrosis 851, 852  
 Shwachman score 851, 852  
 Shwachman’s syndrome 1384  
 sibling-pair analysis 93, 93  
 sick building syndrome 1444  
 sickle cell disease 1382–4  
 sickle cell trait 1382, 1383  
 siderosis 1435, 1436  
 sigh, positive-pressure ventilators 1496  
 sighing breathlessness 1267  
 ‘signet ring’ sign 146  
 signs of respiratory disease 109–16

- silhouette sign 128, 130
- silica exposure
  - dust standard 1424
  - silicosis relationship 1417–18
  - workplaces 1416, 1416
- silica flour 1416
- silicates
  - diseases due to 1433–5
  - fibrous 1434–5
  - non-fibrous 1433–4
  - synthetic fibres 1435
- silicon carbide 1440
- silicon dioxide *see* silica exposure
- silicosis 1404, 1416–24
  - accelerated 1418, 1421, 1422
  - acute and chronic types 1418, 1421
  - asbestosis with 1429
  - chest radiography 1418–21, 1419, 1420, 1421
  - clinical features 1418–21
  - complications 1422
  - epidemiology 1416–18
  - lung function 1421–2
  - management and prevention 1423–4
  - pathogenesis 1423
  - pathology 1422, 1423
  - progressive massive fibrosis 1419, 1421–2, 1422
  - reactivation of tuberculosis 514
- silicotic nodules 1422, 1423
- silofiller's lung 1003, 1012, 1447
- silver polishers 1435
- singer's nodules 8
- single-breath analysis
  - anatomical dead space measurement 27
  - COPD 627, 656
  - cryptogenic fibrosing alveolitis 886
- single-breath nitrogen test, COPD 627
- Sin Nombre (SN) virus 418–19
- sinus disease, cystic fibrosis 848, 855
- sinus infections, chronic, panbronchiolitis 831
- sinusitis 341–5
  - acute 341–2
  - allergic fungal 342, 345
  - bronchiectasis complication 823
  - causes and causative organisms 341, 342
  - chronic 342, 344, 823
  - clinical manifestations 342–3
  - common cold complication 338
  - complications 345
  - cystic fibrosis 848, 855
  - fungal 342, 344
  - intractable 342
  - investigations 343, 343–4
  - treatment 198, 344–5
  - surgical 345
- sinus surgery, endoscopic 345
- Sjögren's syndrome 1395
  - bronchiectasis association 803
- skeletal muscles, low-frequency fatigue 49, 49
- skin
  - cancer 1434
  - sarcoidosis 1050
  - tuberculosis 539
  - Wegener's granulomatosis 1068
- skin-prick tests 194, 961
- skin testing
  - opportunistic mycobacterial disease 568
  - tuberculin *see* tuberculin skin testing
- skull radiograph, Langerhans' cell histiocytosis 1131
- sleep
  - arousal triggered by respiratory effort 1252, 1257
  - COPD assessment 657
  - impairment in COPD 652
  - insufficient 1256
  - paralysis 1255
  - quality and duration assessment 1257
  - REM 281
  - studies 1256–7
  - thoracoabdominal movements recording 1257
  - unrefreshing 1253
- sleep apnoea/hypopnoea syndromes (SAHS) 5, 281, 1229, 1250–63
  - British guidelines on training 1261
  - central 1257, 1261
  - clinical features 1253, 1253–4
  - consequences 1254–5
    - of airway narrowing 1252–3, 1253
  - death due to 1254
  - definition 1250
  - diagnosis 1256–9
  - differential diagnosis 1255–6
  - epidemiology 1250–1
  - historical aspects 1250
  - hypopnoea detection 1257, 1258
  - mechanisms of airway narrowing 1251, 1251–2, 1253
  - patient characteristics 1254, 1258
  - patients at risk 1258–9
  - protriptyline use 281
  - terminology and 1257
  - training 1261
  - treatment 1259–61
- sleep attacks 1253
- sleep laboratories 1257, 1258
- sleeplessness, relief in terminal care 1532
- 'sleeve resection' of tumour 1099
- 'slim disease' 529
- slipping rib syndrome 1219
- slow reacting substance of anaphylaxis 261
- small airway function tests 653
- small bowel
  - obstruction 537
  - tuberculosis 537
- small-cell lung cancer (oat-cell) 1083, 1083–4
  - clinical features 1085
  - combined histological subgroup 1083
  - metastases 1095, 1147
  - peptide hormones 1110, 1110
  - prognosis 1117, 1118
  - staging 1098
  - survival time 1105, 1106
  - treatment 291, 1104–10, 1105
    - chemotherapy 1104–8
    - complications 1107
    - high-dose chemotherapy 1106
    - palliative 1107–8
    - radiotherapy 1108–9
    - surgery 1109–10
    - vinca alkaloids 290
- smallpox workers' lung 1016
- smogs 324, 329, 898
- smoke
  - mutagenic action 98
  - oxidant effect 638
  - see also* cigarette smoke
  - smoke inhalation 1449
  - acute and long-term effects 1449
  - allergic alveolitis due to 1016
- see also* inhalational injury
- smokers' bronchiolitis 830–1, 831
- smoking 311–23
  - acute-on-chronic bronchitis 345
  - airway responsiveness increase 625, 898
  - airways resistance after 622
  - $\alpha_1$ -antitrypsin deficiency and 623
  - asbestos synergy 311, 1426
  - asthma aetiology 897–8, 942, 947–8, 951
  - avoidance in  $\alpha_1$ -antitrypsin deficiency 95
  - banning 314
  - bronchiolitis 830–1, 831
  - carboxyhaemoglobin levels 36
  - cessation 311, 314–18
    - advice to patients 315, 316
    - benefits 312
    - booklets/leaflets 317
    - clinics 317–18
    - COPD prevention 662–3, 668
    - cough resolution 651
    - counsellor 317
    - effect on COPD 627
    - effect on FEV<sub>1</sub> 621, 621, 662–3
    - in general practice 314–16
    - hospital patients 316–17
    - lung cancer risk decline 1077
    - mass media methods 318
    - other clinical settings 317
    - quit rates 315
    - strategy 663, 663
    - trials 316
    - workplace 319
  - children and 314, 319
  - chronic bronchitis and 621, 621
  - cigar *see* cigar smokers
  - coal dust additive effect 1414–15
  - COPD risk factor *see* chronic obstructive pulmonary disease (COPD)
  - cough and sputum prevalence 103, 619
  - cryptogenic fibrosing alveolitis aetiology 878
  - in developing countries 319–20
  - elastase–antielastase imbalance 636, 637
  - elastin synthesis decreased 636
  - forced expiratory volume in 1 s (FEV<sub>1</sub>) 620, 626–7
  - goblet cell increase 628
  - Goodpasture's syndrome 1331
  - harm caused by 311–13
  - harm to non-smokers *see* passive smoking
  - history, COPD 651
  - IgE levels and 625
  - lung cancer association *see* lung cancer
  - maternal 313, 898
  - mechanisms of harm 313
  - mortality 311, 319, 621
  - neutrophil changes 629, 637
  - passive *see* passive smoking
  - pipe *see* pipe smokers
  - in pregnancy 1477
  - prevalence (UK) 318
  - prevention strategy 663
  - reactivation of tuberculosis 515
  - reasons for 311
  - safer cigarettes 318–19
  - spontaneous pneumothorax link 1184–5
  - trends 1078
  - weight and 319
  - in workplace 319
- smooth muscle, airways *see* airway smooth muscle

- smooth muscle relaxation  
  anticholinergic bronchodilators 250  
  theophylline 253  
smooth muscle relaxing factor *see* nitric oxide  
snoring 1251, 1253–4  
  patient types 1258  
  recording devices 1258  
social factors  
  asthma and 896  
  COPD prevalence 619  
  smoking and lung cancer 1078  
  tuberculosis 496  
sodium  
  absorption, airways epithelium 844  
  bronchial responsiveness increased 900  
  retention, corticosteroid-induced 271  
  sweat 844, 849, 849  
sodium cromoglycate (sodium cromoglicate) 256–7  
  administration and excretion 256–7  
  adverse effects 257, 1458  
  asthma treatment 979  
  bronchoconstriction due to 1460  
  dosage and modes of use 257  
  mode of action 256  
  nedocromil sodium comparison 258  
  structure 256  
sodium fusidate (fusidic acid) 225  
sodium–potassium ATPase 844  
sodium valproate 1528  
soft tissues  
  chest radiography 121  
  sarcoidosis 1052  
  tumours, chest wall 1221–3, 1222  
soil, fungal spores 575  
somnolence, daytime *see* daytime somnolence  
soot 325  
sore throat 339  
  causes 337  
  persistent 351  
  treatment 338  
soybean, allergens 897, 898  
space-occupying lesions, CNS tuberculosis *vs* 529  
spacers 246, 279, 989  
  large-volume 987, 989  
  'tube' 989  
Spanish flu 347  
Spanish toxic oil syndrome 1393, 1471–2  
Sp-A protein 85  
sparfloxacin 225  
spa-whirlpools, *Legionella* infections after 387  
sperm 795  
sphenoidal sinuses 5, 341  
sphenoidal sinusitis 343  
spherulin 579  
sphingolipidoses 1384  
spinal canal, tumours 107  
spinal cord compression  
  mediastinal tumours 1271  
  pain relief 1528  
  schwannoma and neurofibromas causing 1273  
  tumours 1102  
spinal tuberculosis 533, 534  
  metastatic disease *vs* 534–5  
  radiography 535  
spine, immobilization 535  
Spinhaler 989  
spirometry 29, 29  
COPD 653, 654  
  daily, after lung transplantation 1520  
  epidemiological studies 76  
splenectomy, antibiotic prophylaxis after 383  
splenomegaly, tuberculosis 537  
splenosis pleurae 1178  
spores, fungal *see* fungi  
*Sporothrix schenckii* 586  
sporotrichosis 586  
  treatment 230, 231  
spotted fever group 421  
springwater cysts (pleuropericardial) 1295–6, 1296  
sputum 14, 104–5  
  allergic bronchopulmonary aspergillosis 588, 590  
  alveolar macrophage 54  
  'anchovy sauce' 105, 605  
  *Aspergillus fumigatus* in 953, 954  
  asthma 927–8  
  blood-stained *see* haemoptysis  
  bronchiectasis 104, 806, 809  
  bronchioloalveolar cell carcinoma 1529  
  clearance mechanisms, disruption in bronchiectasis 818  
  collection method, suction devices 362  
  colour and consistency 105  
  components 927  
  contamination by oropharyngeal flora 809  
  culture 380  
    anaerobes 413  
    fungal infections 105  
    lung abscess 467  
    pneumonia 361–2  
  cystic fibrosis 865  
  cytology  
    bronchoscopy indication 149  
    in haemoptysis 106  
    lung cancer 1082–3, 1089–90  
  definition 927  
  eosinophils 928, 961, 1022, 1023, 1025  
  foul-smelling 449  
  Gram staining 361  
  history-taking 105  
  immunodetection, pneumonia 361  
  in immunosuppressed patients 1348  
  induced  
    analysis in *Pneumocystis carinii* pneumonia 1368  
    COPD 628, 629  
    method 361, 928, 1368  
  interstitial lung disease 888, 889–90  
  Loeffler's syndrome 1022, 1023  
  mast cells 928  
  microscopy, pneumonia 360  
  mucopurulent 360–1, 806, 809  
  pathogens in 361  
  pneumococcal antigen test 380  
  pneumonia cause diagnosis 361  
  production 104  
    management 105  
  rusty-brown, pneumococcal pneumonia 378  
  saliva contamination 928  
  salivary specimen *vs* 361  
  sarcoidosis 1056  
  smear examination 518–19  
  smell 105  
  specimens 105  
  Staphylococcal pneumonia 404  
  tuberculosis 517  
  postprimary pulmonary 518–19  
  primary pulmonary, diagnosis 509  
  smear and culture negative 520  
  transmission by 478  
  viscosity in cystic fibrosis 865  
  viscous, asthma 927, 941  
  volume 104  
squamous cell carcinoma, lung 1081–2, 1082, 1085  
staphylococcal pneumonia 402–6  
  chest radiograph 403, 404  
  complications 405–6  
  epidemiology and incidence 402–3  
  investigations 403–4  
  mortality 405  
  nosocomial 402  
  pathology and clinical manifestations 403  
  prevention 406  
  treatment 369, 404–5  
    methicillin-sensitive *S. aureus* 369, 404–5  
staphylococci 402  
  coagulase-negative 404  
  coagulase-positive 219, 402, 404  
  encapsulated and unencapsulated 402  
*Staphylococcus aureus* 402  
  age influence on infections 448  
  antibiotic resistance 402, 404  
  antibiotic sensitivity 219, 454  
  bacteraemia 403, 405, 406  
  bacterial croup 347  
  characteristics 402  
  cystic fibrosis 854  
  defence mechanisms against 403  
  empyema 447, 448, 454  
  hospital-acquired pneumonia 371  
  lung abscess 461, 463  
  methicillin-resistance *see* methicillin-resistant *Staphylococcus aureus* (MRSA)  
  methicillin-sensitive, pneumonia treatment 369, 404–5  
  penicillin resistance 404  
  pneumonia *see* Staphylococcal pneumonia  
  reservoir and carriers 402  
  in sputum, bronchiectasis 809  
  vancomycin insensitive 219  
*Staphylococcus pyogenes*, lung abscess 522  
Starling equation 766  
Starling resistors 31  
statistics, epidemiological studies 71  
status asthmaticus 952  
stavudine (d4T) 238  
steatocrit test 849  
Steel's technique, trephine biopsy 177–8  
*Stenotrophomonas (Xanthomonas) maltophilia* 854  
stenting  
  superior vena cava obstruction 1114  
  tracheobronchial narrowing 151  
sternoclavicular joints, synostosis 1219  
sternocostoclavicular hyperostosis 1219–21  
sternomastoid muscle  
  low-frequency fatigue 49  
  prominence 111  
sternum  
  congenital abnormalities 1214  
  depressed 1214, 1215  
  elevation in COPD 652  
  hyperostosis 1219

- sternum (*Continued*)  
 osteomyelitis 1227  
 steroid cards 984  
 steroid myopathy 270, 1229  
 steroids 259  
   high-dose, obliterative bronchiolitis 836  
   *see also* corticosteroids;  
     glucocorticosteroids  
 Stevens–Johnson syndrome (erythema  
   multiforme) 210, 396  
 stonemasons 1416, 1417, 1418, 1420, 1421  
 straight back syndrome 1214  
 stramonium 249  
 streptococci  
   group A, pneumonia 419  
   group A  $\beta$ -haemolytic 419  
   viridans group 462–3  
*Streptococcus anginosus*, lung abscess 466  
*Streptococcus intermedius* (milleri) 447, 462  
*Streptococcus pneumoniae*  
   acute sinusitis 342  
   antibiotic susceptibility 196, 204, 206  
   tetracyclines 210, 211, 212  
   antigenic types and mortality 384  
   appearance 374  
   carrier rates 377  
   ‘carrier’ types and ‘infective’ types 377  
   ciliary activity inhibition 809  
   in COPD 674–5  
   distribution and carriage 376, 377  
   empyema 447, 448, 454  
   penicillin resistance 380, 381, 384  
     cross-resistance 384  
     relative not absolute 384  
   phagocytosis 375  
   pneumonia *see* pneumococcal  
     pneumonia  
   serotypes 375  
   in sputum, bronchiectasis 809  
*Streptococcus pyogenes*  
   antibiotic susceptibility 204  
   lung abscess 463  
   pharyngotonsillitis 339  
   pneumonia 419  
 streptokinase  
   dosage and administration 739  
   empyema treatment 456  
   pulmonary embolism 738–9  
 streptomycin 212, 549  
   adverse effects 547, 549  
   dosage 547  
   *M. avium-intracellulare* complex disease  
     569  
   *M. tuberculosis* resistance 544  
   pneumonic plague 425  
   tuberculosis regimens 544, 553, 554, 558  
   tularaemia 421  
 stress  
   corticosteroid adverse effects 272, 275  
   hyperventilation and 1267  
 striae 268  
 stridor 109, 110, 155  
 stroke 1266  
   smoking and 312  
   *see also* cerebrovascular disease  
*Strongyloides stercoralis* 609  
 strongyloidiasis 609–10  
 subarachnoid haemorrhage, smoking and  
   312  
 subclavian vein cannulation 1187  
 subcutaneous nodules, sarcoidosis 1050  
 suberosion 1013  
 submandibular lymphadenitis,  
   tuberculosis 531, 531  
 submarine escape trainees 1484, 1489–90  
 submucosa 13  
 submucosal glands  
   increase in chronic bronchitis 628  
   ion transport 845  
 subphrenic abscess 1239–40  
 subphrenic infections 1160  
 subpulmonary (intrapulmonary) effusion  
   133  
 substance P, bronchoconstriction 938  
 suction drainage, empyema 456  
 sudden infant death syndrome 313, 1255  
 sulfadiazine  
   glanders 424–5  
   nocardiosis 577  
   toxoplasmosis 607  
 sulfamethoxazole 207–8, 209  
 sulphasalazine (sulfasalazine)  
   alveolitis due to 1463  
   bronchiolitis obliterans due to 1460  
 sulphhaemoglobinaemia 110  
 sulphonamides 209  
   alveolitis 1461, 1463  
   polyarteritis nodosa associated 1028  
 sulphur dioxide 1448  
   asthma trigger 947  
   health effects and mechanisms 330  
   as irritant 330, 1448  
   as pollutant 327, 330, 622, 1448  
 sulphur granules 448, 452, 576, 576  
 sultamicillin (ampicillin–sulbactam) 197  
 superior laryngeal nerve 7  
   paralysis 7  
 superior sulcus tumours 1114–15  
   *see also* Pancoast’s syndrome  
 superior vena cava, lung drainage via 1322  
 superior vena cava obstruction 113, 1049  
   features and diagnosis 1113  
   lung cancer 1087, 1113–14  
   mediastinal fibrosis 1303, 1304  
   treatment 1113–14  
 superior vena cava syndrome 113–14  
 supernumerary arteries 1  
 superoxide anion 1467  
 superoxide dismutase 1467  
 suppurative lung disease  
   empyema pathogenesis 446  
   fiberoptic bronchoscopy 156  
   secondary spontaneous pneumothorax  
     1185  
 supraglottitis, acute (epiglottitis) 340  
 surfactant 18–19, 40–1, 85, 767  
   ARDS pathophysiology 782  
   composition 18, 41, 783  
   damage 85  
   deficiency/absence 19, 40–1, 712  
   exogenous therapy, ARDS 784–5  
   functions 18–19, 85, 782  
   preparations 713  
   protein B absence 96  
   proteins 85  
   replacement 41  
   reprocessing, failure 1334  
   Sp-A, Sp-D proteins 783, 1334  
   Sp-B, Sp-C proteins 783  
   storage 712  
   synthesis 2, 19, 40–1, 712  
     by pneumocytes 85  
 surgery  
   asthma management 992  
   bronchiectasis 820–1, 823  
   deep venous thrombosis prevention  
     after 741, 742  
   empysematous bullae 662  
   empyema pathogenesis 446  
   intracranial metastases 1115  
   low-dose heparin after 741  
   low molecular weight heparin after 742  
   lung abscess 473  
   lung cancer 1099–100, 1103–4  
     mortality 1099  
     small-cell 1109–10  
   radiotherapy and chemotherapy with  
     1103–4  
   scoliosis 1218  
   thrombosis predisposition 719  
   video-assisted thoracoscopic (VATS)  
     1200–2, 1201  
 Survey of Work-Related and Occupational  
   Diseases (SWORD) 67  
 SV40, DNA sequences in mesothelioma  
   1174  
 swallowing 5  
   difficulty *see* dysphagia  
 sweat 844  
   composition 844, 849, 849  
 sweat glands, ion transport 844  
 sweating  
   acute asthma 952  
   night, tuberculosis 516  
 sweat test 844, 848–9  
 swimmers’ itch 611  
 SWORD project/survey 999, 1000, 1079,  
   1405, 1446  
 Swyer–James and MacLeod’s syndrome  
   395–6, 832  
 sympathetic control, asthma 931, 938  
 sympathetic nerve supply 22–3  
 sympathetocoblastoma 1272  
 sympathomimetic bronchodilators 244–9  
   administration 246–7  
   adverse effects 248  
    $\beta_2$ -selective 245  
     *see also*  $\beta_2$ -agonists  
   dosage 247, 249, 249  
   duration of action 245  
   groups 244  
   inhalation 246–7  
   metabolism and excretion 247–8  
   mode of action 245–6  
   non-selective 245  
   oral therapy 247, 247  
   parenteral therapy 247  
   potency 246  
   selectivity 244–5  
   structures 244, 244  
   uses/indications 249  
 sympathomimetic drugs, pulmonary  
   oedema due to 1465  
 symptoms, of respiratory disease 102,  
   103–9  
 synchronized intermittent mandatory  
   ventilation (SIMV) 705, 1499  
 syncope, cough 103  
 syndrome of inappropriate antidiuretic  
   hormone secretion (SIADH) 1111  
 synovialoma, malignant 1223  
 syphilis 7, 1398  
 syphilitic gumma 1227–8, 1398  
 syringe drivers 1527  
 systemic lupus erythematosus (SLE)  
   1389–92  
   acute diffuse pulmonary haemorrhage  
     1391  
   causes, diagnosis and incidence 1389



- chronic interstitial fibrosis 1391  
 drug-induced 1462, 1462  
 lupus pneumonitis 1390–1  
 pleurisy and pleural effusions 1160–1,  
 1389–90, 1390  
 pulmonary hypertension 757  
 pulmonary manifestations 1389–92  
 pulmonary syndromes 1392  
 tetracycline effect 211  
 'vanishing lung' syndrome 1391–2  
 systemic sclerosis  
   aetiology and pathogenesis 1393  
   pulmonary fibrosis 1393, 1394  
   pulmonary hypertension 1393–4  
   pulmonary manifestations 1392–5  
   treatment 1394–5  
 systemic-to-pulmonary shunting *see* shunts
- tachycardia 255, 952  
    $\beta_2$ -agonists causing 248  
 tachypnoea  
   ARDS 783  
   COPD 652  
   pneumococcal pneumonia 378  
*Taenia solium* 614  
 talc 1433  
   diseases due to 1433  
   glove powder, asthma 962  
   pleurodesis 185, 1165, 1200  
 talc miners 1433  
 tank ventilation 1508, 1508  
 tapered element oscillating microbalance  
 (TEOM) 325  
 target population 65  
 tartrazine 946, 1458  
 taxanes 294  
 Tazocin (piperacillin–tazobactam) 199–200  
 T-cell lymphoma, nasal (midline  
 granuloma) 1070–1  
 T-cell receptor,  $\alpha\delta$ , genetics and 95  
 T cells  
   allergic alveolitis pathogenesis 1006–7  
   asthma pathogenesis 912, 934  
   BAL fluid, COPD 628–9  
   bronchiectasis pathogenesis 801  
   cryptogenic fibrosing alveolitis 881  
   deficiency 97  
   helper to suppressor cell ratio,  
   sarcoidosis 1043  
   reduced by glucocorticosteroids 262  
   shift to Th1 cells, by infections 934  
   shift to Th2 cells  
     asthma pathogenesis 912, 934, 940  
     cryptogenic fibrosing alveolitis 881  
   suppressor, soluble protein in allergic  
   alveolitis 1007  
   Th1 cells 934  
     cytokines 912, 934  
     tuberculosis 481  
   Th2 cells 934  
     cytokines 912, 934  
     in fetus 934  
   tuberculosis 481  
   *see also* CD4 T cells; CD8 T cells
- teeth, tetracycline effect 211  
 Teflon 1449  
 teicoplanin 219, 220–1, 405  
 telangiectasia  
   hereditary haemorrhagic 97–8, 1140,  
   1322–6  
   pulmonary *see* pulmonary telangiectasia  
 temafloxacin 225  
 temocillin 200
- temperature, body, pneumococcal  
   pneumonia 377–8, 378  
 tension–time index, diaphragm 645  
 teratocarcinoma 1284, 1287  
 teratogenicity, metronidazole 217  
 teratoma 1143, 1283–4  
   benign mediastinal 1285–7, 1286  
   immature 1287  
   mature cystic 1285–7  
 terbutaline  
   acute severe asthma 987  
   asthma 977  
   controlled-release 247  
   doses and half-life 247, 248  
   parenteral 247  
   slow-release formulations 977  
   structure 245  
 terminal bronchioles 15  
   number 3, 9, 829  
   obstruction 800, 800  
   structure 9  
 terminal care in respiratory disease  
   1524–35  
   organization 1533–4  
   psychological aspects 1533  
   stepwise approach to telling patients  
   1524  
   symptom relief 1525–33  
     constipation 1531  
     cough 1529  
     dehydration 1530–1  
     dyspnoea 109, 1529–30  
     haemoptysis 1531  
     miscellaneous 1531–3  
     pain *see* pain relief  
   truthful explanation 1524–5  
 terminal saccules, development 2  
 testicular tumours 1285, 1288, 1289  
 tetanus, respiratory failure 711–12  
 tetracosactrin (Synacthen) 266  
   short test 272  
 tetracyclines 210–12  
   administration, distribution and  
   excretion 211  
   adverse effects and interactions 211–12  
   chemical pleurodesis using 212, 1200  
   empyema 454  
   lung abscess 472  
   *Mycoplasma pneumoniae* 395  
   principal uses 212  
   resistance 211  
   spectrum of activity 210, 211  
   structure 210, 211  
 Thebesian veins 33  
 theophylline 252–6  
   administration 253–4  
   adverse effects 255, 255–6, 978  
   anti-inflammatory properties 978, 979  
   asthma treatment 978–9  
   bronchodilator action 665  
   COPD 646, 664, 665, 666  
   diving contraindication 1492  
   drug interactions 226  
   excretion 253, 253  
   intravenous dosing and plasma levels  
   254–5  
   metabolism 253–4, 666  
   mode of action 252–3  
   modified loading dose 255  
   narrow therapeutic index 665  
   oral dosing and plasma levels 254  
   overdosage 256  
   respiratory stimulant 282
- sustained-release forms 254  
 therapeutic range 254, 255  
 uses/indications 256  
 thermistor 749  
*Thermoactinomyces vulgaris* 1011  
 thermomodulation 749  
 thiabendazole 609, 610  
 thiacetazone, tuberculosis 550, 550  
 thoracentesis 455  
 thoracic cage  
   ankylosing spondylitis 1396  
   deformities, asthma 955  
   fixation, ankylosing spondylitis 1218  
   tumours 1222, 1223–6  
   *see also* rib cage  
 thoracic duct  
   anatomy 1165–6  
   cyst 1296  
 thoracic empyema *see* empyema  
 thoracic endometriosis syndrome 1186  
 thoracic outlet syndrome 1212  
 thoracic surgery, contraindication to diving  
   1490  
 thoracic vertebrae, chest radiography 122  
 thoracoabdominal movements, recording  
   in sleep 1257  
 thoracoplasty 1228, 1228  
   empyema 458  
   tuberculosis treatment 546  
 thoracoscope, rigid 184  
 thoracoscopy  
   pleural biopsy 184–5  
   procedure 184–5  
   talc pleurodesis 185  
 thoracostomy  
   closed-tube 455–6  
   open-window 457  
 thoracotomy  
   'limited' 179  
   lung abscess 473  
   open lung biopsy 179  
   peripheral mass lesion and biopsy 181  
   pneumothorax 1200  
 thorax, barotrauma 1486  
 throat irritation, inhaled corticosteroid  
   side-effect 982  
 thrombocytopenia  
   *Coxiella pneumoniae* 401  
   ganciclovir causing 241  
   transbronchial lung biopsy and 168, 169  
 thrombocytopenic purpura, rifampicin  
   effect 548  
 thromboembolic pulmonary infarction,  
   lung abscess formation 461  
 thrombogenesis 720–1  
 thrombolytic therapy 114  
   adverse effects 739  
   contraindication 739  
   empyema 456  
   patient selection for 739  
   pulmonary embolism 738–9  
 thrombomodulin 718  
 thrombophilia  
   acquired 743  
   hereditary 719, 720  
 thrombophlebitis  
   amphotericin causing 229  
   superficial 721  
 thrombophlebitis migrans 720  
 thrombosis  
   factors predisposing to 719–20  
   mechanisms 718–19  
   oral contraceptives and 720

- thrombosis (*Continued*)  
   *see also* deep venous thrombosis  
 thromboxane A<sub>2</sub>, inhibition by aspirin 742  
 thromboxanes, ARDS pathogenesis 778  
 thrombus, red 721  
 thrush 595  
   inhaled corticosteroid side-effect 981  
   oral 339  
 thymectomy 1280, 1282  
 thymidine kinase 234  
 thymolipoma 1283  
 thymoma 1279–80, 1281, 1282  
 thymus gland 1278–9  
   cysts 1282–3, 1284  
   disorders 1278, 1278–83  
   myasthenia gravis and 1280–2  
   hypoplasia 1279  
   lymphoid follicular hyperplasia 1279  
   lymphomas 1283  
   masses 1283  
   normal, radiography 1279  
   'rebound' hyperplasia 1279  
   tumours 1279–80, 1283  
 thyroid cartilage 6  
 thyroid gland  
   embryology 1296–7  
   retrosternal extension 8, 8  
 tiabendazole (thiabendazole) 1240  
 tic, diaphragmatic 1239  
 ticarcillin 199, 453  
 ticarcillin–clavulanate 199–200  
 tidal breathing  
   asthma 955  
   COPD 645  
   diaphragm function 1235  
   normal 644  
 tidal volume 26, 55  
   reduction, cryptogenic fibrosing  
     alveolitis 886  
   ventilators 705  
 Tietze's syndrome 1221  
 tight junctions 16, 21, 766  
 Tine test 492  
 tinidazole 218  
 tin miners 1440  
 'tipping,' bronchiectasis treatment 818  
 tissue  
   modelling and repair, alveolar  
     macrophage 90  
   necrosis, doxorubicin 289  
 tissue inhibitor of metalloproteinases 87  
 TNM classification, lung cancer 1097–8,  
   1098  
 tobacco  
   advertising 662  
   market 319  
   substitutes 319  
   *see also* smoking  
 tobramycin 213, 216, 818  
 tocinide, alveolitis due to 1463  
 tolerance, to drugs, induction 1467  
 toluene diisocyanate vapour 932, 1004  
 tomography  
   computed *see* computed tomography  
     (CT)  
   linear 127  
 tongue worms 614  
 tonsillitis 338–40  
   *see also* pharyngotonsillitis, acute  
 tonsils, enlarged 1254  
*Torulopsis glabrata* 598  
 torulosis *see* cryptococcosis  
 total airways resistance, increased in  
   COPD 641  
 total lung capacity (TLC)  
   calculation 29  
   COPD 641  
 totally implantable venous access device  
   (TIVAD) 859, 865  
 total parenteral nutrition, pneumonia 373  
 toxic bronchiolitis 830, 836  
 toxic epidermal necrolysis 550  
 toxic fumes and vapours 1445, 1448–9  
 toxic gases 1444–9, 1445  
   asphyxiant 1444–6  
   obliterative bronchiolitis due to 832  
   *see also* irritant gases  
 toxic oil syndrome 1393, 1471–2  
 toxic shock syndrome 403  
 toxins, childrens' lung sensitivity 1478  
*Toxocara canis* 609  
*Toxocara cati* 609  
*Toxoplasma gondii* 606  
 toxoplasmosis 606–7  
 trachea  
   agenesis (aplasia) 1309  
   bifurcation 8  
   chest radiography 120–1, 1090  
   development 1, 2  
   deviation 114, 1090  
     retrosternal goitre 1297  
   displacement 1223  
   extrathoracic narrowing 8  
   fiberoptic bronchoscopy 155  
   intrathoracic obstruction 8  
   length and mobility 8  
   mucous membrane 8  
   narrowing  
     due to extrinsic pressure 1310  
     lung cancer 1086  
     rigid bronchoscopy 172  
   non-neoplastic lesions, bronchoscopy  
     155  
   obstruction 108, 1320  
   'sabre-sheath' 657  
   shortened 1309  
   smooth muscle 8  
   stenosis 1310, 1310, 1503  
   structure 8  
 tracheal cartilage 8  
 tracheal tomography 1115, 1116  
 tracheal tumours 108, 1115–16  
   asthma *vs* 961  
   fiberoptic bronchoscopy 155  
   lung cancer spread 1115–16, 1116  
   rigid bronchoscopy 172  
   treatment 1115–16  
   types 155  
 tracheitis 107, 346  
   acute 345–7  
 tracheobronchial aspiration, tracheostomy  
   complication 1503, 1504  
 tracheobronchial lymph nodes 21  
 tracheobronchial tree 9  
   amyloidosis 1337, 1338, 1338  
   anomalies 1309–13  
   embryology 1309, 1312  
   mucosa 54, 156, 158  
   narrowing  
     relief by bronchoscopy 151  
     'shelving down' 151, 156  
 tracheobronchitis 345–7  
   acute, sulphur dioxide causing 330  
   adenovirus pneumonia 416  
   common cold complication 338  
   fungal 347  
 tracheobronchomegaly 797, 1310–11  
 tracheo-innominate artery fistula 1503  
 tracheomalacia 1310  
 tracheo-oesophageal fistula  
   H-type 1309, 1310, 1310  
   tracheostomy complication 1503  
 tracheopathia osteoplastica 1338–9  
 tracheostomy 1502–4  
   complications 1503–4  
   composition/dimensions of tubes 1502  
   cuffed or cuffless tubes 1502, 1502–3  
   indications 1507  
   long-term ventilation 1512, 1513  
   for mechanical ventilation 704  
   in poliomyelitis 711  
   sleep apnoea treatment 1261  
   tube displacement/blockage 1503  
   tube features/types 1502, 1502–3  
   tube obstruction 1504  
   wound infections 1503, 1504  
 traction theory, bronchial dilatation 805  
 tranquillizers, respiratory failure due to  
   709  
 transbronchial lung biopsy 158–60  
   after lung transplantation 1520  
   complications 166–9, 1187  
   contraindications 169, 169–70  
   diffuse lung disease diagnosis 149  
   haemorrhage due to 167  
   mechanism 160  
   mortality 167  
   open lung biopsy comparison 165  
   *Pneumocystis carinii* pneumonia 1368–9  
   risks 160  
   sarcoidosis 164, 1055  
   specimens 149–50  
   wedge technique 159, 168  
 transcutaneous electrical nerve stimulation  
   (TENS) 1528–9  
 transdiaphragmatic artery 2  
 transdiaphragmatic pressure 645, 1235,  
   1238  
 transfer coefficient 35  
 transforming growth factor- $\beta$  (TGF- $\beta$ )  
   asthma pathogenesis 915  
   cryptogenic fibrosing alveolitis 880  
   secretion by ciliated cells 12  
 transplant-associated bronchiolitis 833,  
   836  
 transplantation  
   cytomegalovirus pneumonia after 418  
   *Pneumocystis carinii* pneumonia after  
     1363  
   respiratory infections after 1347–8  
   *see also* lung transplantation; *other organs*  
 transtracheal aspiration 185–6, 362  
   anaerobic pneumonia detection 413  
   complications 186  
   diagnostic yield 186  
   lung abscess specimen 468  
   reasons for reduced use 185  
   technique 185–6  
   tuberculosis diagnosis 520  
 transverse myelitis 349  
 'trapped lung' effect 445  
 trauma  
   adult respiratory distress syndrome after  
     773  
   bony, fat embolism 721  
   chylothorax 1166  
   diaphragmatic hernia 1246, 1247  
   diving 1488–9, 1489  
   empyema pathogenesis 446

- thrombosis predisposition 719–20
- travellers
  - advice on air pollution 332
  - amoebiasis 606
  - meliodosis 423, 424
  - oxygen therapy and advice for COPD 671
- treadmill 54
- trematodes 610–12
- tremolite, fibrous 1433
- tremors 113, 248
- trench mouth 339
- triamcinolone 264, 264
  - parenteral 266
- triamcinolone acetonide 278–9
- triatropium bromide 250
- tribavirin (ribavirin) 244, 416
- Trichinella* 604, 608
- Trichinella spiralis* 610, 1240
- trichiniasis (trichinosis) 610
  - of diaphragm 1240
- Trichomonas*, empyema 449, 454–5
- Trichosporon cutaneum* 1014
- tricyclic antidepressants 1528
- trimellitic anhydride 951, 1016, 1449
- trimethoprim 207–8
  - adverse effects 208
  - P. carinii* pneumonia treatment 223
  - sites of action and uses 207, 208
  - uses 207, 208
- trimethoprim–sulfamethoxazole,
  - nocardiosis 577
- trimetrexate 222
- trimetrexate–folinate, *Pneumocystis carinii* pneumonia 1371
- tropical pulmonary eosinophilia 609, 1024–5
- Tru-cut needle 175
- truncus arteriosus, development 1
- trypsin, immunoreactive 850
- tryptophan, metabolism 1135
- tubercle 479
- tubercle bacilli *see Mycobacterium bovis*; *Mycobacterium tuberculosis*
- tuberculin anergy 481
- tuberculin skin testing 479, 490–4, 509, 521
  - booster effect 493–4
  - CNS tuberculosis 530
  - false-negative 494, 494
  - false-positive 491
  - negative tests 481
  - positive tests 479, 481, 499–500
  - repeated, effects 493–4
  - sarcoidosis 1055
  - 'skin-test conversion' 493–4
  - specific/non-specific reactions 491
  - techniques and interpretations 492–3
- tuberculoma 517, 519
  - imaging 138
  - intracerebral 529, 530, 557
  - tuberculosis complication 523–4
- tuberculosis (TB) 476–506
  - anergic 483
  - antituberculosis campaign 500
  - asthma management and 992
  - bacteraemia 541
  - bone and joint 533–6
    - treatment 535–6, 556
  - breast 539–40, 540
  - case definitions 485, 485
  - case finding 494–7
  - chemoprophylaxis 498–500
    - in HIV infection 500
  - mass 498
  - primary 499
    - secondary 499–500, 500
  - chemotherapy 223–5, 554
  - 6-month short course 553–4, 554
  - 9-month regimen 555, 555
    - compliant patients 553–5
    - DOTS 553, 556, 559
    - extrapulmonary disease 556–7
    - failure 555
    - infectivity after 554
    - monitoring 554
    - monotherapy causing resistance 559, 560
    - non-compliant patients 555–6
    - primary disease 557
    - regimens 553–6
    - resistance *see* tuberculosis (TB), drug resistance
    - response assessment 554
    - short-course 544–6
    - short-course concerns 559
    - smear-negative pulmonary disease 554–5
    - special conditions 557–9
    - stepwise approach 556
    - trial in pyrexia of unknown origin 513
  - chest wall 1227
  - CNS 528–31
    - treatment 530–1, 557
    - see also* meningitis, tuberculous; tuberculoma
  - colliquative 539
  - congenital 507
  - contacts 495
  - costal 1227
  - cutaneous 539
  - diagnosis
    - cases confirmed bacteriologically 519
    - delays 476
  - disseminated *see* tuberculosis (TB), miliary
  - drug resistance 544, 556, 559
    - development and spread 559, 559
    - multiple 497, 556, 559, 559
    - prevention 559, 560
    - secondary 559
    - treatment 560
  - epidemics, characteristics/impact 485, 485
  - epidemiology 483–94
    - incidence/case numbers 476, 486
    - trends 488, 488–90
  - extrapulmonary 523, 529–43, 560
    - chemotherapy 556–7
    - distribution of sites 529
    - underdiagnosis 529
    - see also specific types (above/below)*
  - fibreoptic bronchoscopy 156, 165
    - bronchoscope cleaning 171
  - gastrointestinal 536–8
  - genitourinary tract 538–9, 556–7, 560
  - health care workers 478
    - prevention 496
  - hilar enlargement 139
  - historical background 476, 544
  - HIV infection and 486, 495–6, 529, 1354, 1356
    - clinical manifestations 521, 1355
    - impact 490
    - lymphadenitis 531
    - morbidity associated with TB 529
    - pericardial TB 532
  - prevention 1361
  - reactivation of TB and relapse 515, 558
  - treatment 558–9
- immune spectrum and immunity 481
- immunology 479, 481
- in immunosuppressed patients 1348
- infectivity of patients 478
- isolation of patients 478, 479
- larynx 7, 540
- long-term ventilation after 1512
- lung abscess and 463, 470
- lung lobes 479, 509
- lymph node 531, 531, 532
  - treatment 556, 560
- management 544–64
  - historical aspects 544, 545
  - principles 547
  - see also* antituberculosis drugs; tuberculosis (TB), chemotherapy
- mediastinitis 1300, 1302
- meningitis *see* meningitis
- miliary 479, 483, 511–14, 1354
  - chest radiography 140, 140–1
  - clinical manifestations 512, 514
  - complications 514
  - cryptic 481, 483, 511, 512
  - cutaneous 539
  - diagnosis 513–14
  - fibreoptic bronchoscopy 165
  - 'non-reactive' 512, 513
  - pathogenesis 512
  - pathology 512
  - radiology 512–13, 513
  - treatment 557
- mortality 484–5, 486
- multidrug-resistant 497, 556, 559, 559
- natural history (Wallgren's timetable) 481–3
- New York experience 476
- notification rates 485–8, 486, 487, 488
- ocular manifestations 540
- official 539
- pathogenesis 476–83
- pathology 479, 480
- patterns of presentation 481–3
- pericarditis 528, 531–3
- peritoneal 536–8
- pleural effusions *see* pleural effusions
- postprimary pulmonary 144, 144, 483, 514–24
  - assessment of activity 521
  - bacteriological examination 518–21
  - bronchiectasis aetiology 799
  - clinical manifestations 515–16
  - complications 522–4
  - differential diagnosis 521–2
  - investigations 518–21
  - pathogenesis 514–15
  - radiology 516–18, 517, 518
- prevention/control 494–501
  - BCG *see* BCG vaccination
  - chemoprophylaxis *see above*
- primary pulmonary 507–11
  - bronchiectasis 509, 517, 799
  - chemotherapy 553–6, 557
  - chest radiography 508, 508
  - clinical manifestations 508
  - complications 509–11
  - diagnosis 509
  - pathology 479
- progressive primary *see postprimary (above)*
- pulmonary 507–27

- tuberculosis (TB) (*Continued*)  
 reactivation 479, 514–15, 521  
 reinfection 515  
 relapse rates 555, 558  
 risk of disease after infection 490  
 risk of infection 488  
 secondary spontaneous pneumothorax 1185  
 as silicosis complication 1422, 1424  
 skeletal lesions 483  
 spinal *see* spinal tuberculosis  
 spread (lymphatic/haematogenous) 479  
 sputum examination 361  
 superficial lymphadenitis 531  
 testing *see* tuberculin skin testing  
 transmission 477–9  
 prevention in hospitals 478–9  
 upper respiratory tract 540  
 vaccines, MRC trial 483, 483, 484  
 verrucous 539  
 tuberculosis cutis miliaris acuta generalisata 539  
 tuberculosis health visitors 556  
 tuberculous chancre 539, 539  
 tuberin 1381  
 tuberous sclerosis 1140, 1381  
 tube thoracostomy, pneumothorax 1197–8  
 tularaemia 421  
 tumour emboli 722, 757  
 tumour genetics 98  
 tumour markers  
 lung cancer 1085  
 mediastinal germ-cell tumour 1288  
 tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) 914–15  
 ARDS 774  
 asthma 908, 909, 914–15  
 cryptogenic fibrosing alveolitis 880  
 tumour seeding  
 cutting-needle biopsy complication 176  
 lung biopsy 181  
 percutaneous fine-needle biopsy complication 175  
 tumour suppressive genes 98  
 tungsten carbide 1440–1  
 turbinates  
 anatomy 342  
 function 5  
 Turbohaler (Turbuhaler) 990  
 TWAR agent 399  
 twin studies, genetic effects in disease 92  
 typhus 422
- UK CCCR Lung Cancer Working Party 1081, 1081, 1084  
 UK Health and Safety Executive 1490  
 UK Industrial Injuries Advisory Council 1422, 1537  
 ulcerative colitis 1398  
 bronchiectasis association 802, 1398  
 obliterative bronchiolitis and 836, 1398  
 ultrasound 123  
 empyema 450  
 underwater blasts 1488–9, 1489  
 underwater seal drainage 456, 473  
 upper airways *see* airway(s)  
 upper airways resistance syndrome 1257  
 upper respiratory tract  
 anaesthesia 153–4  
 defences 52–3, 83  
 functions 4  
 sarcoidosis 1050  
 structure 4–8  
 tuberculosis 540
- Wegener's granulomatosis 1067  
*see also* larynx; nose; pharynx  
 upper respiratory tract infections 335–55  
 burden/costs 335  
 seasonal 335  
*see also individual infections/anatomic regions*  
 uraemia 789  
 ureidopenicillins 199–200  
 urinalysis, pneumonia 365  
 urinary tract, tuberculosis 538–9, 556–7  
 urogenital tract *see* genitourinary tract  
 urokinase 738, 739  
 ursodeoxycholic acid 860  
 uterine bleeding 248  
 uveitis, sarcoidosis 1049  
 uveoparotid fever 1051  
 uvulopalatopharyngoplasty 1260
- vagal receptors 938  
 vagal reflexes, breathing control 51–2  
 vagus nerve 7, 22  
 valaciclovir 235–6  
 validation of studies 75, 75  
 vanadium exposure 1448  
 vancomycin 219–20, 405  
 adverse effects 219, 220, 405  
 dosage 219–20  
 pneumonia treatment 370, 405  
 resistance 405  
 spectrum of activity 219  
*Staphylococcus aureus* infection 405  
 'vanishing lung' syndrome, SLE 1391–2  
 'vanishing pulmonary tumour' 1154  
 varicella zoster virus (VZV) 416  
 aciclovir use 234–6  
 detection/identification 416  
 in HIV infection 1358  
 immunoglobulin 418  
 pneumonia 416–18  
 vaccine 418  
 vascular system  
 inherited abnormalities 97–8  
*see also* pulmonary vasculature  
 vascular tissue, tumours 1137–42  
 mediastinal 1291  
 vasculitis  
 Churg–Strauss syndrome 1028, 1029  
 cystic fibrosis 862  
 polyarteritis nodosa 1028  
 purpuric 862  
 vasoactive intestinal peptide 23, 844  
 vasodilatation  
 carbon dioxide action 698  
 peripheral, COPD 653  
 vasodilators  
 in primary pulmonary hypertension 756  
*see also* pulmonary vasodilators  
 vasopressin *see* antidiuretic hormone (ADH; arginine vasopressin)  
 vasovagal reactions, fiberoptic bronchoscopy 169  
 vegetable origin, occupational asthma 950, 950  
 vehicles, air pollution due to 324, 327, 328  
 reduction 333  
 vena cava  
 development 2  
 interruption, pulmonary embolism 739–40  
 obstruction *see* superior vena cava obstruction  
 vena cava bronchovascular syndrome 1321–2  
 Venn diagram, COPD 617, 617  
 venography 1113  
 ascending, deep venous thrombosis 724, 725  
 veno-occlusive disease, pulmonary 757–9  
 venous drainage, lung, development 2  
 venous embolization, schistosomiasis 611  
 venous endothelium 718  
 venous stasis, thrombosis predisposition 718  
 venous thromboembolic disease 97, 718  
 risk factors 741  
*see also* deep venous thrombosis  
 venous thrombus, formation 721  
 ventilation 26–9  
 adaptations to high-altitude 55–6  
 alveolar 27–8  
 control 646  
 COPD 646–7  
 type I respiratory failure 697  
 drugs stimulating 280–3  
 maximum voluntary (MVV) and diving 1483  
 minute 26  
 negative-pressure 1507–9, 1513  
 ventilators and chambers 1508, 1508–9  
 nocturnal support, scoliosis 1218  
 non-invasive *see* non-invasive positive pressure ventilation (NIPPV)  
 normal in erect position 31  
 wasted 698–9  
 type I respiratory failure 696  
 ventilation, mechanical 1495–515  
 acute severe asthma 988  
 aims 1500–1  
 airway access 704  
 airway disease 705–6  
 alveolar disease 706  
 ARDS 783–4  
 assist and assist control 1497–9  
 barotrauma causing pneumothorax 1188  
 bilevel via nasal mask 1260  
 complications 708  
 controlled 1497, 1498  
 end-inspiratory pause 1496  
 endotracheal tube 1502–4  
 expiration  
 control 1497  
 initiation 1496  
 termination 1495–6  
 expiratory retard 1497  
 factors influencing institution 702  
 gas exchange during 1501–2  
 general management of patients 706–7  
 high-frequency 705, 1499–500  
 jet 713, 784  
 oscillatory 713  
 indications 704, 1509–911  
 infective polyneuropathy 711  
 inspiration  
 control 1495–7  
 initiation (ventilatory triggering) 1495–6  
 termination 1496  
 inspiratory–expiratory ratio, frequency and times 1496–7  
 inspiratory limitation 1496  
 inspiratory pressure and flow waveforms 1496  
 inspiratory pressure support 1499, 1499  
 intermittent mandatory 704–5, 1499

- inverse ratio, ARDS 784
- long-term 1511–14
  - home or hospital care 1513–14
  - indications and effect on prognosis 1511–12, 1512
  - method selection 1513
  - negative-pressure 1513
  - physiological effects 1512–13
  - quality of life 1512
- management 705
- mandatory minute 705
- mask and mouthpiece 1504–7
- modes 704–5, 1497–500
- mouthpieces 1507
- nasal and face masks 1260, 1504, 1504–7, 1505
  - advantages/disadvantages 1507
  - complications 1505–6
  - displacement/leaks 1505–6
  - initiation 1506–7
  - long-term use 1512, 1513
- negative end-expiratory pressure 1497
- neuromuscular diseases 1230
- nocturnal 1500, 1512
- pneumothorax 1190
- positive end-expiratory pressure *see* positive end-expiratory pressure (PEEP)
- positive-pressure, complications 1507
- principles 1495–7
- proportional assisted 705
- in respiratory failure 700, 704–8
- sigh 1496
- synchronized intermittent mandatory 705, 1499
- tracheostomy *see* tracheostomy
- type I respiratory failure 700
- ventilator lung 1467–8, 1468
- weaning 707–8, 1500, 1511
  - complete or partial 1501
  - factors preventing 1511
  - failure and measurements in 707
  - technique 708
- ventilation–perfusion ( $V_A/Q$ )
  - mismatching 31
- COPD 643, 643, 644
- neonatal respiratory distress syndrome 712
- pulmonary embolism 722
- type I respiratory failure 696
- ventilation–perfusion ( $V_A/Q$ ) ratios 31–3
  - abnormal 31–2, 32
  - hypoxaemia due to 33
  - diaphragmatic paralysis 1238
  - high ratios 31, 32, 33
  - mechanical ventilation aims 1501
- ventilation–perfusion ( $V_A/Q$ ) scans 123–4, 125
  - asthma 956
  - bronchiectasis 808
  - limitations 731
  - pulmonary embolism 730–1, 732, 733
  - pulmonary thromboembolism 124
  - scoliosis 1217
- ventilation scanning 123–4
- ventilator lung 1467–8, 1468
- ventilators 1495
  - Cuirass 1238, 1509, 1509, 1510
  - destination of gas leaving 1501–2
  - flow generators 1496
  - inspiration control 1495–7
  - jacket 1508–9
  - leaks 1501
  - management 705
  - negative-pressure 1495, 1508, 1508–9
  - positive-pressure 1495
  - pressure-cycled 705
  - pressure generators 1496
  - pressure-preset 1513
  - tank 1508, 1508
  - time or volume cycling 1496
  - volume-cycled 705
- ventilatory-assist devices, COPD 673
- ventilatory failure
  - causes 699
  - see also* respiratory failure, type II
- ventilatory support, COPD 646
- ventilatory workload, in type II respiratory failure 698–9
- ventricles
  - left, failure 128
  - see also* entries beginning right ventricular
- ventricular septal defect 761–2
- ventricular tachycardias 255
- venules 15
- verdoperoxidase 105
- vermiculite 1434
- vertebral bodies, tuberculosis 533
- vertebral fractures, corticosteroid-induced osteoporosis 269
- Veterans Administration Surgical Oncology Group 1109
- veterinarians, pneumonic plague 425
- video-assisted thoracoscopic biopsy 179, 183, 184
- video-assisted thoracoscopic surgery 457
  - pneumothorax 1200–2, 1201
- videothoracoscope 184
- Vim biopsy needle 175, 176
- vinblastine 290–1
- vinca alkaloids 290–1
- Vincent's angina 339, 340
- vincristine 290–1
- vindesine 290–1
- vinorelbine 290–1
- vinyl cyanide (acrylonitrile) 1445
- viomycin 550, 551
- viral infections 103
  - asthma trigger 898–9, 946–7
  - attachment and process 336
  - bronchiectasis 810
  - common cold 335–6
  - cystic fibrosis 855
  - fibreoptic bronchoscopy 166
  - pneumonia *see* pneumonia
  - susceptibility, corticosteroid-induced 271
  - see also* respiratory tract infections
- viruses 234
  - antibodies 336, 337
  - culture 337–8
  - shedding 336, 337
- visceral larva migrans 609, 610
- viscosity
  - bronchial mucus 14
  - sputum 865, 927, 941
- visually impaired, asthma management 992
- visual problems, ethambutol causing 549
- vital capacity (VC) 29
  - barotrauma and 1484
  - COPD 641
  - myasthenia gravis 49
  - reduction
    - asthma 955
    - diaphragmatic paralysis 1237, 1238
    - on immersion in water 1482
    - respiratory muscle dysfunction 710
- vitamin C
  - common cold 338
  - low intake, COPD risk factor 625
  - reduced intake, asthma increase 940
  - trials/use in asthma 900, 945
- vitamin D, oral supplements 269
- vitamin E
  - asthma prevention 900, 945
  - intramuscular in oxygen toxicity 1468
  - reduced intake, asthma increase 940
- vocal cords
  - anaesthesia 153–4
  - bronchoscope passage through 155
  - paralysis 7
    - bilateral 154–5
    - bronchoscopy indication 149, 154–5
    - lung cancer 154, 1086
    - unilateral 154
  - singer's nodules 8
  - structure 6
- volatile organic compounds, air pollution due to 332
- vomiting, pneumomediastinum 1205
- von Recklinghausen's syndrome 1143, 1273, 1276
  - malignant transformation in 1275
  - pulmonary manifestations 1381
- Waldenström's macroglobulinaemia 1398
- walking test 55
  - 6-minute 657
  - 12 minute, cryptogenic fibrosing alveolitis 886
- warfarin
  - monitoring therapy 737–8
  - pulmonary embolism 737
  - structure and actions 737
  - teratogenicity 743
- washing powders, biological 950, 1014
- water
  - absorption, airways epithelium 844
  - bronchial secretions 15
  - contaminated, *Legionella* 386, 387
  - decontamination 391
  - inhalation 1487
  - opportunistic mycobacterial infection from 566, 570
  - retention, corticosteroid-induced 271
  - 'waterlily' sign 612, 613
- water systems, contaminated, *Legionella* 386, 387
- WD-40, lipid pneumonia 428
- weather, asthma aetiology 948–9
- Wegener's granulomatosis 5, 1063–70
  - chest radiography 1068
  - clinical features 1067–9
  - fibreoptic bronchoscopy 155
  - frequency 1063
  - interstitial lung disease due to 889
  - investigations and differential diagnosis 1069
  - limited 1070
  - neutrophils 1064, 1064
  - pathogenesis and autoantibodies 1063–5, 1065
  - pathology 1065–7, 1066
  - pleural effusions 1161
  - prognosis 1070
  - treatment 286, 1069–70
- weight
  - gain 268, 319

- weight (*Continued*)  
 high altitude effect 57  
 loss, COPD 644, 652, 673  
 Weil–Felix test 401  
 Weil’s disease 422  
 welders, siderosis 1435, 1436  
 welding, COPD 624  
 Westermarck’s sign 729, 731  
 ‘wet lung’ 770  
 wheeze 110, 115, 249  
   acute bronchitis 346  
   asthma 940–1, 952, 955  
   bronchiectasis 807  
   in children 900, 1478  
   COPD 651–2, 653  
   differential diagnosis 888, 958–959  
   diffuse interstitial lung disease 888  
   irritant gas exposure causing 998, 999  
   polyphonic, hypersensitivity pneumonitis 1002–3  
   recurrent in children 1478  
 wheezy illness  
   adult-onset 999  
   asthma prediction 896–7  
   children 923, 923  
 Whipple’s disease 1398  
 whispering pectoriloquy 115  
 white cell counts  
   FEV<sub>1</sub> relationship in COPD 624  
   Legionnaire’s disease 388  
   Loeffler’s syndrome 1023  
   *Mycoplasma pneumoniae* 394  
   pneumonia 364  
   reduction by glucocorticosteroids 262  
   tuberculosis 521  
 white noise 109, 114  
 ‘whole lung lavage’ *see* bronchoalveolar lavage (BAL)  
 whooping cough *see* pertussis (whooping cough)  
 Willaims–Campbell syndrome (bronchomalacia) 797  
 wines, asthma provoking factor 946, 962  
 Wiskott–Aldrich syndrome 97  
 wollastonite 1435  
 woodworker’s lung 1013  
 woolsorters’ disease (anthrax) 426  
 wool-workers 68–9, 76  
 workplace  
   hazards 1405, 1405  
   influenza vaccination 350  
   passive smoking 314  
   smoking 319  
   *see also* occupation  
 World Health Organization (WHO)  
   air pollution 329, 622  
   byssinosis grading 1442, 1442  
   lung cancer classification 1080, 1081  
   particulate air pollution 329  
   quality of life scales 1116, 1117  
   tuberculosis case estimates 476  
 Wright–Giemsa stain 361  
 Wright peak expiratory flow meter 45  
 wrinkling, facial 313  
*Wuchereria bancrofti* 609  
 xanthines 253, 987  
   *see also* theophylline  
 xanthoma 1131–2  
*Xanthomonas maltophilia* *see* *Stenotrophomonas (Xanthomonas) maltophilia*  
*X* bodies 1131  
 xenon gas 31  
 xenotransplantation 1516, 1522  
 xerophthalmia 802  
 xiphoid process, jointed 1212  
 X-ray planimetry, COPD 655  
 yeasts 574  
 yellow nails syndrome 767  
   bronchiectasis association 803  
   clinical features 1161, 1162  
   pleural effusions 1161  
*Yersinia pestis* 425  
 yolk sac tumour 1284, 1287  
 Young’s syndrome 796  
 zafirlukast 259  
 zalcitabine (ddC) 238  
 zanamivir 243, 350  
 zeolite 671  
 zidovudine 237–8  
   adverse effects 237  
 Ziehl–Nielsen stain  
   atypical mycobacteria 567  
   mycobacteria 476, 477  
   sputum 361  
   in tuberculosis 518, 538  
 zileuton 259  
 zinc chloride fumes 1448  
 zinc coproporphyrin 722  
 zinc oxide fume inhalation 1448  
 zoonoses 400  
   brucellosis 420  
   *Leptospira icterohaemorrhagiae* pneumonia 422  
 zygomycetes 598